J. Braz. Chem. Soc., Vol. 20, No. 7, 1370-1378, 2009.
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0103 - 5053 $6.00+0.00

Article

Preparation of Novel Trifluoroacetylketene *O,N*-Acetals and Trifluoromethyl-Containing *S,S*-Sulfoximido *N*-Substituted Heterocycles

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Este trabalho descreve a síntese de dois novos trifluoracetilceteno *O,N*-acetais [$CF_3C(O)CH=C(OEt)(NS(O)R_2$), onde R = CH_3, Ph], obtidos da reação de 4,4-dietóxi-1,1,1-trifluorbut-3-en-2-ona [$CF_3C(O)CH=C(OEt)_2$] com *S,S*-dimetil- e *S*-metil-*S*-fenil-sulfoximida [$HN=S(O)R_2$], na presença de trietilamina, com rendimentos de 60-72%, e suas aplicações na obtenção de pirazóis, isoxazóis e pirimidinas *S,S*-dimetilsulfoximido substituídos, em 55-89% de rendimento, a partir de reações de 4-etóxi-4-(*S,S*-dimetilsulfoximido)-1,1,1-trifluorbut-3-en-2-ona com hidrazinas, hidrazidas, cloridrato de hidroxilamina e acetilguanidina.

Two new trifluoroacetylketene *O,N*-acetals [$CF_3C(O)CH=C(OEt)(NS(O)R_2$), where R = CH_3, Ph] derived from the reaction of 4,4-diethoxy-1,1,1-trifluorobut-3-en-2-one [$CF_3C(O)CH=C(OEt)_2$] with *S,S*-dimethyl- and *S*-methyl-*S*-phenyl-sulfoximide [$HN=S(O)R_2$], in the presence of triethylamine, have been obtained, in 60-72% yields, and applied in the synthesis of *S,S*-dimethylsulfoximido-substituted pyrazoles, isoxazoles and pyrimidines, in 55-89% yields, from the reactions of 4-ethoxy-4-(*S,S*-dimethylsulfoximido)-1,1,1-trifluorobut-3-en-2-one with hydrazines, hydroxylamine hydrochloride and acetylguanidine.

Keywords: acetals, sulfoximides, pyrazoles, isoxazoles, pyrimidines

Introduction

The synthetic potential of β-alkoxyvinyl trihalomethyl ketones to obtain series of novel trihalomethylated heterocycles of five-,[1] six-,[2] and seven-membered rings,[3] and more recently bisheterocyclic compounds[4] has been reported exhaustively by our research group over the last twenty years. On the other hand, the very interesting and no less important trihaloacetylketene *O,O*-acetal analogues and their synthetic applications have been little studied.

In 1986, Hojo *et al.*[5] reported for the first time the synthesis of trihaloacetylketene *O,O*-acetals by trichloro- and trifluoroacetylation reactions of ethyl orthoacetate with trichloroacetyl chloride and trifluoroacetic anhydride, respectively. In the same paper, the reactions of 1,1,1-trichloro-4,4-diethoxy-3-buten-2-one with dimethylamine to obtain the corresponding trichloroacetylketene *O,N*-acetal was reported (Scheme 1, equation 1). In 1990, Hojo *et al.*[5] demonstrated that trifluoroacetylketene *O,N*-, *S,N*- and *N,N*-acetals are easily obtained by *O-N* and *S-N* exchange reactions of trifluoroacetylketene *O,O*- and *S,S*-acetals with ammonia and primary and secondary alkyl- and arylamines (Scheme 1, equation 2).

In 1994 and 1997, Venkataratnam and co-workers[6] successfully employed trifluoroacetylketene *O,O*-diethyl acetal to introduce the trifluoroacetonyl group in imidazoles, oxazoles, quinazolines and perimidines with the objective of incorporating juvenile hormone esterase inhibitory activity.

In recent publications, our research group has developed a modified procedure to obtain 4,4-diethoxy-1,1,1-trihalobut-3-en-2-one (trifluoro- and trichloro-acetylketene *O,O*-diethyl acetal) and explored their usefulness for the synthesis of ethoxy substituted trihalomethylpyrazoles, isoxazoles and lactams.[7] More recently, in 2009, Okada and co-workers[7] developed a convenient synthetic method for fluorine-containing 4-alkoxy-dihydrobenzo[*b*][1,4]diazepinols and 3*H*-benzo[*b*][1,4]diazepines by the reaction of β-trifluoroacetylketene acetals with 1,2-phenylenediamines.

Although some authors have reported the preparation of only alkoxy substituted trihalomethyl-[7] and non-

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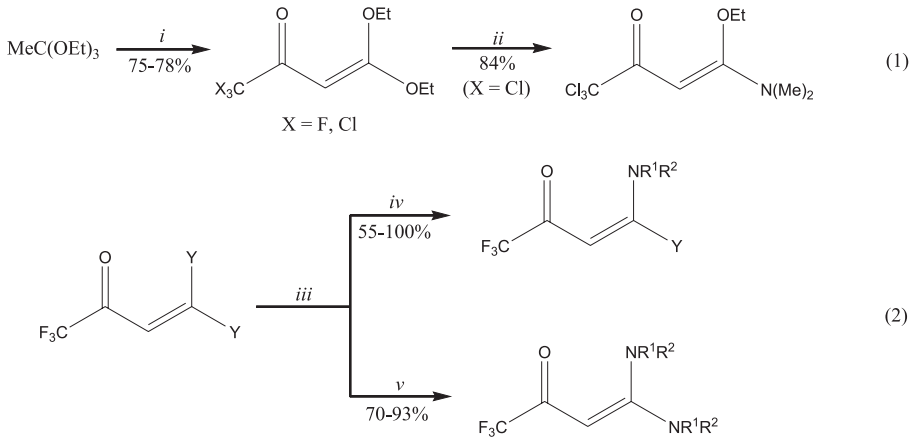


(*i*) = $(CX_3CO)_2O$, Py, $CHCl_3$, 1 d, rt; (*ii*) = $HN(Me)_2$, MeCN, 4 h, rt; (*iii*) = R^1R^2NH, MeCN, 18 h, rt; (*iv*) = 1.2 eq. amine; (*v*) = excess amine.
Y = OEt, SMe
R^1 = H, Alkyl, Aryl
R^2 = H, Alkyl

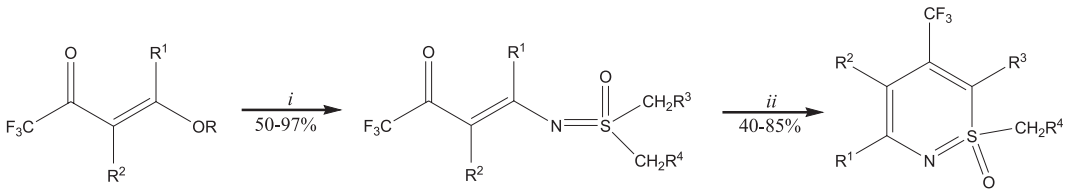
Scheme 1.

substituted trifluoroacetonyl-heterocycles by conventional[6] or microwave procedures,[6] there is a lack of new applications for these halogen-containing substrates in the literature. Moreover, sulfoximide derivatives of 4-alkoxy-1,1,1-trifluorobut-3-en-2-ones have been little studied[10] and sulfoximide derivatives from 4,4-diethoxy-1,1,1-trifluorobut-3-en-2-one have not yet been reported.

A number of patents have been issued claiming uses of sulfoximides as defoliants, herbicides, antifungal agents, antihypertensives and CNS depressants.[8] Several reactions of the imide group of *N*-unsubstituted sulfoximides can take place at the nitrogen atom. Examples of acylations, sulfonylations, alkylations, additions of isocyanates and isothiocyanates[8,9] as well reactions with acylketene *S,S*-acetals have been described.[9]

In 2000, we reported the synthesis of a series of 4-dimethylsulfoximido-1,1,1-trifluorobut-3-en-2-ones by the direct reaction of 4-alkoxy-4-alkyl-(aryl)-1,1,1-trifluorobut-3-en-2-ones with *S,S*-dimethylsulfoximide, in good yields. In the same paper, we isolated a new series of 5-trifluoromethylated 3-alkyl- and 3-aryl-1-methyl-1,2-thiazine 1-oxide derivatives by intramolecular cyclization reactions (Scheme 2).[10] Later, we reported the solvent effects on the NMR chemical shifts of 4-dimethylsulfoximido-1,1,1-trifluoro-3-buten-2-ones.[10]

In 2009, we reported the synthesis of a new series of 4-alkyl(aryl)-4-tetramethylenesulfoximide-1,1,1-trifluoroalk-3-en-2-ones prepared from *O,N*-exchange reactions of 4-alkyl(aryl)-4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones with the cyclic *S,S*-tetramethylenesulfoximide in the absence of solvent, in good yields. In the same paper, the easy preparation of a new series of a fused heterocyclic system of 3-aryl-5-trifluoromethyl-7,8-dihydro-6*H*-thieno[2,1-*f*][1,2]thiazine 1-oxide derivatives (60-85% yields) from intramolecular cyclization reactions of sulfoximido enones employing potassium *t*-butoxide in refluxing diethyl ether was also demonstrated (Scheme 2).[10]



(*i*) = $HN{=}S(O)CH_2R^3CH_2R^4$, 0.5-2 h, 100 ºC, neat; (*ii*) = RONa/ROH, 2 h, 60 ºC (R^3=R^4=H, ref. 10) or *t*-BuOK, Et_2O, 3 h, reflux (R^3-R^4 = -$(CH_2)_2$-, ref.10)
R = Me, Et
R^1 = H, Alkyl, Aryl
R^2 = H, Me
R^3 = R^4 = H; R^3-R^4 = -$(CH_2)_2$-

Scheme 2.

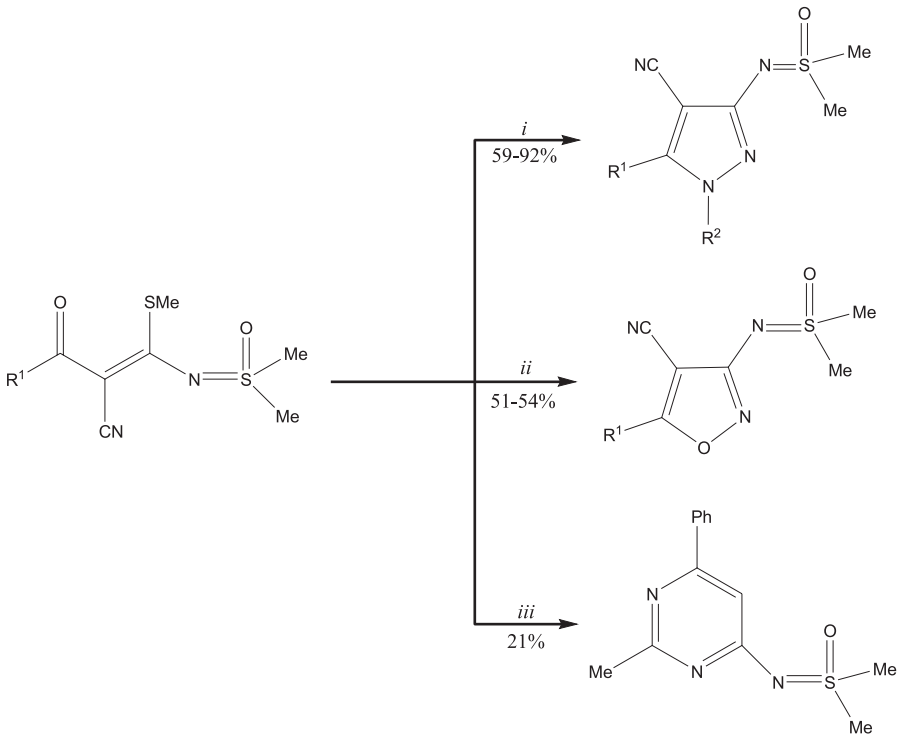
In an interesting communication, Rudorf[11] reported the condensation reaction of 2-acyl-3-methylthio-3-(*S,S*-dimethylsulfoximido)-acrilonitriles, where the acyl groups were C_6H_5CO and $C_6H_{11}CO$, with hydrazines, hydroxylamine and acetamidine to give the corresponding *N*-substituted sulfoximido heterocycles (Scheme 3).

The reactions of acylketene *S,S*-acetals are very interesting because examples of similar *N*-substituted sulfoximido heterocyles have been prepared only by the thermal decomposition of azides[12] or by the trapping of nitrenes by sulfoxides.[13] Reactions involving trifluoroacetylketene *O,O*-diethyl-acetal and *N*-unsubstituted *S,S*-dialkylsulfoximides to obtain interesting acyclic and heterocyclic compounds are so far unknown. On the other hand, fluorine-containing heterocycles are of significant interest due to the biological properties of fluorine, which play a pivotal role in bioactive compounds.[14] Routes to aromatic heterocycles are of ongoing interest, especially,methods of selectively placing fluorine on heterocycle moieties since these derivates often exhibit bioactivity.[15]

Thus, the aim of this work is to report the synthesis of new acyclic sulfoximido enones (**3**) and heterocyclic trifluoromethylated *S,S*-dimethylsulfoximide derivatives (**4**-**8**) from *O,N*-exchange reactions of 4,4-diethoxy-1,1,1-trifluorobut-3-en-2-one (**1**) with *S,S*-dimethyl- and *S*-methyl-*S*-phenyl-sulfoximides (**2**). Their application to obtain *S,S*-sulfoximido-substituted pyrazoles, isoxazoles and pyrimides from the reactions of **3a** with four hydrazines, hydroxylamine hydrochloride and acetylguanidine, respectively, is also demonstrated.

Results and Discussion

In this study, an efficient method for the synthesis of two new 4-ethoxy-4-(*S,S*-disubstituted-sulfoximido)-1,1,1-trifluorobut-3-en-2-ones (**3a-b**) from the reaction of 4,4-diethoxy-1,1,1-trifluorobut-3-en-2-one (**1**) with *S,S*-dimethyl- (**2a**) and *S*-methyl-*S*-phenyl-sulfoximide (**2b**) is presented. In contrast to previous papers,[10] where we explored the basicity of methyl and methylene substituents of the *S,S*-sulfoximido group of 4-alkyl(aryl)-4-sulfoximide-1,1,1-trifluoroalk-3-en-2-ones in intramolecular cyclocondensation reactions to obtain [1,2]thiazine 1-oxide derivatives, here intermolecular reactions involving **3a** with various dinucleophiles have been conducted. Thus, synthetic applications using cyclization reactions of **3a** with hydrazine monohydrochloride, phenylhydrazine, *p*-tosylhydrazine, furan-2-carbohydrazide, nicotinohydrazide, hydroxylamine hydrochloride and acetylguanidine, respectively, to give new *S,S*-dimethylsulfoximido-substituted pyrazoles (**4**, **5**),



(*i*) = R^2NHNH_2, EtOH, reflux; (*ii*) = NH_2OH, DMSO, rt; (*iii*) = $MeC(NH)NH_2$, Et_3N, DMF, rt.
R^1 = Ph, *c*-Hexyl
R^2 = H, Ph, 4-NO_2Ph

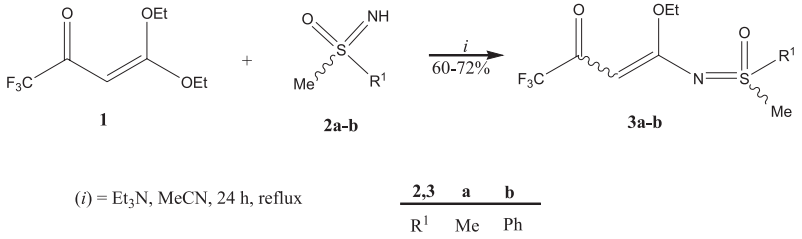
Scheme 3.

isoxazoles (**6**, **7**) and pyrimidine (**8**), are reported (Schemes 4 and 5).

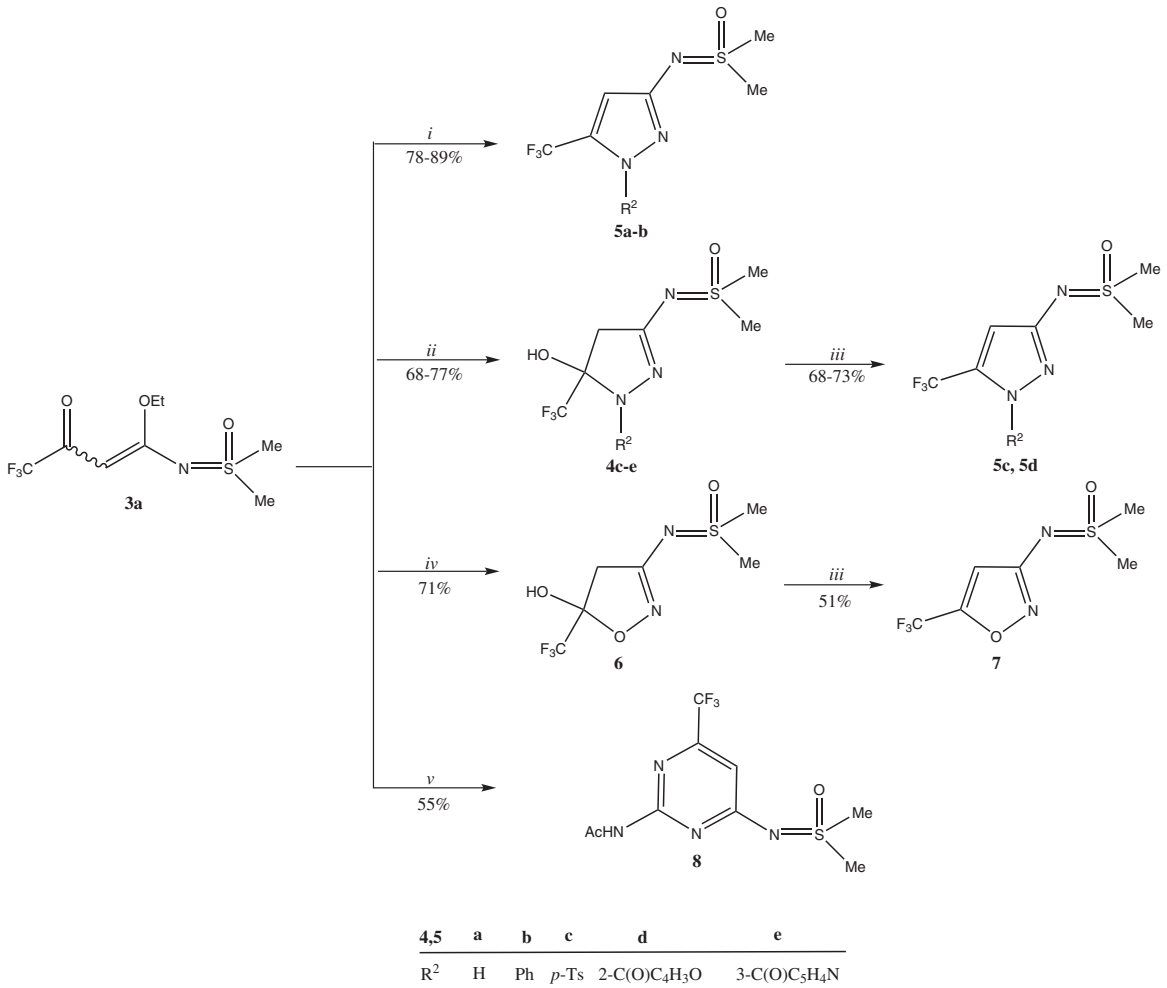
The synthon 4,4-diethoxy-1,1,1-trifluorobut-3-en-2-one (**1**) was prepared from the reaction of triethyl orthoacetate with trifluoroacetic anhydride using the procedure reported by Hojo *et al.*[5]

As a general procedure, firstly the precursor **1** was treated with *S,S*-dimethyl- and *S*-methyl-*S*-phenylsulfoximide (**2a**-**b**) in refluxing acetonitrile and triethylamine as solvent for 24 h to give the new 4-alkoxy-4-substituted-sulfoximido-1,1,1-trifluorobut-3-en-2-ones (**3a**-**b**) in 60% and 72% yields, respectively.

Treatment of **3a** with *p*-tosylhydrazine, furan-2-carbohydrazide and nicotinohydrazide in the presence of triethylamine in refluxing toluene or methanol as solvent for 8-16 h regioselectively furnished 5-hydroxy-3-(*S,S*-dimethylsulfoximido)-5-(trifluoromethyl)-4,5-dihydro-1*H*-1-pyrazoles (**4c**-**e**), in 68-77% yields. When the reactions



Scheme 4.



(*i*) = NH_2NHR^2 (R^2=H, Ph), EtOH, 3-16 h, 78 ºC; (*ii*) = NH_2NHR^2 (R^2= *p*-Ts, C_4H_3OCO, C_5H_4NCO), Toluene or MeOH, 8-16 h, 65-110 ºC; (*iii*) = $SOCl_2$, Py, Benzene, 2 h, 5-80 ºC; (*iv*) = $NH_2OH.HCl$, Py, MeOH, 16 h, 65 ºC; (*v*) = $(NH_2)_2CNHAc$, MeCN, 24 h, 85 ºC.

Scheme 5.

were carried out in refluxing ethanol for 3-16 h, **3a** reacted with hydrazine monohydrochoride and phenylhydrazine giving exclusively the aromatic 3-(*S,S*-dimethylsulfoximido)-5-(trifluoromethyl)-1*H*-pyrazoles (**5a**-**b**), in 78-89% yields, without the isolation of the 2-pyrazoline intermediates.

Subsequently, 5-hydroxy-2-pyrazolines **4c**-**e** were submitted to dehydration reactions using thionyl chloride/pyridine in refluxing benzene as solvent. Due to the strong electron-withdrawing effect of the nicotinoyl substituent, it was not possible to isolate the aromatic pyrazole **5e**. Compounds **5c** and **5d** were isolated after the reaction time, as solids, in high purity and in satisfactory yields (68-73%) by a simple evaporation of the solvent under vacuum.

Treatment of **3a** with hydroxylamine hydrochloride in refluxing methanol and pyridine for 16 h gave the non-aromatic 5-hydroxy-3-(*S,S*-dimethylsulfoximido)-5-(trifluoromethyl)-4,5-dihydroisoxazole (**6**) in 71% yield. Compound **6** was dehydrated with a mixture of thionyl chloride/pyridine in benzene to afford the corresponding 3-(*S,S*-dimethylsulfoximido)-5-(trifluoromethyl)isoxazole **(7)**, in good yield (51%).

In the synthesis of trifluoromethyl-containing pyrazolines (**4**), pyrazoles (**5**), isoxazoline (**6**) and isoxazole (**7**) the cyclocondensation reactions were regioselective. This trend was expected since the regioselective synthesis of similar pyrazoles and isoxazoles from the reactions of 2-benzoyl-3-methylthio-3-(*S,S*-dimethylsulfoximido)-acrylonitrile and substituted hydrazines and hydroxylamine, respectively, has been reported.[11]

Finally, the cyclocondensation reaction of compound **3a** with acetylguanidine (1,3-dinucleophile), carried out in acetonitrile, at 80-85 ºC for 24 h, furnished the 6-(*S,S*-dimethylsulfoximido)-4-(trifluoromethyl)-2-acetylaminopyrimidine (**8**), in 55% yield.

The structure of all compounds was determined from ^{1}H, ^{13}C NMR, mass spectra and by comparison with NMR data of other sulfoximides[10] and heterocycles[1-4,7] previously synthesized in our laboratory.

In all compounds **4**-**8** the carbon attached to the CF_3 presented a characteristic quartet in the range of 90.7-158.0 ppm with a carbon-fluorine coupling constant ($^{2}J_{CF}$) in the range of 32-41 Hz. The CF_3 group shows a typical quartet in the range of 117.7-123.3 ppm due to the $^{1}J_{CF}$ in the range of 267-287 Hz.

Sulfoximido-enones **3a**-**b** presented ^{1}H chemical shifts of vinyl hydrogen H3 as a characteristic singlet at *ca.* 5.14 ppm. Also, compounds **3a**-**b** presented the typical ^{13}C chemical shifts of acyclic carbons, on average at 79.3 ppm (C3) and 169.1 ppm (C4). The C2 (C=O) presented a characteristic quartet, due to attachment to the CF_3 group, on average at 175.3 ppm (32 Hz). The C1 (CF_3 group) showed a typical quartet at *ca.* 117.3 ppm and a CF-coupling constant on average of 292 Hz, due to the carbon-fluorine coupling.

Compounds **4** and **5** were identified as 1,5-isomers, which indicates the position of the *N*-1 substituent in relation to the CF_3 group. Thus, the 2-pyrazolines **4c**-**e** presented ^{1}H chemical shifts of the *S,S*-dimethylsulfoximido group as two characteristic singlets at ca. 3.34 ppm and 3.32 ppm and presented the typical ^{13}C chemical shifts of both methyl carbons on average at 41 ppm. The heterocyclic compounds **5**-**8** presented ^{1}H chemical shifts of the *S,S*-dimethylsulfoximido group as a characteristic singlet at *ca.* 3.37 ppm and presented the typical ^{13}C chemical shifts of both methyl carbons on average at 41.4 ppm.

The 4,5-dihydropyrazoles **4c**-**e** and 4,5-dihydroisozaxole **6** presented ^{1}H chemical shifts of H4a and H4b as two doublets at *ca.* 3.29 ppm and 2.99 ppm (**4c**-**e**) and two doublets at 3.33 ppm and 2.94 ppm (**6**), with a *geminal*-HH coupling constant of *ca.* 18 Hz for both heterocyclic classes. Also, compounds **4c**-**e** presented the typical ^{13}C chemical shifts of ring carbons on average at 154.8 ppm (C3) and 45.2 ppm (C4) while **6** presented the typical ^{13}C chemical shifts of ring carbons at 157.9 ppm (C3) and 44.0 ppm (C4). The C5 presented a characteristic quartet, due to attachment to the CF_3 group, on average at 91.2 ppm (33 Hz) for **4c**-**e** and at 101.4 ppm (32 Hz) for **6**. The CF_3 group showed a typical quartet at *ca.* 123.1 ppm (**4c**-**e**) and 122.5 ppm (**6**) due to the carbon-fluorine coupling with the CF-coupling constant on average of 279 Hz for **4c**-**e** and 284 Hz for dihydroisoxazole **6**.

The aromatic pyrazoles **5a**-**d** and isoxazole **7** presented ^{1}H chemical shifts of H4 as a characteristic singlet in a range of 5.98 to 6.87 ppm (**5a**-**d**) and at 6.35 ppm (**7**). The compounds **5a**-**d** presented the typical ^{13}C chemical shifts of ring carbons on average at 149.3 ppm (C3) and 98.7 ppm (C4). Compound **7** presented the typical ^{13}C chemical shifts of ring carbons at 162.9 ppm (C3) and 102.5 ppm (C4). The C5 for **5**a**-d** and **7** presented a characteristic quartet at *ca.* 136.8 ppm for **5a**-**d** and 158 ppm for **7**, due to attachment to the CF_3 group, on average of 38 Hz (**5a**-**d)** and 42 Hz (**7**). The CF_3 group shows a typical quartet at ca. 120.6 ppm (**5a**-**d**) and 117.7 ppm (**7**) due to the carbon-fluorine coupling with the CF-coupling constant on average of 268 Hz (**5a**-**d**) and 270 Hz (**7**).

The pyrimidine **8** presented ^{1}H chemical shifts of H5 as a characteristic singlet at 6.69 ppm. This compound presented the typical ^{13}C chemical shifts of ring carbons at 156.9 ppm (C2), 103.5 ppm (C5) and 167 ppm (C6). The C4 presented a characteristic quartet at 155.3 ppm due to attachment to the CF_3 group of 34 Hz. The CF_3 group showed a typical quartet at 120.7 ppm due to the carbon-fluorine coupling with CF-coupling constant of 275 Hz.

Conclusions

In summary, we have developed *O,N*-exchange reactions of 4,4-diethoxy-1,1,1-trifluorobut-3-en-2-one with *S,S*-sulfoximides and utilized 4-ethoxy-4-(*S,S*-dimethylsulfoximido)-1,1,1-trifluorobut-3-en-2-one to obtain new trifluoromethylated *S,S*-dimethylsulfoximido-substituted pyrazoles, isoxazoles and pyrimidines. Only a few representative dinucleophiles were selected to test the generality of this methodology, but the results obtained in this initial synthetic application were satisfactory and are promising.

Experimental

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Reichert Thermovar apparatus. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in DMSO-d_6 for **4**, **5a**, **5c**-**d**, **6** and **8** and in chloroform-d_1 for **3a**-**b**, **5b** and **7** using TMS as internal reference. Mass spectra were registered in a HP 6890 GC connected to a HP 5973 MSD and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30m, 0.32mm of internal diameter), and helium was used as the carrier gas. The CHN elemental analyses were performed on a Perkin Elmer 2400 CHN elemental analyzer (São Paulo University, USP / Brazil).

*General procedure for the preparation of 4-ethoxy-4-(S,S-disubstituted-sulfoximido)-1,1,1-trifluorobut-3-en-2-ones (**3a**-**b**)*

A stirred mixture of 4,4-diethoxy-1,1,1-trifluoro-3-buten-2-one (**1**) (10 mmol), the respective *S,S*-disubstituted sulfoximide (**2a** or **2b**) (10 mmol) and triethylamine (10 mmol) in acetonitrile (20 mL) was heated in an oil bath for 24 h at 80-82 °C. The solvent was evaporated under reduced pressure and chloroform (50 mL) was added to the residue. The solution was then extracted with water (3 × 20 mL) and the organic layer dried with magnesium sulfate. The solvent was evaporated and the products **3a**-**b** recrystallized from a mixture of hexane:ethyl acetate (4:1).

*4-Ethoxy-4-(S,S-dimethylsulfoximido)-1,1,1-trifluorobut-3-en-2-one (**3a**)*

This compound was obtained as white solid; yield 72%; mp 117-119 ºC. ^{1}H NMR ($CDCl_3$) δ 5.17 (s, 1H, H-3), 4.18 (q, 2H, OCH_2), 3.38 (s, 6H, $2SCH_3$), 1.42 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 174.9 (q, ^2J 33, C-2), 169.2 (C-4), 117.4 (q, ^1J 292, CF_3), 79.2 (C-3), 65.5 (OCH_2), 43.2 (2C, $2SCH_3$), 14.0 (CH_3). GC-MS (EI, 70 eV): *m/z* (%) for $C_8H_{12}NO_3SF_3$ (259.05): 259 (M^+, 5), 190 (36), 120 (57), 94 (79), 78 (100). Anal. Calc. for $C_8H_{12}NO_3SF_3$: C, 37.06; H, 4.67; N, 5.40%. Found: C, 36.83; H, 4.60; N, 5.40%.

*4-Ethoxy-4-(S-methyl-S-phenylsulfoximido)-1,1,1-trifluorobut-3-en-2-one (**3b**)*

This compound was obtained as white solid; yield 60%; Mp.121-123 ºC. ^{1}H NMR ($CDCl_3$) δ 8.10-8.12 (m, 2H, Ar), 7.64 (m, 3H, Ar), 5.11 (s, 1H, H-3), 3.90-4.02 (m, 2H, OCH_2), 3.38 (s, 3H, SCH_3), 1.13-1.14 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 175.8 (q, ^{2}J 32, C-2), 169.0 (C-4), 138.7, 133.9, 129.6, 127.4 (Ar), 117.3 (q, ^{1}J 292, CF_3), 79.4 (C-3), 65.7 (OCH_2), 45.7 (SCH_3), 13.5 (CH_3). GC-MS (EI, 70 eV): m/z (%) for $C_{13}H_{14}NO_3SF_3$ (321.3): 306 (15), 252 (26), 156 (59), 125 (100), 77 (65). Anal. Calc. for $C_{13}H_{14}NO_3SF_3$: C, 48.59; H, 4.39; N, 4.36%. Found: C, 48.71; H, 4.08; 4.62%.

*General procedure for the preparation of 5-hydroxy-3-(S,S-dimethylsulfoximido)-5-(trifluoromethyl)-4,5-dihydro-1H-1-pyrazoles (**4c**-**e**)*

A stirred mixture of 4-ethoxy-4-(*S,S*-dimethylsulfoximide)-1,1,1-trifluorobut-3-en-2-one (**3a**) (2 mmol) and *p*-tosylhydrazine (2 mmol) in toluene (10 mL) or furan-2-carbohydrazide (2 mmol) or nicotinohydrazide (2 mmol) in methanol (10 mL) was heated in an oil bath for 8 h at 110 °C for **4c**, **4e** or 16 h at 65 ºC for **4d**, respectively. To obtain **4c** and **4e** the solvents were evaporated and the products recrystallized from chloroform. Compound **4d**, crystallized by refrigeration of the reaction mixture at 0-5 ºC, was filtered and also recrystallized from chloroform.

*5-Hydroxy-3-(S,S-dimethylsulfoximido)-5-(trifluoromethyl)-4,5-dihydro-1H-1-(p-tosylpyrazole) (**4c**)*

This compound was obtained as white solid; yield 68%; mp 120-122 ºC. ^{1}H NMR (DMSO-d_6) δ 8.10 (s, 1H, OH), 7.78 (d, 2H, *J* 8, Ts), 7.36 (d, 2H, *J* 8, Ts), 3.31 (s, 3H, SCH_3), 3.28 (s, 3H, SCH_3), 3.21 (d, 1H, *J* 18, H_{4a}), 2.85 (d, 1H, *J* 18, H_{4b}), 2.38 (s, 3H, CH_3Ts). ^{13}C NMR (DMSO-d_6) δ 155.1 (C-3), 143.4, 135.6, 128.9, 128.8 (Ar), 122.7 (q, *J* 284, CF_3), 91.9 (q, ^2J 33, C-5), 45.6 (C-4), 41.2, 40.9 ($2SCH_3$), 21.0 (CH_3Ts). GC-MS (EI, 70 eV): *m/z* (%) for $C_{13}H_{16}N_3O_4S_2F_3$ (399.41): 244 (28), 104 (100), 78 (70), 63 (42). Anal. Calc. for $C_{13}H_{16}N_3O_4S_2F_3$: C, 39.09; H, 4.04; N, 10.52%. Found: C, 39.08; H, 3.89; N, 10.54%.

*5-Hydroxy-3-(S,S-dimethylsulfoximido)-5-(trifluoromethyl)-4,5-dihydro-1H-1-(2-furanoylpyrazole) (**4d**)*

This compound was obtained as white solid; yield 70%; mp 173-175 ºC. ^{1}H NMR (DMSO-d_6) δ 7.93 (s, 1H, OH), 7.92 (s, 1H, H-5'), 7.48 (d, 1H, *J* 3, H-3'), 6.66-6.67 (m, 1H, H-4'), 3.42 (s, 3H, SCH_3), 3.40 (s, 3H, SCH_3), 3.29 (d, 1H, *J* 18, H_{4a}), 3.05 (d, 1H, *J* 18, H_{4b}).^{13}C NMR (DMSO-d_6) δ 155.3 (C=O), 154.5 (C-3), 146.0 (C-5', C-2'), 123.3 (q, *J* 267, CF_3), 118.9 (C-3'), 111.8 (C-4'), 90.9 (q, ^2J 33, C-5), 44.8 (C-4), 40.9 ($2SCH_3$). GC-MS (EI, 70 eV): *m/z* (%) for $C_{11}H_{12}N_3O_4SF_3$ (339.3): 339 (M^+, 14), 270 (10), 95 (100), 78 (26). Anal. Calc. for $C_{11}H_{12}N_3O_4SF_3$: C, 38.94; H, 3.56; N, 12.38%. Found: C, 38.85; H, 3.21; N, 12.02%.

*5-Hydroxy-3-(S,S-dimethylsulfoximido)-5-(trifluoromethyl)-4,5-dihydro-1H-1-(nicotinoylpyrazole) (**4e**)*

This compound was obtained as white solid; yield 77%; mp 136-138 ºC. ^{1}H NMR (DMSO-d_6) δ 8.87 (s, 1H, Py), 8.66 (s, 1H, Py), 8.03-8.08 (m, 1H, Py), 8.04 (s, 1H, OH), 7.46-7.49 (m, 1H, Py), 3.37 (d, 1H, *J* 19, H_{4a}), 3.30 (s, 3H, SCH_3), 3.28 (s, 3H, SCH_3), 3.09 (d, 1H, *J* 19, H_{4b}). ^{13}C NMR (DMSO-d_6) δ 163.5 (C=O), 154.9 (C-3), 151.0, 149.4, 136.5, 131.3, 122.8 (Py), 123.3 (q, *J* 287, CF_3), 90.7 (q, ^2J 33, C-5), 45.3 (C-4), 41.3, 41.1 ($2SCH_3$). GC-MS (EI, 70 eV): *m/z* (%) for $C_{12}H_{13}N_4O_3SF_3$ (350.3): 350 (M^+, 21), 281 (10), 106 (82), 78 (100). Anal. Calc. for $C_{12}H_{13}N_4O_3SF_3$: C, 41.14; H, 3.74; N, 15.99%. Found: C, 41.09; H, 3.43; N, 15.62%.

*General procedure for the preparation of 3-(S,S-dimethylsulfoximido)-5-(trifluoromethyl)-1H-pyrazoles (**5a**, **5b**)*

A stirred mixture of 4-ethoxy-4-(*S,S*-dimethylsulfoximide)-1,1,1-trifluorobut-3-en-2-one (**3a**) (2 mmol) and hydrazine hydrate (2 mmol) or phenylhydrazine (2 mmol) in ethanol (10 mL) was heated in an oil bath for 3 h at 78 °C for **5a** or 16 h at the same temperature for **5b**. The solvent was evaporated and the products **5a**, **5b** were recrystallized from hexane.

*3-(S,S-Dimethylsulfoximido)-5-(trifluoromethyl)-1H-pyrazole (**5a**)*

This compound was obtained as white solid; yield 89%; mp 149-151. ^{1}H NMR (DMSO-d_6) δ 5.98 (s, 1H, H-4), 3.36 (s, 1H, NH), 3.30 (s, 6H, $2SCH_3$). ^{13}C NMR (DMSO-d_6) δ 145.9 (C-3), 140.6 (q, ^2J 36, C-5), 121.8 (q, *J* 268, CF_3), 89.8 (C-4), 41.0 ($2SCH_3$). GC-MS (EI, 70 eV): *m/z* (%) for $C_6H_8N_3OSF_3$ (227.3): 227 (50), 78 (60), 63 (100). Anal. Calc. for $C_6H_8N_3OSF_3$: C, 31.72; H, 3.55; N, 18.49%. Found: C, 31.43; H, 3.36; N, 18.27%.

*3-(S,S-Dimethylsulfoximido)-5-(trifluoromethyl)-1H-1-phenylpyrazole) (**5b**)*

This compound was obtained as white solid; yield 78%; mp 123-125 ºC. ^{1}H NMR ($CDCl_3$) δ 7.41-7.45 (m, 5H, Ar), 6.40 (s, 1H, H-4), 3.29 (s, 6H, $2SCH_3$). ^{13}C NMR ($CDCl_3$) δ 152.7 (C-3), 139.2 (1C, Ar), 132.7 (q, ^2J 38, C-5), 128.8, 128.4, 125.3 (Ar), 119.6 (q, *J* 269, CF_3), 102.3 (C-4), 42.4 ($2SCH_3$). GC-MS (EI, 70 eV): *m/z* (%) for $C_{12}H_{12}N_3OSF_3$ (303.07): 303 (M^+, 47), 240 (21), 77 (100), 51 (28). Anal. Calc. for $C_{12}H_{12}N_3OSF_3$: C, 38.94; H, 3.99; N, 13.85%. Found: C, 38.64; H, 3.89; N, 13.55%.

*General procedure for the preparation of 3-(S,S-dimethylsulfoximido)-5-(trifluoromethyl)-1H-pyrazoles (**5c**, **5d**)*

A solution of 5-hydroxy-2-pyrazolines **4c**, **4d** (2.6 mmol) and pyridine (33.8 mmol) in 50 mL of benzene was cooled to 5-10 ºC and thionyl chloride (16.8 mmol, 1.22 mL) diluted in 25 ml of benzene was added dropwise over 10 min. The solution was stirred for an additional 30 min, during which time the temperature was allowed to rise to 25 ºC. The mixture was then heated under reflux (bath temperature 80 ºC) for 1 h and filtered to remove pyridine hydrochloride at room temperature. The solution was washed twice with water and dried over sodium sulfate. The evaporation of the solvent under vacuum left to the solid products **5c**, **5d** with a high level of purity.

*3-(S,S-Dimethylsulfoximido)-5-(trifluoromethyl)-1H-1-(p-tosylpyrazole) (**5c**)*

This compound was obtained as white solid; yield 73%; mp 96-98 ºC. ^{1}H NMR (DMSO-d_6) δ 7.52 (d, 2H, *J* 8, Ts), 7.15 (d, 2H, *J* 8, Ts), 5.98 (s, 1H, H-4), 3.30 (s, 6H, $2SCH_3$), 2.30 (s, 3H, CH_3Ts). ^{13}C NMR (DMSO-d_6) δ 145.9 (C-3), 144.7 (1C, Ar), 140.5 (q, ^2J 36, C-5), 138.3, 128.3, 125.5 (Ar), 121.8 (q, *J* 267, CF_3), 89.9 (C-4), 41.1 ($2SCH_3$), 20.8 (CH_3Ts). GC-MS (EI, 70 eV): *m/z* (%) for $C_{13}H_{14}N_3O_3S_2F_3$ (381.04): 381 (M^+, 21), 226 (20), 148 (16), 91 (100), 63 (44). Anal. Calc. for $C_{13}H_{14}N_3O_3S_2F_3$: C, 40.94; H, 3.70, N, 11.02%. Found: C, 41.03; H, 3.89; N, 10.75%.

*3-(S,S-Dimethylsulfoximido)-5-(trifluoromethyl)-1H-1-(2-furanoylpyrazole) (**5d**)*

This compound was obtained as white solid; yield 68%; mp 137-139 ºC. ^{1}H NMR (DMSO-d_6) δ 8.21-8.20 (m, 1H, H-5'), 7.96 (dd, 1H, *J* 3, *J* 1, H-3'), 6.88 (m, 1H, H-4'), 6.87 (s, 1H, H-4), 3.46 (s, 6H, $2SCH_3$). ^{13}C NMR (DMSO-d_6) δ 155.5 (C=O), 152.7 (C-3), 149.4 (C-2'), 144.0 (C-5'), 133.5 (q, ^2J 41, C-5), 124.2 (C-3'), 119.2 (q, *J* 268, CF_3), 112.9 (C-4'), 109.9 (C-4), 41.2 ($2SCH_3$). GC-MS (EI, 70 eV):

m/z (%) for $C_{11}H_{10}N_3O_3SF_3$ (321.3): 321 (M^+, 10), 95 (100), 78 (14), 63 (16). Anal. Calc. for $C_{11}H_{10}N_3O_3SF_3$: C, 41.12; H, 3.14; N, 13.08%. Found: C, 41.32; H, 2.84; N, 13.07%.

*General procedure for the preparation of 5-hydroxy-3-(S,S-dimethylsulfoximido)-5-(trifluoromethyl)-4,5-dihydroisoxazole (**6**)*

To a stirred mixture of 4-ethoxy-4-(*S,S*-dimethylsulfoximide)-1,1,1-trifluorobut-3-en-2-one (**3a**) (2 mmol) in methanol at room temperature, a solution of hydroxylamine hydrochloride (2 mmol) and pyridine (2 mmol) was added. The resulting mixture was heated in an oil bath for 16 h at 65 °C. The solvent was evaporated and the product **6** recrystallized from chloroform.

*5-Hydroxy-3-(S,S-dimethylsulfoximido)-5-(trifluoromethyl)-4,5-dihydroisoxazole) (**6**)*

This compound was obtained as white solid; yield 71%; mp 119-121 ºC. ^{1}H NMR (DMSO-d_6) δ 8.18 (s, 1H, OH), 3.34 (s, 6H, 2SCH$_3$), 3.33 (d, 1H, *J* 18, H_{4a}), 2.94 (d, 1H, *J* 18, H_{4b}). ^{13}C NMR (DMSO-d_6) δ 157.9 (C-3), 122.5 (q, *J* 284, CF_3), 101.4 (q, ^2J 32, C-5), 44.0 (C-4), 41.3, 41.1 (2SCH$_3$). GC-MS (EI, 70 eV): *m/z* (%) for $C_6H_9N_2O_3SF_3$ (246.03): 246 (M^+, 58), 177 (14), 78 (100), 63 (45). Anal. Calc. for $C_6H_9N_2O_3SF_3$: C, 29.27; H, 3.68; N, 11.38%. Found: C, 29.38; H, 3.41; N, 11.36%.

*General procedure for the preparation of 3-(S,S-dimethylsulfoximido)-5-(trifluoromethyl)isoxazole (**7**)*

A solution of isoxazoline **6** (2.6 mmol) and pyridine (33.8 mmol) in 50 mL of benzene was cooled to 0 ºC and thionyl chloride (16.8 mmol, 1.22 mL) diluted in 25 mL of benzene was added dropwise over 10 min. The solution was stirred for an additional 30 min, during which time the temperature was allowed to rise to 25 ºC. The mixture was then heated under reflux (bath temperature 80 ºC) for 1 h and filtered to remove pyridine hydrochloride at room temperature. The solution was washed twice with water and dried over sodium sulfate. The evaporation of the solvent under vacuum left the solid product **7**, which was recrystallized from hexane.

*3-(S,S-Dimethylsulfoximido)-5-(trifluoromethyl) isoxazole (**7**)*

This compound was obtained as white solid; yield 51%; mp 94-96 ºC. ^{1}H NMR ($CDCl_3$) δ 6.35 (s, 1H, H-4), 3.34 (s, 6H, 2SCH$_3$). ^{13}C NMR ($CDCl_3$) δ 162.9 (C-3), 158.0 (q, ^2J 42, C-5), 117.7 (q, *J* 270, CF_3), 102.5 (C-4), 42.3 (2SCH$_3$). GC-MS (EI, 70 eV): *m/z* (%) for $C_6H_7N_2O_2SF_3$ (228.2): 228 (M^+, 29), 209 (12), 78 (100), 63 (82). Anal. Calc. for $C_6H_7N_2O_2SF_3$: C, 31.58; H, 3.09; N, 12.28%. Found: C, 31.66; H, 2.88; N, 12.45%.

*General procedure for the preparation of 6-(S,S-dimethylsulfoximido)-4-(trifluoromethyl)-2-acetylaminopyrimidine (**8**)*

To a stirred mixture of 4-ethoxy-4-(*S,S*-dimethylsulfoximide)-1,1,1-trifluorobut-3-en-2-one (**3a**) (2 mmol) in acetonitrile at room temperature, was added acetylguanidine (2 mmol). The resulting mixture was heated in an oil bath for 24 h at 80-85 °C. The solvent was evaporated and the product **8** recrystallized from ethylacetate.

*6-(S,S-Dimethylsulfoximido)-4-(trifluoromethyl)-2-acetylaminopyrimidine (**8**)*

This compound was obtained as white solid; yield 55%; mp 156-158 ºC. ^{1}H NMR (DMSO-d_6) δ 10.76 (s, 1H, NH), 6.69 (s, 1H, H-5), 3.60 (s, 6H, 2SCH$_3$). ^{13}C NMR (DMSO-d_6) δ 168.8 (C=O), 167.0 (C-6), 156.9 (C-2), 155.3 (q, ^2J 34, C-4), 120.7 (q, *J* 275, CF_3), 103.5 (C-5), 41.0 (2SCH$_3$), 24.5 (C-7). GC-MS (EI, 70 eV): *m/z* (%) for $C_9H_{11}N_4O_2SF_3$ (296.06): 296 (M^+, 61), 254 (41), 191 (86), 78 (74), 63 (61). Anal. Calc. for $C_9H_{11}N_4O_2SF_3$: C, 36.49; H, 3.74; N, 18.91%. Found: C, 36.28; H, 3.41; N, 18.64%.

Acknowledgments

The authors are thankful to Conselho Nacional de Desenvolvimento Científico e Tecnológico, CNPq (Process No. 303636/2002-5), for financial support. The students R. P. Vezzosi, I. R. Rodrigues, R. L. Drekener and L. M. F. Porte thank the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, CAPES, for fellowships.

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Received: February 20, 2009
Web Release Date: July 23, 2009