An Easy Synthesis of 3,5-Disubstituted 1,2,4-Oxadiazoles from Carboxylic Acids and Arylamidoximes Mediated by Ethyl Chloroformate

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Uma síntese limpa, fácil e eficiente de vários 1,2,4-oxadiazóis 3,5-dissubstituídos partindo de um anidido misto (gerado a partir de um ácido carboxílico e cloroformiato de etila) e amidoxima é descrita.

An efficient, clean and easy high-yielding synthesis of 3,5-disubstituted 1,2,4-oxadiazoles starting from mixed anhydrides (generated from carboxylic acids and ethyl chloroformate) and arylamidoximes is described.

Keywords: carboxylic acids, arylamidoximes, 1,2,4-oxadiazoles, 1H and 13C NMR spectra

Introduction

1,2,4-Oxadiazoles are well-known nitrogen compounds and sizeable work has been done in this area since their first preparation in 1884. A recent review covering the research papers published from 1996 through 2007 describes the interesting synthetic developments of 1,2,4- and 1,3,4-oxadiazoles. This review also quotes the already established biological attributes to this class of compounds. Although much attention has been given for pharmacological evaluations of 1,2,4-oxadiazoles, recent publications showed also their applicability in the field of luminescent liquid crystals, materials for optical devices, and charge-transporters for organic light-emitting diodes (OLEDs). Because of the vast importance of this class of compounds, which is constantly growing, we decided to develop their simpler and less time-consuming synthesis.

The most prevalent method for synthesizing 1,2,4-oxadiazoles involves O-acylation of amidoximes followed by cyclodehydration. Acyl chlorides, anhydrides, esters, and trichloroalkanes are commonly used as acylating agents. Carboxylic acids in the presence of coupling reagents like DCC, DIC or EDC are also employed to achieve the same goal. These procedures need much work to purify the desired 1,2,4-oxadiazoles. Besides

undesired side products are also formed which require, additional time and efforts for their separation.

One-pot methodologies for organic synthesis have attracted chemists’ and pharmacists’ interest from industries and academia, because these procedures allow reaching the target compounds without isolation of synthetic intermediates. In addition, one-pot reactions also reduce the use of solvents, reagents and adsorbents commonly employed for purifying the intermediates, being considered green protocols. Therefore, we have focused our attention in developing a clean one-pot protocol which allows the synthesis of 1,2,4-oxadiazoles in good yields with less work-up and avoids side product formation. Herein, we would like to report, for the first time, the synthesis of some 2,5-disubstituted 1,2,4-oxadiazoles from carboxylic acids and arylamidoximes in the presence of ethyl chloroformate as a coupling agent (Scheme 1 and Table 1).

Results and Discussion

Although ethyl chloroformate has been used in the presence of a base as carbonyl activator reagent for the one-pot synthesis of esters and amides, it has not been utilized in the synthesis of 1,2,4-oxadiazoles. Therefore, first we carried out various reactions involving benzoic acid 1d and benzamidoxime 4b by using different organic solvents and bases to standardize the reaction conditions. The best result was found when we used CH2Cl2 as solvent and K2CO3.
or Et₃N as bases. We chose to use potassium carbonate because it is cheap as well as easy to remove after the reaction. Thus, a suitable carboxylic acid 1a-g was stirred in the presence of K₂CO₃ in CH₂Cl₂ for 30 min to achieve the formation of carboxylic acid potassium salt which reacts with ethyl chloroformate 2 to generate in situ the mixed anhydrides 3a-g. Then, an appropriate amidoxime 4h-j was added to the same solution followed by stirring for an additional 2 h. The reaction between 3a-g and 4h-j forms O-acylamidoximes 5k-t with the liberation of CO₂ and EtOH. Although the intermediates 5k-t can be isolated and characterized, we avoided their isolation in many cases. In fact, these were cyclodehydrated individually to afford 1,2,4-oxadiazoles (Table 1).

In order to verify the structure of the intermediates 5k-t, we have isolated two known products 5p and 5q whose physical and chemical properties agreed with the literature. Once the structures of the above-cited intermediates have been established, we proceeded to obtain the final products in excellent yields (75-93%). This general protocol has worked well with aromatic, aliphatic and carbocyclic carboxylic acids (entries 1-10, Table 1). Compounds 5k-o,t are new ones and their structures have been confirmed by, IR, ¹H and ¹³C NMR spectra and elemental analyses. The known compounds 5p-r,s were characterized by comparing their reported melting points and spectral data.

Conclusions

In summary, we have developed an alternate new method to synthesize 1,2,4-oxadiazoles from carboxylic acids and arylamidoximes using ethyl chloroformate as a coupling agent. The desired 3,5-disubstituted oxadiazoles 6k-t have been obtained in excellent yields after simple work-up. This protocol is applicable for synthesizing 1,2,4-oxadiazoles containing aryl or alkyl groups attached at their C-5 side-chain. Further, this procedure is also suitable for the obtaining bis-1,2,4-oxadiazoles.

Experimental

General experimental procedures

All reagents were obtained from commercial sources and used without further purification. Infrared spectra were recorded on a Perkin-Elmer model 283 spectrometer in KBr discs. ¹H and ¹³C NMR spectra of CDCl₃ solutions were obtained in a Varian 300-MHz instrument using...
### Table 1. Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles 6k-1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Yield / (%)</th>
<th>mp / (°C)</th>
<th>mp [Lit.°] / (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Compound 1" /></td>
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<td>45</td>
<td>-</td>
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<tr>
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<td><img src="image2" alt="Compound 2" /></td>
<td>80</td>
<td>51</td>
<td>-</td>
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<tr>
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<td><img src="image3" alt="Compound 3" /></td>
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<td>56</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
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<td>79</td>
<td>53</td>
<td>-</td>
</tr>
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<td><img src="image5" alt="Compound 5" /></td>
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<td>57.1</td>
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<td>134</td>
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<tr>
<td>7</td>
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<td>110</td>
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<td>105-106</td>
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<td>84</td>
<td>169-170</td>
<td>171-172</td>
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</table>
tetramethylsilane (TMS) as the internal standard. Elemental analysis was performed with a Carlo Erba instrument model E-1110. Carboxylic acids 1a-f were obtained from commercial sources while 1g and arylamidoximes 4h-j were prepared following the procedures reported earlier. 21,22

**Typical experimental procedure**

A suitable carboxylic acid 1a-f (1.6 mmol) was dissolved in dry CHCl₃ (8.0 mL) and placed in a round bottom flask followed by the addition of K₂CO₃ (0.33g, 2.4 mmol) under stirring and kept as such for 30 min at room temperature. Later, ethyl chloroformate 2 (0.2 mL, 2.4 mmol) was added to the same flask and stirred for an additional 30 min. Finally, the addition of an appropriate amidoxime 4h-j (1.6 mmol) with continuous agitation for 2 h completed the reaction. Filtration and solvent evaporation under reduced pressure furnished the crude product which upon heating in an oil bath at 120 °C for 4 h gave the desired compounds which were crystallized from EtOH.

**3-(4-Tolyl)-5-tridecanyl-1,2,4-oxadiazole (6k)**

Yield: 86%; colorless crystals; mp 45 °C; R, 0.61 (CHCl₃:C₆H₁₂, 1:1). IR (KBr) ν max/cm⁻¹: 3049, 2922, 2926, 2846, 1576. ¹H NMR (300 MHz,CDCl₃); δ 0.87 (t, J 7.5 Hz, 3H), 1.25-1.48 (bs, 22H), 1.86 (quintet, J 7.5 Hz, 2H), 2.93 (t, J 7.5 Hz, 2H), 2.41 (s, 3H), 7.23 (d, J 8.4 Hz, 2H), 7.96 (d, J 8.4 Hz, 2H). ¹³C NMR (75 MHz,CDCl₃); δ 14.13, 21.56, 22.68, 26.67, 29.03, 29.34, 29.54, 29.62, 31.90, 124.07, 127.27, 129.51, 141.34, 168.51, 179.91. Anal. Calc. for C₂₃H₃₈ClN₂O: C, 70.27; H, 9.38; N, 6.69. Found: C, 70.21; H, 9.47; N, 6.98%.

**3,5-Di-p-tolyl-1,2,4-oxadiazole (6n)**

Yield: 79%; colorless crystals; mp 53 °C; R, 0.53 (CHCl₃:C₆H₁₂, 1:1). IR (KBr) ν max/cm⁻¹: 3048, 2925, 2847, 1574. ¹H NMR (300 MHz,CDCl₃); δ 0.88 (t, J 6.6 Hz, 3H), 1.25-1.50 (bs, 28H), 1.86 (quintet, J 8.1 Hz, 2H), 2.94 (t, J 8.1 Hz, 2H), 7.45 (d, J 8.7 Hz, 2H), 8.01 (d, J 8.7 Hz, 2H). ¹³C NMR (75 MHz,CDCl₃); δ 14.11, 22.7, 26.6, 29.0, 29.1, 29.3, 29.5, 29.6, 29.64, 29.67, 31.9, 125.4, 128.7, 131.7, 132.2, 167.4, 180.3. Anal. Calc. for C₂₅H₃₉ClN₂O: C, 71.66; H, 9.38; N, 6.69. Found: C, 72.01; H, 9.47; N, 6.98%.

**5-Pentadecanlyl-3-p-tolyl-1,2,4-oxadiazole (6o)**

Yield: 90%; colorless crystals; mp 57 °C (lit, mp 57.1 °C); R, 0.51 (CHCl₃:C₆H₁₂, 1:1). IR (KBr) ν max/cm⁻¹: 3063, 2954, 2917, 2848, 1588. ¹H NMR (300 MHz,CDCl₃); δ 0.88 (t, J 6.9 Hz, 3H), 1.25-1.44 (bs, 28H), 1.86 (quintet, J 7.8 Hz, 2H), 2.41 (s, 3H), 7.23 (d, J 7.8 Hz, 2H), 7.93 (d, J 8.1 Hz, 2H), 7.95 (d, J 8.1 Hz, 2H).

**3,5-Di-p-tolyl-1,2,4-oxadiazole (6p)**

Yield: 75%; colorless crystals; mp 133 °C (lit, mp 134 °C); R, 0.72 (CHCl₃). IR (KBr) ν max/cm⁻¹: 3023, 2920, 2850, 1594. ¹H NMR (300 MHz,CDCl₃); δ 2.39 and 2.40 (2s, 6H), 7.27 (d, J 7.6 Hz, 2H), 7.28 (d, J 7.8 Hz, 2H), 8.05 (d, J 7.8 Hz, 2H), 8.06 (d, J 7.6 Hz, 2H).

**3,5-Diphenyl-1,2,4-oxadiazole (6q)**

Yield: 86%; colorless crystals; mp 108-109 °C (lit, mp 110 °C); R, 0.70 (CHCl₃). IR (KBr) ν max/cm⁻¹: 3023, 2920, 2839, 1594. ¹H NMR (300 MHz,CDCl₃); δ 7.51-7.62 (m, 6H), 8.14-8.25 (m, 4H).

**3-Phenyl-3-p-tolyl-1,2,4-oxadiazole (6r)**

Yield: 93%; colorless crystals; mp 105-106 °C (lit, mp 105-106 °C); R, 0.52 (CHCl₃:C₆H₁₂, 1:1). IR (KBr) ν max/cm⁻¹: 3049, 2955, 2915, 1560. ¹H NMR (300 MHz,CDCl₃); δ 2.44 (s, 3H), 7.32 (d, J 9.6 Hz, 2H), 7.55-7.60 (m, 3H), 8.07 (d, J 8.7 Hz, 2H), 8.22 (d, J 9.6 Hz, 2H).

**5-Cyclohexyl-4-p-tolyl-1,2,4-oxadiazole (6s)**

Yield: 91%; colorless crystals; mp 55 °C; R, 0.80 (CHCl₃). IR (KBr) ν max/cm⁻¹: 3035, 2918, 2852, 1589. ¹H NMR (300 MHz,CDCl₃); δ 1.25-2.15 (m, 10H), 2.41 (s,
3H), 3.00 (tt, J \_\text{ax}=11.1 \text{ Hz}, J \_\text{eq}=3.6 \text{ Hz}, 1H), 7.27 (d, J 8.4 Hz, 2H), 7.96 (d, J 8.4 Hz, 2H). \text{\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}); \text{δ} 21.5, 25.3, 25.5, 30.2, 36.3, 124.2, 127.3, 129.4, 141.2, 168.0, 182.7. Anal. Calc. for C\textsubscript{15}H\textsubscript{18}N\textsubscript{2}O C, 74.35; H, 7.49; N, 11.56. Found: C, 74.48; H, 7.33; N, 11.62.

1,2-Bis-(3-p-tolyl-1,2,4-oxadiazol-5-yl)ethane (6t)

Yield: 84%; colorless crystals; mp 169-170 °C (lit. 98.2, 98.4 °C); R\(_f\) 0.73 (CHCl\(_3\)). IR (KBr) \text{ν}_{\text{max}}/\text{cm}^{-1}: 21.5, 25.3, 25.5, 30.2, 36.3, 124.2, 127.3, 129.4, 141.2, 168.0, 182.7. Anal. Calc. for C\textsubscript{15}H\textsubscript{18}N\textsubscript{2}O C, 74.35; H, 7.49; N, 11.56. Found: C, 74.48; H, 7.33; N, 11.62.

Acknowledgments

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Supplementary Information

Detailed experimental procedures and full set of \textit{\textsuperscript{1}}H and \textit{\textsuperscript{13}}C NMR spectra are available free of charge at http://jbcs.sbq.org.br as a PDF file.

References


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Experimental

General experimental procedures

All reagents were obtained from commercial sources and used without further purification. Infrared spectra were recorded on a Perkin-Elmer model 283 spectrometer in KBr discs. ¹H and ¹³C NMR spectra of CDCl₃ solutions were obtained in a Varian 300-MHz instrument using tetramethylsilane (TMS) as the internal standard. Elemental analysis was performed with a Carlo Erba instrument model E-1110. Carboxylic acids 1a-f were obtained from commercial sources while 1g and arylamidoximes 4h-j were prepared following the procedure reported earlier.¹²

Typical experimental procedure

A suitable carboxylic acid 1a-f (1.6 mmol) was dissolved in dry CH₂Cl₂ (8.0 mL) and placed in a round bottom flask followed by the addition of K₂CO₃ (0.332 g, 2.4 mmol) under stirring and kept as such for 30 min at room temperature. Later ethyl chloroformate 2 (0.2 mL, 2.4 mmol) was added to the same flask and stirred for an additional 30 min. Finally, the addition of an appropriate amidoxime 4h-j (1.6 mmol) with continuous agitation for 2 h completed the reaction. Filtration and solvent evaporation under reduced pressure furnished the crude product which upon heating in an oil bath at 120 °C for 4 h gave the desired compounds which were crystallized from EtOH.

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3-(4-Chlorophenyl)-5-tridecanyl-1,2,4-oxadiazole (6l)

Yield: 80%; colorless crystals; mp 51 °C; R, 0.62 (CHCl₃:C₆H₁₂, 1:1). IR (KBr) νmax/cm⁻¹: 3049; 2920; 2925; 2843; 1572. ¹H NMR (300 MHz, CDCl₃); δ 0.88 (t, J 7.2 Hz, 3H), 1.25-1.49 (bs, 22H ), 1.86 (quintet, J 7.8 Hz, 2H), 2.93 (t, J 7.5 Hz, 2H), 7.45 (d, J 8.4 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃); δ 14.1, 22.7, 26.6, 29.0, 29.1, 29.3, 29.5, 29.6, 29.65, 29.68, 31.9, 125.4, 128.7, 129.1, 137.2, 167.4, 180.3. Anal. Calc. for C₂₁H₃₃ClN₂O C, 69.11; H, 9.11; N, 7.68. Found: C, 69.21; H, 9.54; N, 7.58.

5-Heptadecanyl-3-p-tolyl-1,2,4-oxadiazole (6m)

Yield: 83%; colorless crystals; mp 56 °C; R, 0.60 (CHCl₃:C₆H₁₂, 1:1). IR (KBr) νmax/cm⁻¹: 3049, 2921, 2846, 1576. ¹H NMR (300 MHz, CDCl₃); δ 0.87 (t, J 5.4 Hz, 3H), 1.25-1.50 (bs, 28H ), 1.86 (quintet, J 6.9 Hz, 2H), 2.41 (s,
3,5-Di-p-tolyl-1,2,4-oxadiazole (6q)

Yield: 86%; colorless crystals; mp 108-109 °C (lit.2 mp 110 °C); R, 0.70 (CHCl₃). IR (KBr) νmax/cm⁻¹: 3022, 2920, 2839, 1594. ¹H NMR (300 MHz, CDCl₃); δ 7.51-7.62 (m, 6H), 8.14-8.25 (m, 4H).

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Yield: 91%; colorless crystals; mp 55 °C; R, 0.80 (CHCl₃). IR (KBr) νmax/cm⁻¹: 3035, 2918, 2852, 1589. ¹H NMR (300 MHz, CDCl₃); δ 1.25-2.15 (m, 10H), 2.41 (s, 3H), 3.00 (tt, Jax-eq 3.6 Hz, Jax-ax 11.1 Hz, 1H), 7.27 (d, J 8.4 Hz, 2H), 7.96 (d, J 8.4 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃); δ 21.5, 25.3, 25.5, 30.2, 36.3, 124.2, 127.3, 129.4, 141.2, 168.0, 182.7. Anal. Calc. for C₁₅H₁₈N₂O C, 74.35; H, 7.49; N, 11.56. Found: C, 74.48; H, 7.33; N, 11.62.

1,2-bis(3-p-tolyl-1,2,4-oxadiazol-5-yl)ethane (6t)

Yield: 84%; colorless crystals; mp 169-170 °C (lit.² mp 171-172 °C); R, 0.73 (CHCl₃). IR (KBr) νmax/cm⁻¹: 3032, 2926, 2854, 1590. ¹H NMR (300 MHz, CDCl₃); δ...
2.41 (s, 6H), 3.57 (s, 4H), 7.28 (d, $J$ 8.4 Hz, 4H), 7.95 (d, $J$ 8.4 Hz, 4H).

References


Figure S1. $^1$H NMR (300 MHz) spectrum of compound 6k in CDCl$_3$. 
An Easy Synthesis of 3,5-Disubstituted 1,2,4-oxadiazoles from Carboxylic Acids

Figure S2. $^{13}$C NMR (75 MHz) spectrum of compound 6k in CDCl$_3$.

Figure S3. $^1$H NMR (300 MHz) spectrum of compound 6l in CDCl$_3$. 
Figure S4. $^{13}$C NMR (75 MHz) spectrum of compound 6l in CDCl$_3$.

Figure S5. $^1$H NMR (300 MHz) spectrum of compound 6m in CDCl$_3$. 
Figure S6. $^{13}$C NMR (75 MHz) spectrum of compound 6m in CDCl$_3$.

Figure S7. $^1$H NMR (100 MHz) spectrum of compound 6n in CDCl$_3$. 
Figure S8. $^{13}$C NMR (75 MHz) spectrum of compound 6$n$ in CDCl$_3$.

Figure S9. $^1$H NMR (300 MHz) spectrum of compound 6$o$ in CDCl$_3$. 
Figure S10. $^1$H NMR (300 MHz) spectrum of compound 6p in CDCl$_3$.

Figure S11. $^1$H NMR (300 MHz) spectrum of compound 6q in CDCl$_3$. 
Figure S12. $^1$H NMR (300 MHz) spectrum of compound 6r in CDCl$_3$.

Figure S13. $^1$H NMR (300 MHz) spectrum of compound 6s in CDCl$_3$. 
Figure S14. $^{13}$C NMR (75 MHz) spectrum of compound 6s in CDCl$_3$.

Figure S15. $^1$H NMR (300 MHz) spectrum of compound 6t in CDCl$_3$. 