J. Braz. Chem. Soc., Vol. 24, No. 6, 895-903, 2013. Printed in Brazil - ©2013 Sociedade Brasileira de Química 0103 - 5053 \$6.00+0.00



Green and Selective Synthesis of *N*-Substituted Amides using Water Soluble Porphyrazinato Copper(II) Catalyst

Sara S. E. Ghodsinia,^a Batool Akhlaghinia,^{*,a} Elham Safaei^b and Hossein Eshghi^a

^aDepartment of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, 9177948974 Mashhad, Islamic Republic of Iran

^bDepartment of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), 45137-66731 Zanjan, Islamic Republic of Iran

N,N',N'',N'''-Tetrametil tetra(2,3-piridil)porfirazinato metil sulfato de cobre(II) ([Cu(2,3-tmtppa)](MeSO₄)₄) catalisou com sucesso a conversão direta de nitrilas a amidas N-substituídas. A síntese seletiva do tipo *one pot* de amidas N-substituídas a partir de nitrilas e aminas primárias foi realizada em refluxo de água. O catalisador foi recuperado e reusado no mínimo 4 vezes, mantendo a sua eficiência.

N,N',N''. Tetramethyl tetra-2,3-pyridinoporphyrazinato copper(II) methyl sulfate ([Cu(2,3-tmtppa)](MeSO₄)₄) efficiently catalyzed the direct conversion of nitriles to *N*-substituted amides. The one pot selective synthesis of the *N*-substituted amides from nitriles and primary amines was performed in refluxing H₂O. The catalyst was recovered and reused at least four times, maintaining its efficiency.

Keywords: [Cu(2,3-tmtppa)](MeSO₄)₄, N-substituted amide, nitrile, amine

Introduction

Amide bond formation is a fundamental reaction of great interest in organic and bioorganic chemistry, peptides and proteins include these bonds. Synthesis of N-alkyl amides has been of great interest because they are versatile synthetic intermediates used in the manufacture of several pharmacological products, polymers, detergents, lubricants and drug stabilizers, as well as key structural motifs present in numerous natural products.¹⁻⁵ Current popular synthesis strategies of amides are the reaction of amines with carboxylic acids, transamidation of amides with amines, or with the reaction of carboxylic acid derivatives such as acyl halides, anhydrides, esters and other activated species usually in the presence of coupling reagents.⁶⁻²⁷ Reactions promoted by coupling reagents are fundamental in organic synthesis. The majority of amide bond syntheses is merely stoichiometric, making these methods generally expensive and wasteful procedures.²⁸ As the society needs forward-looking environmentally acceptable technology, the development of catalytic reactions that use transitionmetal complex catalysts under neutral and mild reaction conditions is particularly important. These criteria include atom efficiency, formation of little inorganic waste, and selective synthesis of desired products, encouraging an effort towards using environmentally friendly catalytic processes that will not produce such waste. The conversion of aldehydes,²⁹⁻³⁶ oxime^{34,37-46} and nitriles⁴⁷⁻⁵⁴ constitute effective methods to access amides.^{31,55-61}

A little-known reaction which yields amides is the hydrolytic amidation of nitriles with amines. A platinum and an iron catalysts were found to perform the coupling.^{53,54} Nitriles can also be coupled with alcohols to form amides in the Ritter reaction. As an alternative to sulfuric acid, the Ritter reaction can be catalyzed by metal complexes such as bismuth triflate⁶² and iron complexes.⁶³

Our group recently reported that [Cu(2,3-tmtppa)](MeSO₄)₄ (*N*,*N*',*N*'',*N*'''-tetramethyl tetra-2,3-pyridinoporphyrazinato copper(II) methyl sulfate) could be used as catalyst for protection of hydroxyl and carbonyl groups.⁶⁴⁻⁶⁶ In the course of our present study, our interesting is in using $[Cu(2,3-tmtppa)](MeSO_4)_4$ (Scheme 1) as a safe, environmentally benign and efficient acid catalyst in the preparation of *N*-substituted amides.

^{*}e-mail: akhlaghinia@um.ac.ir



Scheme 1. The structure of $[Cu(2,3-tmtppa)](MeSO_4)_4$.

Experimental

General

The products were purified by column chromatography. The purity determinations of the products were accomplished by thin layer chromatography (TLC) on silica gel polygram STL G/UV 254 plates. The melting points of the products were determined with an Electrothermal type 9100 melting point apparatus. The Fourier transform infrared (FTIR) spectra were recorded on an Avatar 370 FTIR Therma Nicolet spectrometer. The nuclear magnetic resonance (NMR) spectra were provided on Brucker Avance 100 and 400 MHz instruments in CDCl₃. Elemental analyses were performed using an Elementar Vario EL V5.19.1121 and Thermofinnigan Flash EA 1112 Series instruments. Mass spectra (MS) were recorded with a Shimadzu GC-MS-QP5050 and CH7A Varianmat Bremem instruments at 70 eV. The known products were characterized by FTIR and ¹H NMR spectra and comparisons of their melting points (or those of the derivatives) were done with authentic samples. The catalyst was prepared and purified by the method described in the literature.67-69

Results and Discussion

The optimization of the reaction conditions was carried out for the reaction of phenylacetonitrile with benzylamine in the presence of $[Cu(2,3-tmtppa)](MeSO_4)_4$ under various reaction parameters in order to achieve the maximum chemical yield at the lowest reaction time and lowest reaction temperature. The general reaction is outlined in Scheme 2 and the representative results are shown in Table 1.

In the absence of any catalyst, there was no conversion to N-benzyl-2-phenylacetamide (Table 1, entries 1, 20 and 21). In solvent free condition and applying different molar ratios of phenylacetonitrile, benzylamine, [Cu(2,3-tmtppa)]⁴⁺ was identified as a catalyst for N-benzyl-2-phenylacetamide formation but in prolonged reaction time and low yield (Table 1, entries 2-5). In an effort to develop better reaction conditions, different solvents were screened for the preparation of N-benzyl-2-phenylacetamide from the reaction of phenylacetonitrile with benzylamine in the presence of 0.5 mol% of $[Cu(2,3-tmtppa)](MeSO_4)_4$. No product was obtained when the reaction was performed in dimethyl sulfoxide (DMSO), dimethylformamide (DMF), CH₂Cl₂ and Et₂O (Table 1, entries 6-9). The catalytic effect of $[Cu(2,3-tmtppa)](MeSO_4)_4$ was efficiently decreased in aprotic polar solvents such as DMSO and DMF because of the strong coordination of solvent with Cu^{II}. As shown in Table 1, when the reaction was performed in refluxing 1,4-dioxane and H₂O, N-benzyl-2-phenylacetamide was obtained in good to excellent yields. To improve amide formation, the effect of different molar ratios of phenylacetonitrile, benzylamine was examined in 1,4-dioxane and H₂O (Table 1, entries 10-19). Also, the effect of temperature was studied in 1,4-dioxane and H₂O. No conversion was observed when the reaction was carried out at room temperature (Table 1, entries 22-23). It seems that the temperature is an important factor in the preparation of N-benzyl-2-phenylacetamide. The best results were obtained in 1,4-dioxane, H₂O, toluene and tetrahydrofuran (THF) (Table 1, entries 10-19,25-26). Because of safety, economic and handling considerations, H₂O was chosen for further experiments. Maximum yield was observed in refluxing H₂O with a 1:2 molar ratio of phenylacetonitrile:benzylamine (Table 1, entry 18). To investigate the effect of catalyst loading, the formation of N-benzyl-2-phenylacetamide was carried out in refluxing H₂O in the presence of 1 mol% of catalyst. According to this study, increasing the catalyst loading did not lead to higher conversion (Table 1, entry 24). It is noteworthy that no evidence for reaction of phenylacetonitrile with water was observed in the absence of benzylamine and any tendency between phenylacetonitrile and H₂O can be prohibited (Table 1, entry 27).

To explore the generality and scope of the *N*-substituted amides formation catalyzed by $[Cu(2,3-tmtppa)](MeSO_4)_4$, the optimized reaction conditions (1:2 molar ratio of nitrile:amine, 0.5 mol% catalyst, refluxing H₂O) were used for the synthesis of a series of amide derivatives (Table 2).

According to the results obtained (Table 2), *N*-substituted amides were prepared from the reaction of aromatic and aliphatic nitriles with primary aliphatic amines in the

entry	Molar ratio (phenylacetonitrile:benzylamine)	Solvent	Temperature / °C	time / h	Isolated yield / %
1 ^a	1/1	none	90	30	0
2	1/1	none	90	32	60
3	1/1.5	none	90	30	65
4	1/1.7	none	90	27	68
5	1/2	none	90	24	68
6	1/1	DMSO	90	24	0
7	1/1	DMF	90	24	0
8	1/1	CH_2Cl_2	reflux	24	0
9	1/1	Et ₂ O	reflux	24	0
10	1/1	1,4-dioxane	reflux	30	80
11	1/1.5	1,4-dioxane	reflux	25	85
12	1/1.7	1,4-dioxane	reflux	22	90
13	1/2	1,4-dioxane	reflux	20	95
14	1/2.2	1,4-dioxane	reflux	20	98
15	1/1	H_2O	reflux	23	85
16	1/1.5	H_2O	reflux	23	90
17	1/1.7	H_2O	reflux	22	95
18	1/2	H_2O	reflux	19	98
19	1/2.2	H_2O	reflux	19	97
20 ^a	1/2	1,4-dioxane	reflux	20	0
21ª	1/2	H_2O	reflux	20	0
22	1/2	1,4-dioxane	rt	20	0
23	1/2	H_2O	rt	20	0
24 ^b	1/2	H_2O	reflux	19	98
25	1/2	toluene	reflux	19	98
26	1/2	THF	reflux	23	90
27	1/0	НО	reflux	20	0

Table 1. Synthesis of N-benzyl-2-phenylacetamide in the presence of 0.5 mol% of $[Cu(2,3-tmtppa)](MeSO_4)_4$ in various solvents, different molar ratios and different temperatures

^aThe reaction was performed in the absence of catalyst; ^bthe reaction was performed in the presence of 1 mol% of catalyst.



Scheme 2. Synthesis of *N*-substituted amides.

presence of $[Cu(2,3-tmtppa)](MeSO_4)_4$ in high isolated yields. The mechanism of this transformation is unclear. On the basis of proposed mechanism in Scheme 3, the catalytic activity of $[Cu(2,3-tmtppa)](MeSO_4)_4$ could well be attributed

to the Lewis acidity of the complex. The catalytic reaction of alkyl and aryl nitriles with primary amines was achieved by refluxing aqueous solution of the corresponding nitriles, in the presence of 0.5 mol% $[Cu(2,3-tmtppa)](MeSO_4)_4$, which initially generates the nitrile bound copper species I. This idea is supported by performing the reaction in the absence of catalyst. Without any catalyst, the reaction is not completed even after long period of time (Table 1, entries 1, 20 and 21). Nucleophilic attack of primary amines to I affords intermediate II, which upon reaction with H₂O, produces hydrolyzed product III. The formation of II and III was confirmed by the fact that nucleophilic attack of amine can be catalyzed by $[Cu(2,3-tmtppa)](MeSO_4)_4$, according to the result obtained from Table 1, entry 27 (any tendency between nitrile compound and H₂O can be prohibited). Copper complex III produces N-substituted amide with concomitant loss of an ammonia molecule. Finally, the regeneration of catalyst initiates a second catalytic cycle. Nevertheless, at this time, there is no experimental evidence for I, II and III formation and action in this manner. However, further

entry	Nitrile	Amine	Product	time / h	Yield / %
1	$C\equiv N$ 1a	NH ₂ 1b		19	98
2	CEN 1a	OMe NH ₂ 2b	O OMe N H 2	24	92
3	CEN 1a	4b	O N H 3	15	95
4	CEN 1a	∽ ₀ ∽∽ _{NH₂} 5b		22	83
5		NH ₂ 1b		17	90
6	CI 2a CEN	4b		14	85
7	CEN 3a	NH ₂ 1b		24	98
8	Aa	NH ₂ 1b		11	98
9	$ \begin{bmatrix} N & C \equiv N \\ 4a \end{bmatrix} $	OMe NH ₂ 2b	N N N H Q	13	92
10	V $C \equiv N$ 4a	CI NH ₂ 3b	$ \begin{array}{c} $	15	94

Table 2. Synthesis of different structurally *N*-substituted amides in the presence of $[Cu(2,3-tmtppa)](MeSO_4)_4$

Table 2. continuation

entry	Nitrile	Amine	Product	time / h	Yield / %
11		∽_0 ∽NH ₂ 5b	N H	16	90
12		NH ₂ 7b	$ \begin{array}{c} 0 \\ N \\ H \\ 12 \end{array} $	19	90
13		4b	$ \begin{array}{c} $	14	92
14		6b	$ \begin{array}{c} $	17	91
15	$\sum_{5a}^{N \to C \equiv N}$	Ib NH2		16	92
16	$\mathbb{N} \qquad \mathbf{6a} \qquad \mathbf{C} \equiv \mathbb{N}$	Ib NH2		15	90
17	$N \qquad 6a$	4b ∧ NH ₂	$N \xrightarrow{O}_{H} N$ 17	18	96
18	$\int_{-7a}^{S} C \equiv N$	NH ₂	S H	10	97
19		4b	\sim	15	98
20	$\int_{-7a}^{S} C \equiv N$	OMe NH ₂	S H	12	97

entry Nitrile Amine Product time / h Yield / % Cl 0 Cl C≡N NH₂ 95 21 13 Ĥ 7a 3b 21 0 C≡N NH₂ 22 15 93 Ĥ 7a 6b 22 C≡N NH₂ 23 17 95 N H 7a 5b 23 C_{SN} NH_2 24 24 73 || 0 8a 1b 24 Η CSN NH_2 25 23 78 U O 1b 9a 25 $R^2 NH_2$ R²- $R^1 - C \equiv N$ CuII C≡N R (I) (II) R^2R^3NH or $ArNH_2$ H_2O .. Н₂О no reaction no reaction $R^1 \xrightarrow{V} N^{-R^2} +$ NH₃ R^1 (III)

Table 2. continuation

Scheme 3. A proposed mechanism for the formation of N-substituted amides.

mechanistic studies are required to confirm this mechanism. The catalytic activity of $[Cu(2,3-tmtppa)](MeSO_4)_4$ was examined for the reaction of alkyl and aryl nitriles with secondary amines and aryl amines. Surprisingly, even after long period of time, secondary amines and aryl amines remain intact in the reaction medium.

 $[Cu(2,3-tmtppa)](MeSO_4)_4$ acts as a recyclable catalyst for one pot amide formation from various nitriles and primary amines in refluxing H₂O, which provides a new and green catalytic system for N-substituted amide synthesis. The catalyst can be easily recovered from the reaction mixture by extraction of organic compounds $(3 \times 5 \text{ mL})$ CH₂Cl₂). The aqueous layer was evaporated and the catalyst was washed with CH₂Cl₂ three times to remove the products followed by drving in air at room temperature. Using this treatment, the recyclabilty of the catalsyt was evaluated for the reaction of phenylacetonitrile with benzyl amine (Table 3). The recovered catalyst was reused at least four times without any decrease in the yield of the N-benzyl-2-phenylacetamide. The 5th run gave 95% conversion after 19 h, but complete conversion and similar yield was obtained after 25 h.

 Table 3. Reaction of phenylacetonitrile with benzylamine in the presence of reused catalyst

entry	time / h	Conversion / %	Isolated yield / %
1	19	100	98
2	19	100	98
3	19	100	95
4	19	100	97
5 ^a	25/19	100/95	95
6 ^a	25/19	100/95	96

^aThe second numbers in the third column correspond to yields after 19 h.

The results obtained (Table 2) clearly demonstrate that this method is inapplicable to synthesis of primary and N,N-disubstituted amides. The catalytic activity of $[Cu(2,3-tmtppa)](MeSO_4)_4$ in this reaction is selective.

In our experiments, the completion of the reaction was confirmed by the disappearance of the nitrile on TLC followed by the disappearance of CN stretching frequency at 2230 cm⁻¹ in the FTIR spectra. Also, absorption bands at 1677-1612 and 3396-3284 cm⁻¹ due to carbonyl and NH group of *N*-substituted amide in FTIR spectra confirmed the amide formation. In the ¹H NMR spectrum, the NH proton of *N*-substituted amide showed a downfield shift as compared to the NH₂ protons of amine. In the ¹³C NMR spectrum, a signal at 173-161 ppm is assigned to the quaternary carbonyl carbon. The structure of all products was further confirmed by mass spectroscopy and CHN analysis.

Conclusions

In this study, our group not only investigated another catalytic activity of $[Cu(2,3-tmtppa)](MeSO_4)_4$ in organic synthesis, but also introduced an efficient, clean, convenient, practical and selective synthesis of *N*-substituted amides

from the reaction of alkyl and aryl nitriles with amines in green solvent.

This process is attractive in comparison with the conventional methods because this method offers several advantages: (*i*) the reaction proceeds smoothly and selectively with a wide range of amides (aliphatic and aromatic *N*-substituted); (*ii*) the catalyst is stable and reusable that offers easy handling and simple work-up; (*iii*) this method has satisfactory yields of a variety of amides;⁴⁹ (*iv*) in contrast to the previously reported catalytic systems, which proceeded by hydration of nitrile to the primary amide and subsequent transamidation with amine, in the present method, amides are produced by direct reaction of nitriles with amines; (*v*) in comparison with the previous methods, nitriles are storage-stable and less corrosive substrates.

Supplementary Information

Supplementary data and spectra of the synthesized compounds are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgment

The authors gratefully acknowledge the partial support of this study by Ferdowsi University of Mashhad Research Council (Grant No. p/3/20196).

References

- Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T.; Org. Biomol. Chem. 2006, 4, 2337.
- Zabicky, J.; *The Chemistry of Amides*; Wiley: New York, USA, 1970.
- Greenberg, A.; Breneman, C. M.; Liebman, J. F.; *The Amide Linkage Structural Significance in Chemistry Biochemistry and Materials Science*; Wiley: New York, USA, 2000.
- Deopura, B. L.; Gupta, B.; Joshi, M.; Alagirusami, R.; *Polyesters and Polyamides*; CRC Press: Boca Raton, FL, USA, 2008.
- Johansson, I.; Kirk-Othmer Encyclopedia of Chemical Technology, vol. 2; Wiley: New York, USA, 2004, p. 442.
- Benz, G. In *Comprehensive Organic Synthesis*, vol. 6; Trost, B. M.; Fleming, I., eds.; Pergamon: Oxford, UK, 1991, p. 381.
- Larock, C.; *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, USA, 1999, p.1932.
- Naik, S.; Bhattacharjya, G.; Talukdar, B.; Patel, B. K.; *Eur. J.* Org. Chem. 2004, 1254.
- Katritzky, A. R.; He, H. Y.; Suzuki, K.; J. Org. Chem. 2000, 65, 8210.

- Katritzky, A. R.; Cai, C.; Singh, S. K.; J. Org. Chem. 2006, 71, 3375.
- 11. Hosseini-Sarvari, M.; Sharghi, H.; J. Org. Chem. 2006, 71, 6652.
- Shekhar, A. C.; Kumar, A. R.; Sathaiah, G.; Paul, V. L.; Sridhar, M.; Rao, P. S.; *Tetrahedron Lett.* **2009**, *50*, 7099.
- 13. Kim, J. G.; Jang, D. O.; Synlett. 2000, 1231.
- 14. Ranu, B. C.; Dutta, P.; Synth. Commun. 2003, 33, 297.
- 15. Arora, R.; Paul, S.; Gupta, R.; Can. J. Chem. 2005, 83, 1137.
- Maki, T.; Ishihara, K.; Yamamoto, H.; Org. Lett. 2006, 8, 1431.
- Al-Zoubi, R. M.; Marion, O.; Hall, D. G.; Angew. Chem., Int. Ed. 2008, 47, 2876.
- 18. Marcelli, T.; Angew. Chem., Int. Ed. 2010, 49, 6840.
- Charville, H.; Jackson, D.; Hodge, G.; Whiting, A.; *Chem. Commun.* 2010, 46, 1813.
- Arnold, K.; Batsanov, A.S.; Davies, B.; Whiting, A.; Green Chem. 2008, 10, 123.
- 21. Starkov, P.; Sheppard, D. T.; Org. Biomol. Chem. 2011, 9, 1320.
- 22. Stephenson, N. A.; Zhu, J.; Gellman, S. H.; Stahl, S. S.; *J. Am. Chem. Soc.* **2009**, *131*, 10003.
- Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Cui, Q.; Stahl, S. S.; J. Am. Chem. Soc. 2008, 130, 647.
- Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Stahl, S. S.; J. Am. Chem. Soc. 2006, 128, 5177.
- Kissounko, D. K.; Hoerter, J. M.; Guzei, I. A.; Cui, Q.; Gellman, S. H.; Stahl, S. S.; *J. Am. Chem. Soc.* 2007, *129*, 1776.
- Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S.; J. Am. Chem. Soc. 2003, 125, 3422.
- 27. de Oliveira, V. M.; de Jesus, R. S.; Gomes, A. F.; Gozzo, F. C.; Umpierre, A. P.; Suarez, P. A. Z.; Rubim, J. C.; Neto, B. A. D.; *ChemCatChem* **2011**, *3*, 1911.
- Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.;
 J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Leazer, B. A.;
 Pearlman, Wells, A.; Zaks, A.; Zhang, T. Y.; *Green Chem.* 2007, 9, 411.
- Hamid, M.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum,
 H. C.; Watson, A. J. A.; Williams, J. M. J.; *J. Am. Chem. Soc.* 2009, 131, 1766.
- 30. Ekoue-Kovi, K.; Wolf, C.; Chem. Eur. J. 2008, 14, 6302.
- Suto, Y.; Yamagiwa, N.; Torisawa, Y.; *Tetrahedron Lett.* 2008, 49, 5732.
- Qian, C.; Zhang, X.; Zhang, Y.; Shen, Q.; J. Organomet. Chem. 2010, 695, 747.
- 33. Naota, T.; Murahasi, S. I.; Synlett 1991, 693.
- Gunanathan, C.; Ben-David, Y.; Milstein, D.; *Science* 2007, *317*, 790.
- Nordstrom, L. U.; Vogt , H.; Madsen, R.; J. Am. Chem. Soc. 2008, 130, 17672.
- Zhang, Y.; Chen, C.; Ghosh, S. C.; Li, Y.; Hong, S. H.; Organometallics 2010, 29, 1374.

- 37. Hyan, D.; Jang, C. D. O.; Tetrahedron Lett. 2004, 45, 2285.
- Fujiwara, H.; Ogasawara, Y.; Kotani, M.; Yamaguchi, K.; Mizuno, N.; Asian J. Chem. 2008, 3, 1715.
- Gnanamgari, D.; Crabtree, R. H.; Organometallics 2009, 28, 922.
- Owston, N. A.; Parker, A. J.; Williams, J. M. J.; Org. Lett. 2007, 9, 3599.
- Owston, N. A.; Parker A. J.; Williams, J. M. J.; Org. Lett. 2007, 9, 73.
- Ramon, R. S.; Bosson, J.; Diez-Gonzalez, S.; Marion, N.; Nolan, S. P.; J. Org. Chem. 2010, 75, 1197.
- Ali, M. A.; Punniyamurthy, T.; Adv. Synth. Catal. 2010, 352, 288.
- Allen, C. L.; Burel, C.; Williams, J. M. J.; *Tetrahedron Lett.* 2010, *51*, 2724.
- Kim, M.; Lee, J.; Lee, H. Y.; Chang, S.; Adv. Synth. Catal. 2009, 351, 1807.
- 46. Gnanamgari, D.; Crabtree, R. H.; Organometallics 2009, 28, 922.
- Fujiwara, H.; Ogasawara, Y.; Yamaguchi, K.; Mizuno, N.; Angew. Chem., Int. Ed. 2007, 46, 5202.
- 48. Shie, J. J.; Fang, J. M.; J. Org. Chem. 2003, 68, 1158.
- Tamura, M.; Tonomura, T.; Shimizu, K-I.; Satsuma, A.; *Appl. Catal.*, A 2012, 417, 6.
- Murahashi1, Sh. I.; Takaya, H.; Naota, T.; *Pure Appl. Chem.* 2002, 74, 19.
- Dijk, A. J. M.; Heyligen, T.; Duchateau, R.; Meuldijk, J.; Koning, C. E.; *Chem. Eur. J.* 2007, *13*, 7664.
- Rousselet, G.; Capdeviclle, P.; Maumy, M.; *Tetrahedron Lett.* 1993, 34, 6395.
- Liana Allen, C.; Lapkin, A. A.; Williams, J. M. J.; *Tetrahedron Lett.* 2009, 50, 4262.
- Cobley, Ch. J.; Heuvel, M.; Abbadi, A.; Vries, J. G.; *Tetrahedron* Lett. 2000, 41, 2467.
- Perreux, L.; Loupy, A.; Volatron, F.; *Tetrahedron* 2002, 58, 2155.
- 56. Wu, X.; Wannberg, J.; Larhed, M.; Tetrahedron 2006, 62, 4665.
- 57. Sureshbabu, V. V.; Hemantha, H. P.; ARKIVOC 2008, 2, 243.
- 58. Moorthy, J. N.; Singhal, N. J.; Org. Chem. 2005, 70, 1926.
- Kabalka, G. W.; Despande, S. M.; Wadgaonkar, P. P.; Synth. Commun. 1990, 20, 1445.
- Yasushi Imada, Y.; Shibata, O.; Murahashi, S. I.; J. Organomet. Chem. 1993, 451, 183.
- 61. Allen, C. L.; Williams, J. M. J.; Chem. Soc. Rev. 2011, 40, 3405.
- Callens, E.; Burton, A. J.; Barrett, A. G. M.; *Tetrahedron Lett.* 2006, 47, 8699.
- Anxionnat, B.; Guerinot, A.; Reymond, S.; Cossy, J.; *Tetrahedron Lett.* 2009, 50, 3470.
- Akhlaghinia, B.; Asadi, M.; Safaei, E.; Heydarpoor, M.; J. Porphyrins Phthalocyanines 2004, 8, 1285.
- Akhlaghinia, B.; Asadi, M.; Safaei, E.; Heydarpoor, M.; Phosphorus, Sulfur Silicon Relat. Elem. 2004, 179, 2099.

- Akhlaghinia, B.; Tavakoli, S.; Asadi, M.; Safaei, E.; J. Porphyrins Phthalocyanines 2006, 10, 167.
- Smith, T. D.; Livorness, J.; Taylor, H.; J. Chem. Soc., Dalton Trans. 1983, 7, 1391.
- 68. Marti, C.; Nonell, S.; Nicolau, M.; Torres, T.; *Photochem. Photobiol.* **2000**, *71*, 53.
- Thamae, M.; Nyokong, T.; J. Electroanal. Chem. 1999, 470, 126.

Submitted: December 9, 2012 Published online: May 21, 2013



Green and Selective Synthesis of *N*-Substituted Amides using Water Soluble Porphyrazinato Copper(II) Catalyst

Sara S. E. Ghodsinia,^a Batool Akhlaghinia,^{*,a} Elham Safaei,^b and Hossein Eshghi^a

^aDepartment of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, 9177948974 Mashhad, Islamic Republic of Iran

^bDepartment of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), 45137-66731 Zanjan, Islamic Republic of Iran

Experimental

General

The products were purified by column chromatography. The purity determinations of the products were accomplished by thin layer chromatography (TLC) on silica gel polygram STL G/UV 254 plates. The melting points of products were determined with an Electrothermal Type 9100 melting point apparatus. The Fourier transform infrared (FTIR) spectra were recorded on an Avatar 370 FTIR Therma Nicolet spectrometer. The nuclear magnetic resonance (NMR) spectra were provided on Brucker Avance 100 and 400 MHz instruments in CDCl₃. Elemental analyses were performed using an Elementar, Vario EL V5.19.1121 and Thermofinnigan Flash EA 1112 Series instruments. Mass spectra (MS) were recorded with a Shimadzu GC-MS-QP5050 and CH7AV arianmat Bremem instruments at 70 eV.

Preparation of *N*-benzyl-2-phenylacetamide from phenyl acetonitrile and benzylamine (1)

To a solution of phenylacetonitrile (0.1171 g, 1 mmol) in H₂O (1 mL), [Cu(2,3-tmtppa)](MeSO₄)₄ (0.0054 g, 0.5 mol%) was added at room temperature with continuous stirring. Benzylamine (0.2143 g, 2 mmol) was added with stirring at room temperature. The temperature was raised up to 100 °C. The progress of the reaction was followed by TLC. Upon completion of the reaction, the reaction mixture was extracted with 3×5 mL CH₂Cl₂. The organic layer was dried with anhydrous Na₂SO₄ and concentrated under reduced pressure. The resultant crude viscous product was recrystallized from *n*-hexane:dichloromethane (4:1) obtaining 0.2207 g of pale yellow crystals (98% yield). Characterization data of spectra for representative compounds

N-Benzyl-2-phenylacetamide (1)

mp 118-120 °C (lit. 118-120 °C);¹ FTIR (KBr) v_{max} /cm⁻¹ 3289 (N–H), 3080, 3062, 3030, 2917, 1638 (C=O), 1551, 1493, 1453, 1028, 771, 694; ¹H NMR (400 MHz, CDCl₃) δ /ppm 7.34-7.24 (m, 9H, ArH), 7.17 (d, 1H, *J* 4.76 Hz, ArH), 6.06 (br, 1H, NH), 4.42 (d, 2H, *J* 5.6 Hz, <u>CH₂NH), 3.61 (s, 2H, CH₂CO); ¹³C NMR (100 MHz, CDCl₃) δ /ppm 170.6, 137.5, 135.0, 129.6, 129.6, 128.9, 128.8, 127.3, 126.7, 43.9, 42.9.</u>

N-(2-Methoxybenzyl)-2-phenylacetamide (2)

mp 88-90 °C; FTIR (KBr) v_{max}/cm^{-1} 3281(N–H), 3076, 3027, 2917, 1645 (C=O), 1603, 1550, 1491, 1455, 1242, 1028, 753, 699; ¹H NMR (400 MHz, CDCl₃) δ /ppm 7.35-7.21 (m, 7H, ArH), 6.91 (t, 1H, *J* 7.6 Hz, ArH), 6.83 (d, 1H, *J* 8.4 Hz, ArH), 6.05 (br, 1H, NH), 4.42 (d, 2H, *J* 5.6 Hz, <u>CH</u>₂NH), 3.69 (s, 3H, O<u>CH</u>₃), 3.61 (s, 2H, <u>CH</u>₂CO); ¹³C NMR (100 MHz, CDCl₃) δ /ppm 170.6, 157.5, 135.0, 129.6, 129.6, 128.9, 128.8, 127.3, 126.0, 120.7, 110.2, 55.1, 43.9, 39.9; MS (EI) *m*/*z* (%) 255 [M⁺], 254 (100) [M⁺ – H], 253 (100) [M⁺ – 2H], 136 [M⁺ – C₇H₈O], 121 (100) [M⁺ – C₈H₈NO], 91 [C₇H₇⁺]; CHN (C₁₆H₁₇NO₂) calc. (%) C (75.27), H (6.71), N (5.49); found (%) C (74.99), H (6.78), N (5.52).

N-Butyl-2-phenylacetamide (3)

mp 35-37 °C (Lit. 37-38 °C);² FTIR (Neat) v_{max} /cm⁻¹ 3354 (N–H), 3178, 3080, 3064, 3027, 2802, 1638 (C=O), 1491, 1416, 1286, 1180, 747, 698; ¹H NMR (400 MHz, CDCl₃) δ /ppm 7.40-7.29 (m, 5H, ArH), 5.61 (br, 1H, NH), 3.56 (s, 2H, <u>CH₂CO</u>), 3.18 (q, 2H, *J* 6.8 Hz, NH<u>CH₂CH₂CH</u>₂), 1.38 (qn, 2H, *J* 6.8 Hz, CH₂<u>CH</u>₂Et), 1.23 (sx, 2H, *J* 7.2 Hz, CH₂<u>CH</u>₂CH₃), 0.85 (t, 3H, *J* 7.2 Hz, CH₂CH₃); ¹³C NMR

^{*}e-mail: akhlaghinia@um.ac.ir

(100 MHz, CDCl₃) δ/ppm 173.5, 134.9, 129.5, 129.1, 127.5, 43.6, 39.5, 31.2, 19.7, 13.4.

N-(3-Ethoxypropyl)-2-phenylacetamide (4)

mp 136-138 °C; FTIR (KBr) v_{max}/cm^{-1} 3352 (N–H), 3180, 3062, 3028, 2974, 2867, 1647 (C=O), 1550, 1496, 1453, 1416, 1289, 1114, 747, 700; ¹H NMR (400 MHz, CDCl₃) δ /ppm 7.41-7.29 (m, 5H, ArH),5.85 (br, 1H, NH), 3.81 (s, 2H, CH₂CO), 3.64-3.59 (m, 4H, NH<u>CH₂CH₂CH₂O</u>), 3.542 (q, 2H, *J* 7.2 Hz, OCH₂CH₃), 1.95 (qn, 2H, *J* 6.4 Hz, CH₂<u>CH₂CH₂O), 1.29 (t, 3H, *J* 7.2 Hz, CH₂<u>CH₃</u>); ¹³C NMR (100 MHz, CDCl₃) δ /ppm 171.1, 135.1, 129.5, 129.1, 127.5, 69.4, 66.3, 41.8, 38.5, 29, 15.1; MS (EI) *m/z* (%) 221 [M⁺], 219 [M⁺ – 2H], 191 [M⁺ – C₂H₅], 134 (100) [M⁺ – C₅H₁₁O], 91 [C₇H₇⁺]; CHN (C₁₃H₁₉NO₂) calc. (%) C (70.56), H (8.65), N (6.33); found (%) C (69.94), H (8.26), N (6.24).</u>

N-Benzyl-2-(4-chlorophenyl)acetamide (5)

mp 150-151 °C (Lit. 151-153 °C);³ FTIR (KBr) v_{max} /cm⁻¹ 3279 (N–H), 3056, 3027, 2913, 2872, 1644 (C=O), 1594, 1542, 1492, 1453, 1417, 1086, 1013, 800, 742, 692: ¹H NMR (100 MHz, CDCl₃) δ /ppm 7.52–6.97 (m, 9H, ArH), 5.74 (br, 1H, NH), 4.44 (d, 2H, *J* 6 Hz, <u>CH₂NH), 3.56 (s, 2H, CH₂CO).</u>

N-Butyl-2-(4-chlorophenyl)acetamide (6)

mp 80-81 °C; FTIR (KBr) v_{max} /cm⁻¹ 3301 (N–H), 3066, 2959, 2931, 2872, 1649 (C=O), 1595, 1543, 1492, 1417, 1089, 804, 740; ¹H NMR (400 MHz, CDCl₃) δ/ppm 7.36 (d, 2H, *J* 8 Hz, ArH), 7.21(d, 2H, *J* 8.4 Hz, ArH), 5.47 (br, 1H, NH), 3.53 (s, 2H, *J* 6 Hz, <u>CH</u>₂CO), 3.22 (q, 2H, *J* 6.8 Hz, NH<u>CH</u>₂CH₂), 1.43 (qn, 2H, *J* 6.8 Hz, CH₂<u>CH</u>₂Et), 1.29 (sx, 2H, *J* 7.2 Hz, CH₂<u>CH</u>₂CH₃), 0.90 (t, 3H, *J* 7.2 Hz, CH₂<u>CH</u>₃); ¹³C NMR (100 MHz, CDCl₃) δ/ppm 170.3, 133.5, 133.3, 130.8, 129.1, 43.1, 39.5, 31.6, 20.0, 13.7; MS (EI) *m*/*z* (%) 227 [M⁺ + 2], 225 [M⁺], 190 [M⁺ - Cl], 125 [M⁺ - C₅H₁₀NO], 100 [M⁺ - C₇H₆Cl], 57 (100) [C₄H₉⁺]; CHN (C₁₂H₁₆ClNO) calc. (%) C (63.85), H (7.14), N (6.21); found (%) C (64.32), H (7.49), N (6.63).

N-Benzylbenzamide (7)

mp 89-90 °C (Lit. 90-91 °C);⁴ FTIR (KBr) ν_{max}/cm⁻¹ 3342(N–H), 3088, 3063, 3029, 2861,1643(C=O), 1603, 1540, 1494, 1453,1361, 1207, 1071, 1027, 736, 697; ¹H NMR (100 MHz, CDCl₃) δ/ppm 7.92-7.18 (m, 10H, ArH), 6.46 (br, 1H, NH), 4.68 (d, 2H, *J* 5.56 Hz, <u>CH</u>₂NH).

N-Benzylpicolinamide (8)

mp 84-85 °C (Lit. 85 °C);⁵ FTIR (KBr) v_{max}/cm⁻¹ 3305 (N–H), 3080, 3031, 2920, 1660(C=O), 1527, 1457, 1433,

1355, 1251, 1081, 999, 744, 702, 689; ¹H NMR (400 MHz, CDCl₃) δ /ppm 8.55 (d, 1H, Pyr), 8.42 (br, 1H, NH), 8.26 (d, 1H, Pyr), 7.88 (td, 1H, J_1 7.6 Hz, J_2 1.2 Hz, Pyr), 7.46-7.43 (m, 1H, Pyr), 7.41-7.29 (m, 5 H, ArH) 4.70 (d, 2H, *J* 6.0 Hz, <u>CH</u>₂NH); ¹³C NMR (100 MHz, CDCl₃) δ /ppm 164.3, 149.8, 148.1, 138.2, 137.4, 128.7, 127.9, 127.5, 126.3, 122.4, 43.5; CHN (C₁₃H₁₂N₂O) calc. (%) C (73.56), H (5.7), N (13.2); found (%) C (73.15), H (5.7), N (3.16).

N-(2-Methoxybenzyl)picolinamide (9)

mp 89-91°C; FTIR (KBr) v_{max}/cm^{-1} 3396 (N–H), 3072, 2966, 2835, 1665 (C=O), 1593, 1524, 1493,1462, 1437,1247, 1119, 997, 816, 755, 616; ¹H NMR (400 MHz, CDCl₃) δ /ppm 8.56 (d, 1H, J 4.4 Hz, Pyr), 8.49 (br, 1H, NH), 8.24 (d, 1H, J 8 Hz, Pyr), 7.82 (td, 1H, J_1 7.6 Hz, J_2 1.6 Hz, Pyr), 7.44-7.41 (m, 1H, Pyr), 7.39-7.27 (m, 2H, ArH), 6.97-6.91 (m, 2H, ArH), 4.70 (d, 2H, J 6 Hz, <u>CH₂NH</u>), 3.92 (s, 3H,CH₃); ¹³C NMR (100 MHz, CDCl₃) δ /ppm 164.1, 157.7, 150.2, 148.1, 137.3, 129.6, 128.8, 126.3, 126.0, 122.4, 120.6, 110.3, 55.4, 39.1.

N-(2-Chlorobenzyl)picolinamide (10)

mp 84-85 °C (Lit. 84-85 °C);⁶ FTIR (KBr) v_{max} /cm⁻¹ 3321 (N–H), 3076, 3056, 2913, 1663(C=O), 1593, 1564, 1528, 1464, 1444, 1432, 1286, 1041, 1004, 745, 686; ¹H NMR (400 MHz, CDCl₃) δ /ppm 8.56 (d, *J* 4.4 Hz, 1H, Pyr), 8.53 (br, 1H, NH), 8.23 (d, 1H, *J* 7.6 Hz, Pyr), 7.86 (td, 1H, *J*₁ 7.6 Hz, *J*₂ 1.2 Hz, Pyr), 7.48-7.24 (m, 5H, Pyr, ArH), 4.78 (d, 2H, *J* 6 Hz, <u>CH</u>₂NH); ¹³C NMR (100 MHz, CDCl₃) δ /ppm 164.4, 149.7, 148.2, 137.4, 135.7, 133.7, 130.0, 129.6, 128.9, 127.1, 126.3, 122.4, 41.4; CHN (C₁₃H₁₁ClN₂O) calc. (%) C (63.29), H (4.49), N (11.36); found (%). C (62.86), H (4.22), N (10.93).

N-(3-Ethoxypropyl)picolinamide (11)

Oil; FTIR (neat) $v_{max}/cm^{-1} 3350$ (N–H), 3060, 2974, 2930, 2867, 2798, 1675 (C=O), 1569, 1527, 1464, 1434, 1377, 1282, 1112, 997, 824, 751, 691; ¹H NMR (400 MHz, CDCl₃) δ /ppm 8.56 (*d*, 1H, *J* 4 Hz, Pyr), 8.50 (br, 1H, NH), 8.21 (d, 1H, *J* 8 Hz, Pyr), 7.86 (td, 1H, *J*₁ 7.6 Hz, *J*₂ 1.6 Hz, Pyr), 7.44 -7.41 (m, 1H, Pyr), 3.64-3.59 (m, 2H, CH₂CH₂OEt, 2H, OCH₂CH₃), 3.54 (q, 2H, *J* 7.2 Hz, NHCH₂CH₂), 1.93 (qn, 2H, *J* 6.4 Hz, CH₂CH₂CH₂), 1.28 (t, 3H, *J* 6.8 Hz, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ /ppm 164.3, 150.9, 148.1, 137.3, 126.00, 122.1, 69.3, 66.5, 37.8, 29.3, 15.2; MS (EI) *m*/*z* (%) 208 [M⁺], 179 [M⁺ - C₂H₅], 163 [M⁺ - C₂H₅O], 149 [M⁺ - C₃H₇O], 135 [M⁺ - C₄H₉O], 106 [C₆H₄NO⁺], 78 [C₅H₄N⁺]; CHN (C₁₁H₁₆N₂O₂) calc. (%) C (63.44), H (7.74), N (13.45). found (%) C (63.04), H (7.65), N (13.67).

N-Cyclohexylpicolinamide (12)

mp 50-51 °C; FTIR (KBr) v_{max}/cm^{-1} 3345 (N–H), 3064, 2931, 2850, 2965, 1677 (C=O), 1568, 1525, 1462, 1425, 1323, 1278, 1164, 1084, 996, 976, 891, 821, 753, 651, 619; ¹H NMR (400 MHz, CDCl₃) δ /ppm 8.56 (d, 1H, J 4.4 Hz, Pyr), 8.22 (d, 1H, J 7.6 Hz, Pyr), 7.98 (br, 1H, NH), 7.85 (td, 1H, J_1 7.8 Hz, J_2 2 Hz, Pyr), 7.44-7.42 (m, 1H, Pyr), 4.04-3.94 (m, 1H, <u>CH</u>NH), 2.05-2.01 (m, 2H, CH₂<u>CH₂</u>CH), 1.82-1.76 (m, 2H, CH₂<u>CH₂</u>CH), 1.70-1.20 (m, 6H, <u>CH₂CH₂CH₂); ¹³C NMR (100 MHz, CDCl₃) δ /ppm 163.3, 150.3, 147.9, 137.3, 126.0, 122.2, 48.2, 33.1, 30.4, 25.6, 24.9, 23.0.</u>

N-Butylpicolinamide (13)

Oil; FTIR (Neat) v_{max}/cm^{-1} 3391 (N–H), 3056, 2958, 2930, 2871, 1670 (C=O), 1590, 1568, 1527, 1464, 1434, 1275, 1261, 997, 765, 749, 691; ¹H NMR (100 MHz, CDCl₃) δ /ppm 8.54-8.43 (d, 1H, *J* 3.5 Hz, Pyr), 8.25-8.15 (d, 1H, *J* 7.5 z, Pyr), 8.05 (br, 1H, NH), 7.93-7.7 (t, 1H, *J* 7.6 Hz, Pyr), 7.5-7.3 (m, 1H, Pyr), 3.49 (q, 2H, NH<u>CH</u>₂CH₂), 1.84-1.19 (m, 4H, CH₂CH₂CH₂CH₃), 1.12-0.79 (t, 3H, *J* 7.3 Hz, CH₂CH₃).

N-(Furan-2-ylmethyl)picolinamide (14)

mp 100-102 °C; FTIR (KBr) v_{max}/cm^{-1} 3344 (N–H), 3133, 3105, 3047, 2925, 1661 (C=O), 1525, 1464, 1352, 1306, 1212, 1148, 1014, 927, 745, 664, 600; ¹H NMR (400 MHz, CDCl₃) δ /ppm 8.56 (d, 1H, *J* 3.6 Hz, Pyr), 8.37 (br, 1H, NH), 8.24 (d, 1H, *J* 7.6 Hz, Pyr), 7.87 (td, 1H, *J*₁ 7.6 Hz, *J*₂ 1.2 Hz, Pyr), 7.40 (t, 1H, *J* 6.4 Hz, Pyr), 6.52 (d, 1H, *J* 0.8 Hz, furan), 6.36-6.31 (m, 2H, furan), 4.68 (d, 2H, *J* 6 Hz, <u>CH</u>₂NH); ¹³C NMR (100 MHz, CDCl₃) δ /ppm 164.2, 151.3, 149.7, 148.1, 142.3, 137.4, 126.3, 122.4, 110.4, 107.5, 36.5; MS (EI) *m/z* (%) 202 [M⁺], 106 [M⁺ - C₅H₆NO], 96 (100) [M⁺ - C₆H₄NO], 81 [M⁺ - C₆H₅N₂O]; CHN (C₁₁H₁₀N₂O₂) calc. (%) C (65.34), H (4.98), N (13.85); found (%) C (66.09), H (4.93), N (13.91).

N-Benzylnicotinamide (15)

mp 72-74 °C (Lit. 73-74 °C);⁷ FTIR (KBr) v_{max} /cm⁻¹ 3295, 3088, 3055, 3038, 2930, 1634, 1592, 1547, 1482, 1457, 1453, 1420, 1306, 1233, 1157, 1081, 1024, 750, 704, 670; ¹H NMR (400 MHz, CDCl₃) δ /ppm 9.01 (s, 1H, Pyr), 8.75 (d, 1H, *J* 4 Hz, Pyr), 8.17 (d, 1H, *J* 8 Hz, Pyr), 7.44-7.29 (m, 5H, ArH ,1H, Pyr); 6.50 (br, 1H, NH); 4.70 (d, 2H, *J* 5.6 Hz, <u>CH₂NH</u>); ¹³C NMR (100 MHz, CDCl₃) δ /ppm 165.55, 152.23, 147.9, 137.78, 135.32, 130.13, 128.87, 127.99, 127.80, 123.57, 44.21; CHN (C₁₃H₁₂N₂O) calc. (%) C (73.56), H (5.7), N (13.2); found (%) C (73.08), H (5.64), N (13.52).

N-Benzylisonicotinamide (16)

mp 81-83 °C (Lit. 83-85 °C);⁷ FTIR (KBr) ν_{max} /cm⁻¹ 3313 (N–H), 3060, 3027, 2880, 2843, 1646 (C=O), 1599, 1543, 1494, 1452, 1413, 1300, 845, 735, 697; ¹H NMR (400 MHz, CDCl₃) δ /ppm 8.91 (d, 2H, *J* 4.4 Hz, Pyr), 7.77 (d, 2H, *J* 4.8 Hz, Pyr), 7.45-7.29 (m, 5H, ArH), 6.95 (br, 1H, NH), 4.64 (d, 2H, *J* 5.2 Hz, <u>CH₂NH</u>); ¹³C NMR (100 MHz, CDCl₃) δ /ppm 165.6, 150.4, 141.3, 137.5, 128.9, 128.0, 127.7, 122.0, 44.3.

N-Butylisonicotinamide (17)

mp 41-42 °C (Lit. 41-42 °C);⁴ FTIR (KBr) ν_{max}/cm^{-1} 3312 (N–H), 2958, 2931, 2872, 1650 (C=O), 1600, 1552, 1491, 1409, 1308, 1218, 1066, 998, 847, 758, 670; ¹H NMR (100 MHz, CDCl₃) δ /ppm 8.67 (d, 2H, *J* 4.7 Hz, Pyr), 7.63 (d, 2H, *J* 3.09 Hz, Pyr), 6.95 (br, 1H, NH), 3.43 (q, 2H, *J* 4 Hz, CH₂CH₂NH), 1.85-1.17 (m, 4H, CH₂CH₂CH₂CH₃), 0.91 (t, 3H, *J* 4.5 Hz, CH₂CH₃).

N-Benzylthiophene-2-carboxamide (18)

mp 116-118 °C (Lit. 119.5-120.5 °C);⁸ FTIR (KBr) v_{max} /cm⁻¹ 3351 (N–H), 3109, 3088, 3064, 3031, 2929, 1622 (C=O), 1545, 1511, 1422, 1303, 1246, 861, 772, 718, 696; ¹H NMR (100 MHz, CDCl₃) δ /ppm 7.62-7.45 (m, 2H, thiophene), 7.4-7.2 (m, 1H, thiophene, 4H, ArH), 7.04 (t, 1H, *J* 4 Hz, ArH), 6.36 (br, 1H, NH), 4.61 (d, 2H, *J* 6 Hz, <u>CH₂</u>NH); CHN (C₁₂H₁₁NOS) calc. (%) C (66.3), H (5.10), N (6.45), S (14.76); found (%) C (66.8), H (5.33), N (6.95), S (13.99).

N-Butylthiophene-2-carboxamide (19)

mp 64-66 °C (Lit. 67-68 °C);⁹ FTIR (KBr) v_{max}/cm^{-1} 3280 (N–H), 3105, 3084, 2953, 2924, 2876, 1612 (C=O), 1557, 1421, 1356, 1307, 1247, 1220, 1139, 980, 869, 772, 735; ¹H NMR (100 MHz, CDCl₃) δ /ppm 7.65-7.38 (m, 2H, thiophene), 7.05 (t, 1H, *J* 3.8 Hz, thiophene), 6.11(br, 1H, NH), 3.4 (q, 2H, *J* 4.8 Hz, NH<u>CH</u>₂CH₂), 1.75-1.13 (m, 4H, CH₂<u>CH</u>₂CH₂CH₃), 0.94 (t, 3H, *J* 6 Hz, CH₂<u>CH</u>₃); CHN (C₉H₁₃NOS) calc. (%) C (58.98), H (7.15), N (7.64), S (17.50); found (%) C (59.02), H (7.38), N (7.66), S (17.28).

N-(2-Methoxybenzyl)thiophene-2-carboxamide (20)

mp 154-156 °C (Lit. 157-159 °C);⁹ FTIR (KBr) v_{max} /cm⁻¹ 3311 (N–H), 3084, 3015, 2831, 1618 (C=O), 1553, 1461, 1295, 1247, 1106, 1026, 771, 732; ¹H NMR (100 MHz, CDCl₃) δ /ppm 7.58-7.12 (m, 3H, thiophene, 1H, ArH), 7.12-6.85 (m, 3H, ArH), 6.69 (br, 1H, NH), 4.6 (d, 2H, *J* 4.5 Hz, <u>CH₂NH</u>), 3.83 (s, 3H, OCH₃); CHN (C₁₃H₁₃NO₂S) calc. (%) C (63.13), H (5.3), N (5.66), S (12.9); found (%) C (62.93), H (5.57), N (6.19), S (12.7).

N-(2-Chlorobenzyl)thiophene-2-carboxamide (21)

mp 116-118 °C; FTIR (KBr) v_{max}/cm^{-1} 3306 (N–H), 3080, 2958, 2908, 2851, 1620 (C=O), 1553, 1442, 1417, 1301, 1246, 1147, 1037, 755, 724, 681; ¹H NMR (400 MHz, CDCl₃) δ /ppm 7.55 (dd, 1H, J_1 3.8 Hz, J_2 2.8 Hz, thiophene); 7.51-7.47 (m, 2H, thiophene), 7.42-7.37 (m, 1H, ArH), 7.32-7.23 (m, 2H, ArH), 7.09 (dd, 1H, J_1 5 Hz, J_2 1.2 Hz, ArH), 6.56 (br, 1H, NH), 4.72 (d, 2H, J 6.4 Hz, <u>CH₂NH</u>); ¹³C NMR (CDCl₃, 100 MHz) δ /ppm 162.1, 138.7, 135.5, 133.5, 130.3, 129.5, 129.0, 128.4, 127.7, 127.4, 127.1, 41.8; MS (EI) m/z (%) 253 [M⁺+2], 251 [M⁺], 216 [M⁺ - Cl], 139 [M⁺ - C₅H₄OS], 126 [C₇H₆C⁺l], 111 [M⁺ - C₇H₇ClN], 57 [C₂H₃NO²⁺]; CHN (C₁₂H₁₀ClNOS) calc. (%) C (57.25), H (4.00), N (5.56), S (12.74); found (%) C (57.41), H (4.25), N (5.75), S (12.55).

N-(Furan-2-ylmethyl)thiophene-2-carboxamide (22)

mp 97-100 °C (Lit. 100-102 °C);¹⁰ FTIR (KBr) v_{max} /cm⁻¹ 3284 (N–H), 3076, 2933, 2835, 1620 (C=O), 1550, 1515, 1413, 1308, 1200, 1148, 1003, 859, 711, 668; ¹H NMR (100 MHz, CDCl₃) δ/ppm 7.67-7.22 (m, 3H, thiophene), 7.02 (t, 1H, *J* 3.2 Hz, furan), 6.65 (br, 1H, NH), 6.42-6.18 (m, 2H, furan), 4.6 (d, 2H, *J* 5.5 Hz, <u>CH₂NH</u>); CHN (C₁₀H₉NO₂S) calc. (%) C (57.95), H (4.38), N (6.76), S (15.47); found (%) C (8.35), H (4.63), N (7.04), S (15.43).

N-(3-Ethoxypropyl)thiophene-2-carboxamide (23)

mp 56-58 °C; FTIR (KBr) $v_{max}/cm^{-1} 3309$ (N–H), 3084, 2979, 2872, 2796, 1615 (C=O), 1555, 1515, 1354, 1221, 1105, 1053, 953, 861, 812, 719; ¹H NMR (400 MHz, CDCl₃) δ/ppm 7.48 (dd, 1H, J_1 3.6 Hz, J_2 1.2 Hz, thiophene), 7.46 (dd, 1H, J_1 4.8 Hz, J_2 1.2 Hz, thiophene), 7.08 (t, 1H, J 2.4 Hz, thiophene), 6.21 (br, 1H, NH), 3.63 (t, 2H, J 5.6 Hz, CH₂CH₂OEt), 3.60-3.51 (m, 4H, CH₂CH₃,CH₂NH), 1.89 (qn, 2H, J 5.6 Hz, CH₂CH₂CH₂), 1.27 (t, 3H, J 7.2 Hz, CH₂CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ/ppm 161.8, 139.5, 129.5, 127.7, 127.5, 70.3, 66.6, 39.2, 28.9, 15.4; MS (EI) m/z (%) 213 [M⁺], 183 [M⁺ - C₂H₆], 168 [M⁺ - C₂H₅O], 140 [M⁺ - C₄H₉O], 111 (100) [C₅H₃OS⁺]; CHN (C₁₀H₁₅NO₂S) calc. (%) C (56.31), H (7.09), N (6.57), S (15.03); found (%) C (56.86), H (7.64), N (6.88), S (14.79).

N-Benzyl-3-methylbutanamide (24)

mp 56-58 °C (Lit. 58-59 °C);¹¹ FTIR (KBr) v_{max}/cm⁻¹ 3275 (N–H), 3062, 3028, 2960, 2949, 2873, 1643 (C=O), 1578, 1495, 1425, 1336, 737, 695.

N-Benzylpropionamide (25)

mp 40-42 °C (Lit. 42-43 °C);¹² FTIR (KBr) v_{max}/cm⁻¹ 3266 (N–H), 3130, 3063, 3032, 2975, 2937, 1658 (C=O), 1463, 1278, 1172, 1075, 997, 813, 700.

References

- 1. Starkov, P.; Sheppard, T. D.; Org. Biomol. Chem. 2011, 9, 1320.
- Pelletier, G.; Bechara, W. S.; Charette, A. B.; *J. Am. Chem. Soc.* 2010, *132*, 12817.
- Nordstrom, L. U.; Vogt , H.; Madsen, R.; J. Am. Chem. Soc. 2008, 130, 17672.
- Kim, B. R.; Lee, H. G.; Kang, S. B.; Sung, G. H.; Kim, J. J.; Park, J. K.; Lee, S. G.; Yoon, Y. J.; *Synthesis* 2012, 42.
- Benincori, T.; Brennaand, E.; Sannicolo, F.; J. Chem. Soc., Perkin Trans. 1 1993, 675.
- Strupinska, M.; Rostafinska-Suchar, G.; Stables, J. P.; Paruszewski, R.; Acta Pol. Pharm. 2009, 66, 155.
- Bukhtiarova, T. A.; Trinus, F. P.; Danilenko, V. F.; Danilenko, G. I.; Ovrutskii, V. M.; Sharykina, N. I.; *Pharm. Chem. J.* **1997**, *31*, 597.
- Kametani, T.; Ogaswara, K.; Kozuka, A.; Yakugaka Zasshi 1966, 86, 815.
- Khelili, S.; Florence, X.; Bouhadja, M.; Abdelaziz, S.; Mechouch, N.; Mohamed, Y.; de Tullio, P.; Lebrun, P.; Pirotte, B.; Pirotte, B.; *Bioorg. Med. Chem.* 2008, *16*, 6124.
- Katritzky, A. R.; Cai, C.; Singh, S. K.; J. Org. Chem. 2006, 71, 3375.
- 11. Starkov, P.; T Sheppard, D.; Org. Biomol. Chem. 2011, 9, 1320.
- Takeda, K.; Kobayashi, T.; Ogura, H.; *Chem. Pharm. Bull.* 1979, 27, 536.



Figure S1. FTIR spectrum of *N*-benzyl-2-phenylacetamide (1).



Figure S2. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-benzyl-2-phenylacetamide (1).



Figure S3. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-benzyl-2-phenylacetamide (1) expanded.



Figure S4. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-benzyl-2-phenylacetamide (1) expanded.



Ghodsinia et al.

Figure S5. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-benzyl-2-phenylacetamide (1).



Figure S6. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-benzyl-2-phenylacetamide (1) expanded.



Figure S7. FTIR spectrum of *N*-(2-methoxybenzyl)-2-phenylacetamide (2).



Figure S8. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(2-methoxybenzyl)-2-phenylacetamide (2).



Figure S9. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(2-methoxybenzyl)-2-phenylacetamide (2) expanded.



Figure S10. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(2-methoxybenzyl)-2-phenylacetamide (2) expanded.



Figure S11. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-(2-methoxybenzyl)-2-phenylacetamide (2).



Figure S12. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-(2-methoxybenzyl)-2-phenylacetamide (2) expanded.



Figure S13. MS spectrum (EI, 70 eV) of N-(2-methoxybenzyl)-2-phenylacetamide (2).

```
Eager 300 Summarize Results
                            Date : 23/05/2012 at 11:12:17
                      Method Name : NCHS
                   Method Filename : Copy of Copy of N C H S-bkp .mth
     Filename
                      AS Method
                                        Vial
     _____
     emamjomeh-130
     # Group Sample Name Type Weig. Pro.F ---
     --- ---- ----- ----- ---- ----
     130 1
          S3
                           UNK 1.027 6.25 ---
     Component name Element %
                                           Calcd for C16H17NO2
     ------
                                         Nitrogen%
                                                     5.49
                  5.52717638
     Nitrogen%
                                         Carbon%
                                                     75.27
                  74.99708557
     Carbon%
                                         Hydrogen%
                                                     6.71
     Hydrogen%
                  6.786919594
                                          Suphur%
                                                      0
     Sulphur%
                  0
            1 Sample(s) in Group No : 1
Component Name Average
------
            5.52717638
Nitrogen%
            74.99708557
Carbon%
            6.786919594
Hydrogen%
Sulphur%
            0
```

Figure S14. Elemental analysis data of N-(2-methoxybenzyl)-2-phenylacetamide (2).



Figure S15. FTIR spectrum of *N*-butyl-2-phenylacetamide (3).



Figure S16. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-butyl-2-phenylacetamide (3).



Figure S17. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-butyl-2-phenylacetamide (3) expanded.



Figure S18. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-butyl-2-phenylacetamide (3) expanded.



Figure S19. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-butyl-2-phenylacetamide (3) expanded.



Figure S20. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-butyl-2-phenylacetamide (3).



Figure S21. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-butyl-2-phenylacetamide (3) expanded.



Figure S22. FTIR spectrum of N-(3-ethoxypropyl)-2-phenylacetamide (4).



Figure S23. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(3-ethoxypropyl)-2-phenylacetamide (4).



Figure S24. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(3-ethoxypropyl)-2-phenylacetamide (4) expanded.



Figure S25. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(3-ethoxypropyl)-2-phenylacetamide (4) expanded.



Figure S26. ¹³C NMR spectrum (100 MHz, CDCl₃) of N-(3-ethoxypropyl)-2-phenylacetamide (4).



Figure S27. ¹³C NMR spectrum (100 MHz, CDCl₃) of N-(3-ethoxypropyl)-2-phenylacetamide (4) expanded.



Figure S28. MS spectrum (EI, 70 eV) of N-(3-ethoxypropyl)-2-phenylacetamide (4).

Ghodsinia et al.

	Eager 300 Su	ummarize Results		
	Date Method Name Method Filename	e : 22/08/2012 a e : NCHS e : Copy of Copy	at 11:55:10 7 of N C H S-bk	p .mth
Filenam	AS Method	Vial		
rezazad	eh-79			
# Gro	up Sample Name Type	Weig. Pro.F		
79 1	10-S UNK	1.044 6.25		
Compone	nt name Element %	G 1 1 6		
		Caled for	C ₁₃ H ₁₉ NO ₂	
Nitroge	n% 6.249336052	Nitrogen%	0.33	
Carbon*	69.9406662	Hydrogen%	8.65	
Hydroge	n% 8.260183811	Suphur%	0	
Sulphur	* 0			
Component Nam	l Sample(s) in Group N e Average 	o : 1		
Nitrogen%	6.249336052			
Carbon%	69.9406662			
Hydrogen%	8.260183811			
Sulphur%	0			

Figure S29. Elemental analysis data of N-(3-ethoxypropyl)-2-phenylacetamide (4).



Figure S30. FTIR spectrum of N-benzyl-2-(4-chlorophenyl)acetamide (5).



Figure S31. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-benzyl-2-(4-chlorophenyl)acetamide (5).



Figure S32. FTIR spectrum of *N*-butyl-2-(4-chlorophenyl)acetamide (6).





Figure S33. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-butyl-2-(4-chlorophenyl)acetamide (6).



Figure S34. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-butyl-2-(4-chlorophenyl)acetamide (6) expanded.



Figure S35. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-butyl-2-(4-chlorophenyl)acetamide (6) expanded.

S22



Figure S36. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-butyl-2-(4-chlorophenyl)acetamide.



Ghodsinia et al.

Figure S37. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-butyl-2-(4-chlorophenyl)acetamide (6).



Figure S38. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-butyl-2-(4-chlorophenyl)acetamide (6) expanded.



Figure S39. MS spectrum (EI, 70 eV) of N-butyl-2-(4-chlorophenyl)acetamide (6).

```
Eager 300 Summarize Results
                              Date : 04/07/2012 at 11:01:53
                        Method Name : NCHS
                    Method Filename : Copy of Copy of N C H S-bkp .mth
     Filename
                       AS Method
                                          Vial
     -----
                   emamjomeh-41
     # Group Sample Name
                             Type Weig. Pro.F ---
     --- ---- ----- ----- ---- ----- -----
     41 1
              6-S
                             UNK 1.335 6.25 ---
     Component name Element %
                                     Calcd for C12H16CINO2
        -------
     Nitrogen%
                   6.636153698
                                     Nitrogen%
                                               6.21
                                     Carbon%
                                               63.85
     Carbon%
                   64.32457886
                                                7.14
                                     Hydrogen%
     Hydrogen%
                   7.490045547
                                     Suphur%
                                                0
     Sulphur%
                   0
             1 Sample(s) in Group No : 1
Component Name Average
------
Nitrogen%
             6.636153698
Carbon%
             64.32457886
Hydrogen%
             7.490045547
Sulphur%
             0
```

Figure S40. Elemental analysis data of N-butyl-2-(4-chlorophenyl)acetamide (6).



Figure S41. FTIR spectrum of *N*-benzylbenzamide (7).



Figure S42. ¹H NMR spectrum (100 MHz, CDCl₃) of *N*-benzylbenzamide (7).



Figure S43. FTIR spectrum of *N*-benzylpicolinamide (8).



Figure S44. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-benzylpicolinamide (8).



Figure S45. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-benzylpicolinamide (8) expanded.



Figure S46. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-benzylpicolinamide (8).


Figure S47. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-benzylpicolinamide (8) expanded.



Figure S48. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-benzylpicolinamide (8) expanded.

	Eager 300 Summarize	Results	
	Date : 18/04 Method Name : NCHS Method Filename : Copy	4/2012 at 10:34:40 of Copy of N C H S-bkp .m	th
Filename	AS Method	Vial	
emamjone # Grouy 52 1 Componen	h-52 p Sample Name Type Weig. Pr b-2 UNK 1.078 6. t name Element %	co.F .25 Caled for CuaHuaNaO	
Nitrogen Carbon% Hydrogen Sulphur%	% 13.16875935 73.15912628 % 5.701982021 0	Nitrogen% 13.20 Carbon% 73.56 Hydrogen% 5.70 Suphur% 0	
Component Name Nitrogen% Carbon% Hydrogen%	1 Sample(s) in Group No : 1 Average 13.16875935 73.15912628 5.701982021		

Figure S49. Elemental analysis data of *N*-benzylpicolinamide (8).



Figure S50. FTIR spectrum of *N*-(2-methoxybenzyl)picolinamide (9).



Figure S51. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(2-methoxybenzyl)picolinamide (9).



Figure S52. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(2-methoxybenzyl)picolinamide (9) expanded.



Figure S53. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(2-methoxybenzyl) picolinamide (9) expanded.



Figure S54. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-(2-methoxybenzyl)picolinamide (9).



Figure S55. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-(2-methoxybenzyl)picolinamide (9) expanded.



Figure S56. FTIR spectrum of N-(2-chlorobenzyl)picolinamide (10).



Figure S57. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(2-chlorobenzyl)picolinamide (10).



Figure S58. ¹H NMR (400 MHz, CDCl₃) of *N*-(2-chlorobenzyl)picolinamide (10) expanded.



Figure S59. ¹H NMR spectrum (400 MHz, CDCl₃) of N-(2-chlorobenzyl)picolinamide (10) expanded.



Figure S60. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-(2-chlorobenzyl)picolinamide (10).



Figure S61. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-(2-chlorobenzyl)picolinamide (10) expanded.

```
Eager 300 Summarize Results
                            Date : 02/05/2012 at 09:42:59
                      Method Name : NCHS
                   Method Filename : Copy of Copy of N C H S-bkp .mth
                      AS Method
     Filename
                                       Vial
     ----- ----
     emamjomeh-80
                         Type Weig. Pro.F ---
     # Group Sample Name
     --- ---- ----- ----- ---- -----
     80 1
                           UNK 0.993 6.25 ---
            b8
     Component name Element %
                                      Calcd for C13H11ClN2O
     -----
                                      Nitrogen%
                                                   11.36
     Nitrogen%
                 10.93560867
                                                   63.29
     Carbon%
                 62.86192093
                                       Carbon%
     Hydrogen%
                 4.222644806
                                      Hydrogen%
                                                   4.49
     Sulphur%
                  0
                                                    0
                                       Suphur%
            1 Sample(s) in Group No : 1
Component Name Average
Nitrogen%
            10.93560867
            62.86192093
Carbon%
Hydrogen%
            4.222644806
Sulphur%
            0
```

Figure S62. Elemental analysis data of N-(2-chlorobenzyl)picolinamide (10).



Figure S63. FTIR spectrum of *N*-(3-ethoxypropyl)picolinamide (11).



Figure S64. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(3-ethoxypropyl)picolinamide (11).



Figure S65. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(3-ethoxypropyl)picolinamide (11) expanded.



Figure S66. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(3-ethoxypropyl)picolinamide (11) expanded.



Figure S67. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-(3-ethoxypropyl)picolinamide (11).



Figure S68. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-(3-ethoxypropyl)picolinamide (11).



Figure S69. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-(3-ethoxypropyl)picolinamide (11) expanded.





						00.00.12
			Content [%]			
	1.2310 Inde	Index 2	3 N: 13.67 C: 63.04	Calcd for C11H16N2O2		
		Index 3		Nitrogen%	13.45	
				Carbon%	63.44	
			S: 0.000	Hydrogen%	7.74	
			H: 7.650	Suphur%	0	
cument: 900511 (varioEL),	Name: eas	superuser,	Access: varioEL superuse	er		

Page 1/1

Figure S71. Elemental analysis data of *N*-(3-ethoxypropyl)picolinamide (11).



Figure S72. FTIR spectrum of *N*-cyclohexylpicolinamide (12).



Figure S73. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-cyclohexylpicolinamide (12).



Figure S74. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-cyclohexylpicolinamide (12) expanded.



Figure S75. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-cyclohexylpicolinamide (12) expanded.

S42



Figure S76. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-cyclohexylpicolinamide (12) expanded.



Figure S77. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-cyclohexylpicolinamide (12).



Figure S78. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-cyclohexylpicolinamide (12) expanded.



Figure S79. ¹³C NMR (100 MHz, CDCl₃) of *N*-cyclohexylpicolinamide (12) expanded.



Figure S80. FTIR spectrum of *N*-butylpicolinamide (13).







Figure S82. FTIR spectrum of *N*-(furan-2-ylmethyl)picolinamide (14).



Figure S83. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(furan-2-ylmethyl)picolinamide (14).



Figure S84. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(furan-2-ylmethyl)picolinamide (14) expanded.



Figure S85. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(furan-2-ylmethyl)picolinamide (14) expanded.



Figure S86. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(furan-2-ylmethyl)picolinamide (14) expanded.



Figure S87. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-(furan-2-ylmethyl)picolinamide (14).



Figure S88. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-(furan-2-ylmethyl)picolinamide (14) expanded.



Figure S89. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-(furan-2-ylmethyl)picolinamide (14) expanded.



Figure S90. MS spectrum (EI, 70 eV) of *N*-(furan-2-ylmethyl)picolinamide (14).

Eager 300 Summarize Results

Date : 25/07/2012 at 11:20:39 Method Name : NCHS Method Filename : Copy of Copy of N C H S-bkp .mth Filename AS Method Vial -------------emamjome-50 Type Weig. Pro.F ---Group Sample Name # ---------- ----- ------ --------50 1 b10 UNK 1.055 6.25 ---Component name Element % Calcd for C11H10N2O2 -----Nitrogen% 13.85 Nitrogen% 13.91787334 Carbon% 65.34 Carbon% 66.09168976 4.98 Hydrogen% Hydrogen% 4.931604862 Sulphur% 0 Suphur% 0 1 Sample(s) in Group No : 1 Component Name Average -----Nitrogen% 13.91787334 Carbon% 66.09168976

Hydrogen% 4.931604862 Sulphur% 0

Figure S91. Elemental analysis data of N-(furan-2-ylmethyl)picolinamide (14).



Figure S92. FTIR spectrum of N-benzylnicotinamide (15).



Figure S93. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-benzylnicotinamide (15).



Figure S94. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-benzylnicotinamide (15) expanded.



Figure S95. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-benzylnicotinamide (15).



Figure S96. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-benzylnicotinamide (15) expanded.

Eager 300 Summarize Results

Date : 16/05/2012 at 11:01:15 Method Name : NCHS Method Filename : Copy of Copy of N C H S-bkp .mth

Vial Filename AS Method zhaleh-116 # Group Sample Name Type Weig. Pro.F ------ ---- ----- ---- ---- ----UNK 1.042 6.25 --al 116 1 Component name Element % Caled for C13H12N2O ------Nitrogen% 13.20 Nitrogen% 13.52048206 Carbon% 73.56 73.0827713 Carbon% 5.70 Hydrogen% Hydrogen% 5.643310547 Suphur% 0 Sulphur% 0 1 Sample(s) in Group No : 1 Component Name Average 13.52048206 Nitrogen% Carbon% 73.0827713 Hydrogen% 5.643310547 Sulphur% 0

Figure S97. Elemental analysis data of *N*-benzylnicotinamide (15).



Figure S98. FTIR spectrum of *N*-benzylisonicotinamide (16).



Figure S99. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-benzylisonicotinamide (16).



Figure S100. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-benzylisonicotinamide (16) expanded.



Figure S101. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-benzylisonicotinamide (16).



Figure S102. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-benzylisonicotinamide (16) expanded.



Figure S103. FTIR spectrum of *N*-butylisonicotinamid (17).



Figure S104. ¹H NMR spectrum (100 MHz, CDCl₃) of *N*-butylisonicotinamide (17).



Figure S105. FTIR spectrum of *N*-benzylthiophene-2-carboxamide (18).



Figure S106. ¹H NMR spectrum (100 MHz, CDCl₃) of *N*-benzylthiophene-2-carboxamide(18).

Eager 300 Summarize Results

Date : 06/06/2012 at 11:11:39 Method Name : NCHS Method Filename : Copy of Copy of N C H S-bkp .mth

Filename AS Method Vial ------ ----- ---afroogh-150 Group Sample Name Type Weig. Pro.F ---# --- ---- ------ ---- ---- ---- -----UNK 1.049 6.25 ---150 1 11 Component name Element % -----Calcd for C12H11NOS Nitrogen% 6.957777405 Nitrogen% 6.45 Carbon% 66.81091003 Carbon% 66.33 Hydrogen% 5.336242676 Hydrogen% 5.10 Sulphur% 13.9931646 Suphur% 14.76 1 Sample(s) in Group No : 1 Component Name Average 6.957777405 Nitrogen% 66.81091003 Carbon% Hydrogen% 5.336242676 Sulphur% 13.9931646

Figure S107. Elemental analysis data of N-benzylthiophene-2-carboxamide (18).



Figure S108. FTIR spectrum of N-butylthiophene-2-carboxamid (19).



Figure S109. ¹H NMR spectrum (100 MHz, CDCl₃) of *N*-butylthiophene-2-carboxamid (19).

Eager 300 Summarize Results Date : 06/06/2012 at 11:11:49 Method Name : NCHS Method Filename : Copy of Copy of N C H S-bkp .mth Vial AS Method Filename ----emamjome-151 Type Weig. Pro.F ---# Group Sample Name --- ---- ----- ----- ---- ----UNK 1.083 6.25 ---151 1 h-2 Component name Element % Calcd for C9H13NOS -----Nitrogen% 7.64 Nitrogen% 7.662646294 58.98 Carbon% 59.02895737 Carbon% Hydrogen% 7.15 7.385498047 Hydrogen% Suphur% 17.50 17.28616905 Sulphur% 1 Sample(s) in Group No : 1 Component Name Average -----7.662646294 Nitrogen% Carbon% 59.02895737 Hydrogen% 7.385498047 Sulphur% 17.28616905

Figure S110. Elemental analysis data of N-butylthiophene-2-carboxamid (19).



Figure S111. FTIR spectrum of N-(2-methoxybenzyl)thiophene-2-carboxamide (20).



Figure S112. ¹H NMR spectrum (100 MHz, CDCl₃) of N-(2-methoxybenzyl)thiophene-2-carboxamide (20).

	Eage	er 300 Su	mmariz	ze Resu	lts		
	Method	Date thod Name Filename	e : 20, e : NCH e : Cop	/06/201 HS py of (l2 at Copy c	11:59:49 of N C H S	-bkp .mth
Filename	AS	Method		V	al		
emamjomer # Grou <u>r</u>	o Sample Name	Туре	Weig.	Pro.F			
176 1 Component	h3 name Element	UNK %	1.027	6.25			
				Calcd	for C1	3H13NO ₂ S	_
Nitrogen	6.19896	8601		Nitro	gen%	5.66	
Carbon%	62.9316	4902		Hydre	bon%	5 30	-
Hydrogen Sulphur%	12.7062	4828		Supl	hur%	12.97	
	1 Sample(s) in	Group No	o:1				
Component Name	Average						
Nitrogen%	6.198968601						
Carbon%	62.93164902						
Hydrogen% Sulphur%	12.70624828						





Figure S114. FTIR spectrum of *N*-(2-chlorobenzyl)thiophene-2-carboxamide (21).



Figure S115. ¹H NMR spectrum (400 MHz, CDCl₃) of N-(2-chlorobenzyl)thiophene-2-carboxamide (21).

S62



Figure S116. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(2-chlorobenzyl)thiophene-2-carboxamide (21) expanded.



Figure S117. ¹H NMR spectrum (400 MHz, CDCl₃) of N-(2-chlorobenzyl)thiophene-2-carboxamide (21) expanded.



Figure S118. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(2-chlorobenzyl)thiophene-2-carboxamide (21) expanded.


Figure S119. ¹³C NMR spectrum (100 MHz, CDCl₃) of N-(2-chlorobenzyl)thiophene-2-carboxamide (21).



Figure S120. ¹³C NMR spectrum (100 MHz, CDCl₃) of N-(2-chlorobenzyl)thiophene-2-carboxamide (21) expanded.



Chem. Dep., Sciences Faculty, Ferdowsi Univ., Mashhad, IRAN Mass Spectroscopy Laboratory



Eager 300 Summarize Results Date : 25/06/2012 at 11:41:18 Method Name : NCHS Method Filename : Copy of Copy of N C H S-bkp .mth Vial Filename AS Method _____ ----emamjome-19 Group Sample Name Type Weig. Pro.F ---# ----- ----- ----- ----- -----UNK 1.064 6.25 ---19 1 h5 Component name Element % Calcd for C12H10CINOS Nitrogen% 5.56 5.756523228 Nitrogen% Carbon% 57.25 57.4144783 Carbon% Hydrogen% 4.00 4.259230137 Hydrogen% Suphur% 12.74 12.55812168 Sulphur% 1 Sample(s) in Group No : 1 Component Name Average ------Nitrogen% 5.756523228 Carbon% 57.4144783 Hydrogen% 4.259230137 Sulphur% 12.55812168



Figure S123. FTIR spectrum of N-(furan-2-ylmethyl)thiophene-2-carboxamide (22).



Figure S124. ¹H NMR spectrum (100 MHz, CDCl₃) of N-(furan-2-ylmethyl)thiophene-2-carboxamid (22).

Ghodsinia et al.

1	Eager 300 Summari	ze Results	
	Date : 15	/08/2012 at	12:08:16
	Method Name : NC	HS	
	Method Filename : Co	py of Copy of	of N C H S-bkp .mth
Filename	AS Method	Vial	
# Group	p Sample Name Type Weig.	Pro.F	
70 1 Component	h-4 UNK 1.241	6.25	
		Calcd for C1	0H9NO ₂ S
Nitrogen	7.040726185	Nitrogen%	6.76
Carbon%	58.35287476	Carbon%	57.95
Hydrogen	4.636273861	Hydrogen%	4.38
Sulphur%	15.43068123	Suphur%	15.47
	1 Sample(s) in Group No : 1		
Component Name	Average		
Nitrogen*	7.040726185		
Carbon%	58.35287476		
Sulphurs	4.0302/3801 15 43060133		
parpuar o	10.4000120		

Figure S125. Elemental analysis data of *N*-(furan-2-ylmethyl)thiophene-2-carboxamide (22).



Figure S126. FTIR spectrum of N-(3-ethoxypropyl)thiophene-2-carboxamide (23).



Figure S127. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(3-ethoxypropyl)thiophene-2-carboxamide (23).



Figure S128. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(3-ethoxypropyl)thiophene-2-carboxamide (23) expanded.



Figure S129. ¹H NMR spectrum (400 MHz, CDCl₃) of N-(3-ethoxypropyl)thiophene-2-carboxamide (23) expanded.



Figure S130. ¹H NMR spectrum (400 MHz, CDCl₃) of *N*-(3-ethoxypropyl)thiophene-2-carboxamide (23) expanded.



Figure S131. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-(3-ethoxypropyl)thiophene-2-carboxamide (23).



Figure S132. ¹³C NMR spectrum (100 MHz, CDCl₃) of *N*-(3-ethoxypropyl)thiophene-2-carboxamide (23) expanded.

Chem. Dep., Sciences Faculty, Ferdowsi Univ., Mashhad, IRAN Mass Spectroscopy Laboratory



Figure S133. MS spectrum (EI, 70 eV) of N-(3-ethoxypropyl)thiophene-2-carboxamide (23).

Eager 300 Summarize Results Date : 01/08/2012 at 13:10:41 Method Name : NCHS Method Filename : Copy of Copy of N C H S-bkp .mth Vial AS Method Filename ----- ---emamjome-54 Type Weig. Pro.F ---# Group Sample Name --- ---- ----- ----- -----h-8 UNK 1.109 6.25 ---54 1 Component name Element % Calcd for C10H15NO₂S ------Nitrogen% 6.57 Nitrogen% 6.881211758 Carbon% 56.31 56.86362457 Carbon% Hydrogen% 7.09 7.642203808 Hydrogen% Suphur% 15.03 14.79428101 Sulphur% 1 Sample(s) in Group No : 1 Component Name Average ------6.881211758 Nitrogen% 56.86362457 Carbon% 7.642203808 Hydrogen% 14.79428101 Sulphur%

Figure S134. Elemental analysis data of *N*-(3-ethoxypropyl)thiophene-2-carboxamide (23).



Figure S135. FTIR spectrum of *N*-benzyl-3-methylbutanamide (24).



Figure S136. FTIR of *N*-benzylpropionamide (25).