Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 9155–9158

Reductive acylation of 2- and 3-nitropyrroles—efficient syntheses of pyrrolylamides and pyrrolylimides

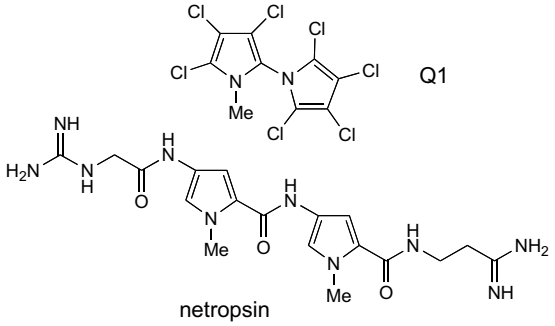
Liangfeng Fu and Gordon W. Gribble*

Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA

Received 17 September 2007; revised 20 October 2007; accepted 22 October 2007
Available online 25 October 2007

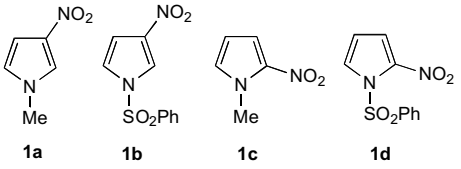
Abstract—An efficient one-pot synthesis of pyrrolylamides and pyrrolylimides is described under mild reaction conditions by the catalytic hydrogenation of 2- and 3-nitropyrroles.

Pyrrolylamides and pyrrolylimides are potentially useful intermediates for the construction of pyrrole-based heterocycles and medicinal compounds.[1,2] For example, pyrrolylimide **6c** was employed in the first synthesis of the naturally occurring bipyrrole Q1,[1c] and the well-known distamycin antitumor agents are pyrrolylamides (e.g., netropsin).

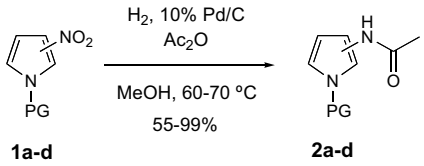


As an extension of our recent catalytic reductive acylation of 2- and 3-nitroindoles,[3] we now describe a new route to pyrrolylamides and pyrrolylimides via the Pd/C catalyzed reductive acylation of 2- and 3-nitropyrroles. Catalytic hydrogenation has long been utilized as a convenient and efficient nitro group to primary amine reduction method.[4] However, in the present case the relative instability of 2- and 3-aminopyrroles normally precludes their isolation and handling.[5]

We now report that 2- and 3-nitropyrroles are smoothly reduced and N-acylated under atmospheric catalytic hydrogenation conditions in the presence of carboxylic acid anhydrides to afford the expected pyrrolylamides (Scheme 1 and Tables 1 and 2). A previously reported reductive acylation of nitropyrrole **1a** was carried out under high pressure in THF.[1a] Four readily prepared nitropyrroles (1-methyl-3-nitropyrrole (**1a**), 3-nitro-1-(phenylsulfonyl)pyrrole (**1b**), 1-methyl-2-nitropyrrole (**1c**), and 2-nitro-1-(phenylsulfonyl)pyrrole (**1d**))[6] were subjected to catalytic reductive acylation.



Thus, 1-methyl-3-nitropyrrole (**1a**) is hydrogenated using 10% palladium on carbon in the presence of acetic anhydride in MeOH at 70 °C at atmospheric pressure to



Scheme 1.

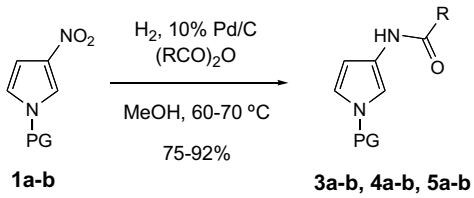
* Corresponding author. Tel.: +1 603 646 3118; fax: +1 603 646 3946; e-mail: ggribble@dartmouth.edu

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.10.113

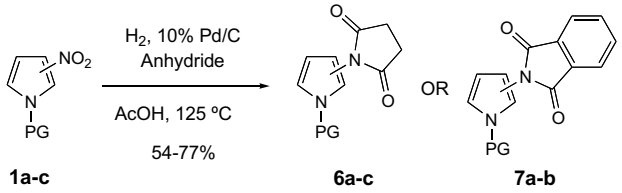
Table 1. Catalytic reductive acylation of nitropyrroles with H_2, Pd/C, and acetic anhydride in methanol at 70 °C[a]

Nitropyrrole	PG	Product	Yield[b] (%)
1a	Me	**2a**	91
1b	SO_2Ph	**2b**	99
1c	Me	**2c**	Decomposition during workup
1d	SO_2Ph	**2d**	55

[a] Temperature of the oil bath.
[b] Yield after column chromatography.



Scheme 2.



Scheme 3.

provide the desired pyrrole acetoamide **2a** in 91% yield (Scheme 1 and Table 1).[7] Likewise, nitropyrroles **1b** and **1d** are converted to **2b** and **2d** under the same reaction conditions in 99% and 55% yields, respectively.[8] The attempted reductive acylation of nitropyrrole **1c** led to decomposition and product **2c** was not isolated.

Moreover, the reductive acylation using other carboxylic acid anhydrides and Boc anhydride is successful. As shown in Table 2 and Scheme 2, benzoic acid anhydride gives pyrrole benzamides **3a** and **3b** in 79% and 80% yields, respectively.[8] Hexanoic anhydride affords the expected pyrrole hexamides **4a** and **4b** in 88% and 92% yields, respectively.[8] The *t*-butoxycarbonyl-protected amides **5a** and **5b** are obtained in yields of 79% and 75%, respectively.[8]

The same reaction conditions were extended to the preparation of pyrrolylimides. Unfortunately, when 1-methyl-3-nitropyrrole (**1a**) was hydrogenated in the presence of succinic anhydride, none of the expected succinimide was obtained and **1a** was recovered. In contrast, when acetic acid rather than methanol was used as the solvent, the desired pyrrolylimides were obtained (Scheme 3 and Table 3). Thus, nitropyrroles **1a**, **1b**, and **1c** were hydrogenated in the presence of succinic anhydride in acetic acid at 125 °C to give the desired pyrrolylimides **6a**, **6b**, and **6c** in 77%, 72%, and 54% yields, respectively.[8] In addition, phthalic anhydride furnishes pyrrolylimides **7a** and **7b** in 75% and 69% yields, respectively.[8]

In summary, we have described an efficient synthesis of pyrrolylamides and pyrrolylimides via the reductive acylation of 2- and 3-nitropyrroles in the presence of carboxylic acid anhydrides. In general, 3-nitropyrroles afford higher yields of reductive acylation products than do 2-nitropyrroles. Noteworthy is the synthesis of *t*-butoxylcarbonyl-protected pyrrolylamides **5a** and **5b**, which could serve as precursors for in situ generation of 2- and 3-aminopyrroles for use in synthesis.

Table 2. Catalytic reductive acylation of 3-nitropyrroles with H_2, Pd/C and different anhydrides in methanol at 70 °C[a]

Entry	Nitropyrrole	PG	Anhydride	R	Product	Yield[b] (%)
1	**1a**	Me	$(PhCO)_2O$	Ph	**3a**	79
2	**1b**	SO_2Ph	$(PhCO)_2O$	Ph	**3b**	80
3	**1a**	Me	$(C_5H_{11}CO)_2O$	$(CH_2)_4CH_3$	**4a**	88
4	**1b**	SO_2Ph	$(C_5H_{11}CO)_2O$	$(CH_2)_4CH_3$	**4b**	92
5	**1a**	Me	$(Boc)_2O$	Boc	**5a**	79
6	**1b**	SO_2Ph	$(Boc)_2O$	Boc	**5b**	75

[a] Temperature of the oil bath.
[b] Yield after column chromatography.

Table 3. Reductive acylation of nitropyrroles with H_2, Pd/C, and cyclic anhydrides in acetic acid at 125 °C[a]

Entry	Nitropyrrole	PG	Anhydride	Product	Yield[b] (%)
1	**1a**	Me	Succinic anhydride	**6a**	77
2	**1b**	SO_2Ph	Succinic anhydride	**6b**	72
3	**1c**	Me	Succinic anhydride	**6c**	54
4	**1a**	Me	Phthalic anhydride	**7a**	75
5	**1b**	SO_2Ph	Phthalic anhydride	**7b**	69

[a] Temperature of the oil bath.
[b] Yield after column chromatography.

Acknowledgments

This work was supported by the Donors of the Petroleum Research Fund (PRF), administrated by the American Chemical Society, and by Wyeth.

References and notes

1. Pyrrole-based heterocycles: (a) Grehn, L. *Chem. Scripta* **1980**, *16*, 77–84; (b) Grehn, L. *Chem. Scripta* **1980**, *16*, 85–96; (c) Wu, J.; Vetter, W.; Gribble, G. W.; Schneekloth, J. S., Jr.; Blank, D. H.; Gorls, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1740–1743.
2. Pyrrole-based drugs: (a) Baraldi, P. G.; Preti, D.; Fruttarolo, F.; Tabrizi, M. A.; Romagnoli, R. *Bioorg. Med. Chem.* **2007**, *15*, 17–35; (b) Baraldi, P. G.; Zaid, A. N.; Preti, D.; Fruttarolo, F.; Tabrizi, M. A.; Iaconinoto, A.; Pavani, M. G.; Carrion, M. D.; Cara, C. L.; Romagnoli, R. *Arkivoc* **2006**, *7*, 20–34; (c) Broggini, M.; Marchini, S.; Fontana, E.; Moneta, D.; Fowst, C.; Geroni, C. *Anti-cancer Drugs* **2004**, *15*, 1–6; (d) Baraldi, P. G.; Núnez, M. D. C.; Espinosa, A.; Romagnoli, R. *Curr. Top. Med. Chem.* **2004**, *4*, 231–239; (e) Neamati, N.; Mazumder, A.; Sunder, S.; Owen, J. M.; Tandon, M.; Lown, J. W.; Pommier, Y. *Mol. Pharmacol.* **1998**, *54*, 280–290.
3. (a) Roy, S.; Gribble, G. W. *Heterocycles* **2006**, *70*, 51–56; (b) Roy, S.; Roy, S.; Gribble, G. W. *Tetrahedron Lett.*, submitted for publication.
4. (a) Smith, H. A.; Bedoit, W. C., Jr. *Catalysis* **1955**, *3*, 149–170; (b) Downing, R. S.; Kunkeler, P. J.; van Bekkum, H. *Catal. Today* **1997**, *37*, 121; (c) Figueras, F.; Coq, B. *J. Mol. Catal. A: Chem.* **2001**, *173*, 223–230.
5. (a) De Rosa, M.; Stepani, N.; Cole, T.; Fried, J.; Huang-Pang, L.; Peacock, L.; Pro, M. *Tetrahedron Lett.* **2005**, *46*, 5715–5717; (b) De Rosa, M.; Sellitto, L.; Issac, R. P.; Ralph, J.; Timken, M. D. *J. Chem. Res. (S)* **1999**, 262–263.
6. Fu, L.; Gribble, G. W. *Synthesis*, submitted for publication.
7. *Representative procedure* (**2a**): To a solution of 1-methyl-3-nitropyrrole (**1a**) (32 mg, 0.25 mmol) and acetic anhydride (77 mg, 0.75 mmol) in anhydrous methanol (3 mL) was added 10% palladium on carbon (10 mg). The atmosphere of the flask was replaced by hydrogen gas and the reaction was cooled to −78 °C. After three vacuum/hydrogen cycles to remove air from the reaction flask, the reaction mixture was heated to 60 °C under atmospheric pressure for 2.5 h, having the hydrogen atmosphere maintained by a balloon. The catalyst was removed by filtration through Celite. The filtrate was evaporated and the crude product was purified by column chromatography (Hex/EtOAc = 2:1) to give the desired product (**2a**) (32 mg, 91%) as a yellow solid: mp 121–122 °C (lit.[1a] mp 120.5–121 °C); ^{1}H NMR (acetone-d_6): δ 9.01 (br s, 1H), 7.10 (t, 1H), 6.47 (t, 1H), 5.93 (dd, 1H), 3.61 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (acetone-d_6): δ 166.1, 124.2, 119.3, 112.1, 100.0, 35.6, 22.6.
8. *Compound* **2b**: White solid; mp 169–170.5 °C; ^{1}H NMR (acetone-d_6): δ 9.27 (br s, 1H), 7.94–7.97 (m, 2H), 7.71–7.74 (m, 1H), 7.69 (t, 1H), 7.62–7.66 (m, 2H), 7.18 (dd, 1H), 6.27 (dd, 1H), 2.01 (s, 3H); ^{13}C NMR (acetone-d_6): δ 167.8, 139.8, 134.9, 130.4, 129.1, 127.6, 120.5, 109.6, 108.5, 23.1; Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60; S, 12.13. Found: C, 54.36; H, 4.49; N, 10.49; S, 12.05.
Compound **2d**: white solid; mp 128–129 °C; ^{1}H NMR ($CDCl_3$): δ 8.57 (br s, 1H), 7.74–7.76 (m, 2H), 7.62 (m, 2H), 7.52 (m, 2H), 6.90 (dd, 1H), 6.55 (t, 1H), 6.24 (t, 1H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.8, 138.5, 134.6, 130.0, 128.6, 126.8, 116.7, 113.1, 104.0, 24.3; Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60; S, 12.13. Found: C, 54.27; H, 4.58; N, 10.48; S, 12.28.
Compound **3a**: white solid; mp 169–170.5 °C; ^{1}H NMR ($CDCl_3$): δ 7.84–7.86 (m, 2H), 7.81 (br s, 1H), 7.45–7.53 (m, 3H), 7.32 (t, 1H,), 6.49 (t, 1H,), 6.05 (dd, 1H, J), 3.65 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 164.6, 135.1, 131.6, 128.9, 127.1, 122.8, 120.0, 113.5, 100.7, 36.8; Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.92; H, 6.06; N, 14.02.
Compound **3b**: white solid; mp 170.5–172 °C; ^{1}H NMR ($CDCl_3$): δ 7.90–7.92 (m, 2H), 7.85 (t, 1H), 7.80–7.82 (m, 3H), 7.45–7.60 (m, 6H), 7.14 (dd, 1H), 6.32 (dd, 1H); ^{13}C NMR ($CDCl_3$): δ 165.0, 138.9, 134.2, 134.1, 132.2, 129.7, 129.1, 127.2, 127.1, 127.0, 120.0, 110.3, 107.7; Anal. Calcd for $C_{17}H_{14}N_2O_3S$: C, 62.56; H, 4.32; N, 8.58; S, 9.83. Found: C, 62.40; H, 4.28; N, 8.56; S, 9.90.
Compound **4a**: yellow solid (solid upon staying); ^{1}H NMR ($CDCl_3$): δ 7.27 (br s, 1H), 7.15 (t, 1H), 6.42 (t, 1H), 5.92 (dd, 1H), 3.60 (s, 3H), 2.29 (t, 2H, $J = 7.6$ Hz), 1.70 (m, 2H), 1.33 (m, 4H), 0.90 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$): δ 170.4, 122.8, 119.7, 113.2, 100.5, 37.2, 36.7, 31.7, 25.8, 22.7, 14.2; MS (EI): m/z (%) = 194 ([M^+]), 156, 138, 123, 112, 96 (100), 81, 68, 57; HRMS (EI): m/z calcd for $C_{11}H_{18}ON_2$: 194.1419. Found: 194.1420.
Compound **4b**: Brown oil; ^{1}H NMR ($CDCl_3$): δ 7.89 (br s, 1H), 7.81–7.82 (m, 2H), 7.66 (dd, 1H), 7.42–7.56 (m, 3H), 7.03 (dd, 1H), 6.18 (dd, 1H), 2.26 (t, 2H, $J = 7.6$ Hz), 1.59–1.65 (m, 2H), 1.22–1.28 (m, 4H), 0.84 (t, 3H, $J = 6.8$ Hz); ^{13}C NMR ($CDCl_3$): δ 171.3, 138.8, 134.1, 129.6, 127.3, 127.1, 119.8, 109.8, 107.8, 36.9, 31.6, 25.5, 22.6, 14.1; MS (EI): m/z (%) = 320 ([M^+]), 277, 264, 238, 222 (100), 179, 157, 141, 126, 99, 81; HRMS (EI): m/z calcd for $C_{16}H_{20}N_2O_3S$: 320.1195. Found: 320.1190.
Compound **5a**: white solid; mp 88–89 °C; ^{1}H NMR ($CDCl_3$): δ 6.84 (m, 1H), 6.41 (t, 1H), 6.27 (br s, 1H), 5.88 (m, 1H), 3.59 (s, 3H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 153.6, 123.0, 120.0, 111.8, 100.7, 79.9, 36.7, 28.7; MS (EI): m/z (%) = 196 ([M^+]), 153, 140 (100), 123, 96, 81, 68, 57; HRMS (EI): m/z calcd for $C_{10}H_{16}O_2N_2$: 196.1212. Found: 196.1213.
Compound **5b**: white solid; mp 172–173 °C; ^{1}H NMR ($CDCl_3$): δ 7.86 (m, 2H), 7.58 (m, 1H), 7.48 (m, 2H), 7.35 (br s, 1H), 7.05 (t, 1H), 6.34 (m, 1H), 6.14 (m, 1H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 152.7, 139.1, 134.0, 129.5, 128.1, 127.8, 127.1, 120.1, 107.9, 80.8, 28.5; MS (EI): m/z (%) = 322 ([M^+]), 266 (100), 248, 222, 191, 158, 141, 125, 108, 77; HRMS (EI): m/z calcd for $C_{15}H_{18}O_4N_2S$: 322.0987. Found: 322.0988.
Compound **6a**: white solid; mp 99.5–101 °C; ^{1}H NMR (acetone-d_6): δ 7.11 (m, 1H), 6.61 (m, 1H), 6.48 (m, 1H), 3.68 (s, 3H), 2.77 (s, 4H); ^{13}C NMR (acetone-d_6): δ 176.0, 119.9, 117.9, 115.6, 103.3, 35.8, 28.1; Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.62; H, 5.66; N, 15.71.
Compound **6b**: white solid; mp 161–162 °C; ^{1}H NMR (acetone-d_6): δ 8.02 (m, 2H), 7.77–7.80 (m, 2H), 7.67 (m, 2H), 7.34 (dd, 1H), 6.99 (dd), 2.82 (s, 4H); ^{13}C NMR (acetone-d_6): δ 175.8, 138.9, 134.8, 130.1, 127.2, 123.1, 119.6, 112.8, 109.0, 28.2; Anal. Calcd for $C_{14}H_{12}N_2O_4S$: C, 55.26; H, 3.97; N, 9.16; S, 10.59. Found: C, 55.00; H, 4.16; N, 9.16; S, 10.59.
Compound **6c**: white solid; mp 166–167 °C (lit.[9] mp 163–164 °C); ^{1}H NMR (acetone-d_6): δ 6.72 (dd, 1H), 6.05 (dd, 1H), 5.93 (dd, 1H), 3.41 (s, 3H), 2.89 (s, 4H); ^{13}C NMR (acetone-d_6): δ 176.8, 121.5, 120.6, 106.7, 106.4, 32.4, 28.5.
Compound **7a**: yellow solid; mp 172.5–174 °C; ^{1}H NMR ($CDCl_3$): δ 7.73–7.91 (m, 4H), 7.07 (t, 1H), 6.63 (t, 1H), 6.53 (dd, 1H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 167.5,

134.3, 132.3, 123.6, 121.0, 116.4, 116.3, 104.5, 37.0; Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.80; H, 4.40; N, 12.33.

Compound **7b**: yellowish solid; mp 166–168 °C; ^{1}H NMR ($CDCl_3$): δ 7.89–7.94 (m, 4H), 7.85 (dd, 1H), 7.75–7.85 (m, 2H), 7.52–7.64 (m, 3H), 7.22 (dd, 1H), 7.03 (dd, 1H); ^{13}C NMR ($CDCl_3$): δ 166.5, 138.9, 134.7, 134.4, 131.9, 130.0, 127.3, 123.9, 122.1, 120.0, 112.9, 108.9; Anal. Calcd for $C_{18}H_{12}N_2O_4S$: C, 61.35; H, 3.43; N, 7.95; S, 9.10. Found: C, 61.56; H, 3.44; N, 8.03; S, 9.10.

9. De Rosa, M.; Nieto, G. C.; Gago, F. F. *J. Org. Chem.* **1989**, *54*, 5347–5350.