A Convenient Synthesis of *N*-Acylpyrroles from Primary Aromatic Amides

Anil R. Ekkati, Dallas K. Bates*

Department of Chemistry, Michigan Technological University, 1400 Townsend Drive, Houghton, MI 49931, USA
Fax +1(906)4872061; E-mail: dbates@mtu.edu

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Abstract: Synthesis of *N*-acylpyrroles in 45–85% isolated yield from primary aromatic amides and excess 2,5-dimethoxytetrahydrofuran in presence of one equivalent of thionyl chloride is reported. This method has several advantages including short reaction times, mild reaction conditions, and easy workup. The technique works particularly well for deactivated aromatic amides.

Key words: *N*-acylpyrroles, primary amides, condensation, 2,5-dimethoxytertahydrofuran

N-Acylpyrroles are useful compounds; they have been used as acylating agents, they can be regarded as activated carboxylic acid equivalents[1] and many are biologically active.[2] Delocalization of the nitrogen lone pair into the pyrrole ring of pyrrole amides alters amide reactivity significantly. The reduced electron density on the *N*-acylpyrrole carbonyl favors nucleophilic attack and the derived tetrahedral intermediate in many cases readily ejects pyrrole. Thus, conversion to the corresponding *N*-acylpyrrole permits facile transformation of primary amides into esters, secondary amides and tertiary amides as well as reduction to aldehydes and alcohols.[1c] *N*-Acylpyrroles are also useful in other synthetic methodologies. Reaction between lithium ester enolates and *N*-acylpyrroles produces isolable carbinols, which upon heating or treatment with basic reagents afford β-ketoesters in good yields.[1a] Enolsilanes derived from *N*-acylpyrroles exhibit high levels of diastereoselection in concert with good enantioselection in Lewis acid catalyzed Mukaiyama–Michael reaction with acryloyl oxazolidinones.[3] Our interest in *N*-acylpyrroles derives from their use as precursors for SES reactions.[4]

Preparation of *N*-acylpyrroles traditionally has involved pyrrole acylation by reaction of an alkali salt of pyrrole with an equivalent amount of acyl halide.[5] Due to the typical harshly basic reaction conditions this procedure is unsuitable for the preparation of substituted pyrroles containing base labile protecting groups or π-deficient aromatics containing ring functionality sensitive to nucleophilic displacement.[6,7]

An alternative route involves formation of the pyrrole ring from a primary amide. Gross[8] and Menger and Donohue[9] applied the general Clauson-Kaas[10] method for converting primary amines into pyrroles (2,5-dialkoxytetrahydrofuran in refluxing acetic acid) to primary amides. However with amides, this method requires longer reaction times than with amines because the amide nitrogen is not particularly nucleophilic and this method is not applicable to compounds that are acid or heat sensitive. Recently, it was reported[11] that the reaction of amides with 2,5-dimethoxytetrahydrofuran in the presence of P_2O_5 gives good yields of *N*-acylpyrroles. However, P_2O_5 is very hygroscopic and reaction conditions must avoid moisture. Nitriles are by-products in this process and in some cases are the sole products, as with acetamide. Based on our experience, if this reaction is not conducted under rigorously dry conditions, yields of the nitrile side product will increase.

2,5-Dichloro-2,5-dimethoxybutane has also been used to prepare *N*-acylpyrroles.[1c] For reactive amides formation of *N*-acylindoles[4b] and *N*-acylcarbazoles[12] can occur and the procedure does not work well for deactivated aromatic amides. For example, 2-methylthionicotinamide is recovered unchanged under this protocol.[13] Additionally, 2,5-dichloro-2,5-dimethoxybutane[14] has a short shelf life and is not commercially available.

In an attempt to overcome problems with existing methods, we sought to improve the reaction of 2,5-dimethoxytetrahydrofuran with amides by attempting to prepare in situ an activated 1,4-butanedial equivalent. To this end, we have found that addition of one equivalent of thionyl chloride to a mixture of the amide in 2,5-dimethoxytetrahydrofuran (as both solvent and reactant) rapidly produces *N*-acylpyrroles. We have not studied the mechanism of the conversion, but the reaction gives poor yields if substantially less than one equivalent of $SOCl_2$ is added. Addition of a second equivalent of $SOCl_2$ improves neither rate nor yield. Finally, substituting P_2O_5 for $SOCl_2$ produces the product in poor yield accompanied by black polymeric material.

Reaction times are short (10 min to 2 h) and workup is simple since 2,5-dimethoxytetrahydrofuran is both volatile (bp 143–146 °C) and water soluble. The results obtained for a variety of primary aromatic amides are shown in Table 1. The only byproduct sometimes observed is the corresponding indole derivative; the amount depends both on reaction time and amide reactivity.[15] For very reactive amides (acetamide), the indole is the sole product even after short reaction times.

All chemicals were obtained from commercial suppliers and used without further purification. Thin layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized with UV light. Column chromatography was per-

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Table 1 Summary of *N*-Acylpyrroles Prepared

Product	Ar =	Yield of *N*-Acylpyrrole (%)	Time (min)/ Temp (°C)[a]	Mp (°C)	IR (C=O, cm^{-1})	Partial ^1H NMR (δ)[f] (pyrrole proton absorptions)
1	Ph	78	10/r.t. to 80	oil[9]	1694 (neat)	7.27, 6.33
2	4-OMePh	75	10/r.t. to 80	oil[5a]	1693 (neat)	7.27, 6.31
3	Cinnamyl	68	10/r.t. to 80	108–110 (108)[16]	1688 ($CHCl_3$)	7.46, 6.35
4	2-Cl-4-OMePh	85	10/r.t. to 80	oil[b]	1704 (neat)	6.86, 6.28
5	2-MeS-4-OMePh	75	10/r.t. to 80	oil[c]	1694 (neat)	7.12, 6.26
6	4-NO_2Ph	70	120/50–60	131–133 (127–128)[9]	1703 ($CHCl_3$)	7.20, 6.37
7	3-NO_2Ph	66	120/50–60	oil[5e]	1698 (neat)	7.22, 6.39
8	4-CF_3Ph	60	120/50–60	92.5–93.5[d]	1701 ($CHCl_3$)	7.22, 6.36
9	4-CNPh	80	120/50–60	84–86 (87)[5e]	1698 ($CHCl_3$)[e]	7.19, 6.36
10	2-Methylthiopyridinyl	45	60/80–90	80–82 (78–79)[13]	1698 ($CHCl_3$)	7.12, 6.32

[a] For activated compounds **1**–**5** the reaction mixture was heated from r.t. to 80 °C over 10 min, then immediately cooled.
[b] Anal. Calcd for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; N, 5.94. Found: C, 60.81; H, 4.26; N, 6.12.
[c] Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66. Found: C, 62.92; H, 5.36; N, 5.81.
[d] Anal. Calcd for $C_{12}H_8F_3NO$: C, 60.26; H, 3.37; N, 5.86. Found: C, 60.26; H, 3.36; N, 5.8.
[e] IR (C ≡ N) = 2234 cm^{-1}.
[f] Multiplicity = both pyrrole signals appear as an apparent triplet with apparent *J* = ca. 2.3 Hz.

formed using silica gel (0.060–0.200 nm, pore diameter ca. 6 nm). Melting points are uncorrected. ^1H and ^{13}C NMR spectra were acquired at 400 MHz and 100 MHz, respectively, in $CDCl_3$ solution unless otherwise specified. 2-Chloro-4-methoxybenzamide[17] and 2-methylthionicotinamide[13] were prepared according to literature procedures.

Synthesis of *N*-Acylpyrroles; General Procedure

To the amide (1 g) in 2,5-dimethoxytetrahydrofuran (20 mL) was added drop-wise thionyl chloride (1 equiv). The mixture was heated (see Table 1), during which time the mixture turned brown or black, then cooled to 40 °C by immersion of the reaction flask into an ice water bath. In cases where the starting material was not completely soluble, dissolution occurred after $SOCl_2$ addition or upon heating. The cooled reaction mixture was poured into H_2O (200 mL), shaken thoroughly and allowed to settle. For solids, vacuum filtration was used to collect the product. Liquid products pool at the bottom of the flask. A majority of the aqueous layer (ca. 100 mL) was decanted away from the pooled liquid and discarded. Another portion of H_2O (100 mL) was added, gently swirled, and the aqueous layer decanted away from the pooled liquid product and discarded. After repeating this process again, CH_2Cl_2 was added to the pooled liquid and the mixture gently shaken. The organic layer was collected, washed with H_2O (2 × 100 mL), and dried (Na_2SO_4). The solvent was evaporated to give the crude acylpyrrole which was purified by silica gel column chromatography (eluant: CH_2Cl_2) to afford pure products in the yields listed in Table 1. Additional spectral data for **1**–**10** are provided in Table 2.

4-Methoxy-2-(methylthio)benzamide

To an ice-cold, stirred solution of 4-methoxy-2-(methylthio)benzonitrile[18] (1.38 g, 7.7 mmol) in DMSO (17 mL), 30% H_2O_2 (6.9 mL) and anhyd K_2CO_3 (0.27 g) were added. The mixture was allowed to warm to r.t. After 1 h, H_2O (75 mL) was added, the product isolated by filtration and dried to yield 1.1 g of the solid product.

Table 2 ^{13}C NMR and EIMS Data Summary for *N*-Acylpyrroles

Nr	^{13}C NMR (δ)	EIMS [*m*/*z* (%)]
1	167.6, 133.2, 132.2, 129.4, 128.4, 121.3, 113.1	171 (27), 105 (100)
2	167.1, 162.9, 131.9, 125.2, 121.3, 113.7, 112.7, 55.4	201 (19), 135 (100)
3	162.9, 147.5, 134.2, 130.9, 129.0, 128.4, 119.2, 115.7, 113.3	197 (31), 131 (100)
4	165.1, 161.8, 133.0, 130.5, 125.6, 120.4, 115.5, 113.5, 112.6, 55.6	235 (100), 169 (100)
5	166.3, 161.7, 141.3, 130.9, 124.9, 120.7, 113.0, 112.9, 109.2, 55.3, 16.2	247 (9), 181 (100)
6	165.6, 149.8, 138.8, 130.3, 123.7, 121.0, 114.2	216 (36), 150 (100)
7	165.2, 148.0, 134.9, 134.8, 129.9, 126.7, 124.3, 121.0, 114.2	216 (32), 150 (100)
8	166.4, 136.6, 133.9 (q, J_{C-F} = 33.7 Hz), 129.7, 125.6 (q, J_{C-F} = 4.6 Hz), 123.5 (q, J_{C-F} = 272.6 Hz), 121.1, 113.8	239 (28), 173 (100)
9	165.8, 137.1, 132.3, 129.8, 120.9, 117.6, 115.8, 114.0	196 (33), 130 (100)
10	165.3, 158.8, 151.1, 135.8, 127.8, 120.5, 118.1, 113.9, 13.4	218 (26), 152 (100)

Yield 74%; mp 180–182 °C.

IR (Nujol): 3363 (NH), 3189 (NH), 1622 (CO) cm^{-1}.

^1H NMR: δ = 7.68 (d, 1 H, *J* = 8.5 Hz), 6.82 (d, 1 H, *J* = 2.4 Hz), 6.69 (dd, 1 H, *J* = 2.4, 8.9 Hz), 3.83 (s, 3 H), 2.45 (s, 3 H).

^{13}C NMR: δ = 169.2, 161.7, 139.9, 131.3, 125.5, 113.6, 109.8, 55.4, 16.9.

MS (EI): *m*/*z* (%) = 197 (M^+, 53), 182 (100), 180 (69), 135 (67), 63 (90).

Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62; N, 7.10. Found: C, 54.81; H, 5.79; N, 7.12.

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