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Remarkable solvent effect in Barton–Zard pyrrole synthesis: application in an efficient one-step synthesis of pyrrole derivatives

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Abstract—A unique solvent effect encountered in the Barton–Zard pyrrole synthesis was exploited to develop an efficient synthesis of pyrrole-2-esters. The chemistry was extended to a one-pot synthesis of pyrrole-2,4-dicarboxylates.

As part of our ongoing industry-university collaborative research program directed towards developing efficient processes for pharmaceutical intermediates, we needed an expeditious entry into a diverse spectrum of 3,4-disubstituted pyrrole-2-esters (**1**).[1] The most advantageous and conceptually unique synthesis developed by Barton and Zard involves condensation of nitroolefins or β-acetoxy-nitro derivatives with α-isocyanoacetates in the presence of a non-ionic base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and guanidine (Table 1). Despite its attractiveness, the method is often complicated by poor yields and unwanted by-products.[2] A potential improvement has been reported by Varkade that uses proazaphosphotranes as a non-ionic superbase, however, that option for a base, while recyclable, must be prepared independently.[3] Herein we report a significant improvement in the Barton–Zard protocol by exploiting a unique and serendipitous solvent effect discovered in the nitroalkene–isocyanoacetate condensations.

Our improved process for the preparation of the pyrrole derivatives via the corresponding nitroolefins is outlined in Table 1. Nitroaldols were prepared in >90% yield by addition of nitroalkanes with aldehydes under surfactant-mediated solvent-free conditions recently developed in our laboratories.[4] Acylation of nitroalcohols in the presence of catalytic amount of amberlyst IR-120 ion-exchange resin (60 °C, 1 h) affords β-acetoxy-nitro derivatives (>95% yield) after filtration of the resin, followed by aqueous sodium carbonate wash. The crude product was carried forward into the Barton–Zard condensation without any further purification. Resin catalysis is superior in efficiency to the existing H_2SO_4-catalyzed acylation, which is cumbersome and low yielding. Furthermore, the product needed to be isolated by high vacuum distillation.[2d,5] Initial Barton–Zard condensations with ethyl isocyanoacetate and 4-acetoxy-3-nitrohexane as representative examples under established conditions (DBU, tetrahydrofuran (THF)-isopropanol), followed by aqueous work-up, produced the desired ethyl 3,4-diethylpyrrole-2-carboxylate in 38% yield, as reported earlier.[2d] Commercial THF is stabilized with trace amounts of the radical inhibitor, butylated hydroxytoluene (BHT), to prevent the formation and/or accumulation of THF–peroxide.[6] It occurred to us that BHT, being a radical inhibitor, could potentially interfere with the condensation process, thereby lowering the yield which proved to be the case.[7] Further investigations revealed that when THF–isopropanol was replaced with distilled THF or *tert*-butyl methyl ether (MTBE), neither of which contains a stabilizer, under otherwise identical conditions, the reaction was faster

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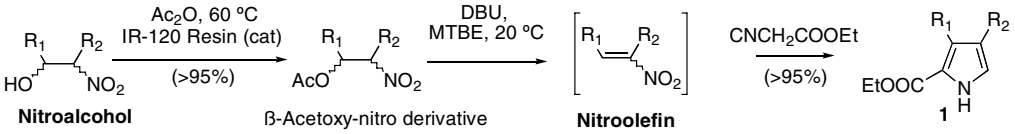
Table 1. Preparation of 3,4-dialkylpyrrole-2-carboxylates from nitroalcohols

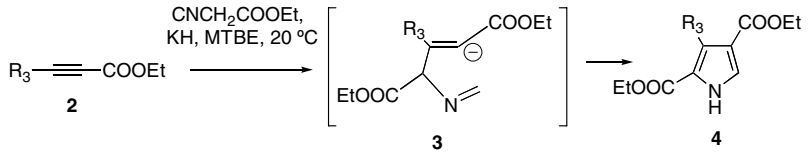


Entry	R_1	R_2	% Yield **1** (over 3 steps)
1	Me–	Me–	94
2	Et–	Et–	96
3	*n*-Pr–	*n*-Pr–	93
4	Et–	Me–	92
5	*n*-Pr–	Et–	93
6	*n*-Pr–	Me–	91

(cf. 2 h from 4 h), cleaner, and the product was obtained in near quantitative yield (98–100%). Control experiments conducted by adding trace amounts of BHT (100 ppm) to the above solvents again resulted in lower yield (ca. 45–50%) of the product 3,4-diethylpyrrole-2-carboxylate. We have not carried out detailed mechanistic studies and further work is warranted to gain better understanding in this process. However, replacing THF with MTBE in the process offers an additional advantage from commercial standpoint since MTBE, unlike distilled THF, can be stored for an indefinite period. A typical experimental procedure is as follows: under nitrogen, acetic anhydride (345.23 g, 3.38 mol) was added to a stirred mixture of 3-nitro-4-hexanol (1:1 diastereomeric mixture, 246.3 g, 1.7 mol) and Amberlite IR-(120) plus cation exchange resin (18.7 g) over a period of 1 h maintaining the batch-temperature between 55 and 65 °C. The reaction mixture was stirred at 60 °C for another hour. The mixture was cooled to room temperature, filtered, washed with an aqueous solution of sodium carbonate (1380 g of 2 M solution) and dried over molecular sieves to produce 311.8 g of 4-acetoxy-3-nitrohexane (yield 98%) and was carried to the next step without any further purification. In the next step, under nitrogen, DBU (498.3 g, 3.3 mol) was added to a stirred mixture of 4-acetoxy-3-nitrohexane (311.2 g, 1.7 mol), MTBE (363.8 g) and ethyl isocyanoacetate (187.1 g, 1.7 mol) over a period of 85 min maintaining a temperature of 10–20 °C. The reaction mixture was stirred at 20 °C for 2 h. To the stirred mixture was added MTBE (540 g), water (614 g), NaCl (43 g) and concd HCl (222 g) and the stirred mixture was warmed to 35–40 °C and allowed to settle. The MTBE solution containing the product was washed with saturated aqueous sodium bicarbonate solution (600 g). Evaporation of the solvent in vacuo produced 322.2 g (100% yield) of ethyl 3,4-diethylpyrrole-2-carboxylate.[8]

Exploiting the ability of acetylenic esters (**2**) to act as Michael acceptors coupled with the propensity of the initial adduct (**3**) to cyclize, the above isocyanoacetate condensation protocol was extended to an efficient, one-pot synthesis of pyrrole-2,4-dicarboxylate derivatives (**4**).[9] The optimal conditions to effect the transformation involves treating a mixture of the acetylenic esters (1 equiv) and ethyl isocyanoacetate (1 equiv) with KH (1.4 equiv) as an irreversible base in MTBE (10 mL/g of isocyanoacetate) for 4–20 h at 20 °C producing the pyrrole derivatives (**4**) in good to excellent yields (Table 2).[10] A typical experimental procedure is as follows: a suspension of potassium hydride (0.49 g, 12.4 mmol) in MTBE (10 mL) was added to a stirred mixture of ethyl 2-butynoate (1.0 g, 8.9 mmol) and ethyl isocyanoacetate (1 g, 8.9 mmol) in MTBE (10 mL) and the reaction mixture was stirred at 22 °C for 4 h.[11] The resulting mixture was acidified to pH 3 using 1 N HCl. The organic layer containing the produce was separated from the aqueous layer and the aqueous layer was extracted with two 25 mL portions of MTBE. The combined organic extracts were washed with brine solution (2×10 mL), dried over magnesium sulfate, and evaporation of the solvent in vacuo produced 1.6 g of

Table 2. Preparation of pyrrole-2,4-dicarboxylate derivatives from acetylenic esters



Entry	R_3	Time (h)	% Conversion[a] (% Yield **4**)
1	Me–	5	100 (78)
2	H–	4	100 (84)
3	Ph–	20	100 (81)
4	*n*-Pr–	5	100 (85)
5	Et–	5	100 (91)

[a] Conversion based on GC and HPLC.

3-methyl-1H-pyrrole-2,4-dicarboxylic acid diethyl ester (78%).

In summary, we have exploited a unique solvent effect encountered in Barton–Zard synthesis to develop an efficient and operationally simple process for 3,4-disubstituted pyrrole-2-esters. The isocyanoacetate condensation was also extended to a simple, one-step, conceptually distinct methodology for the synthesis of pyrrole-2,4-dicarboxylate derivatives.[12]

Selected NMR data. *3,4-Dimethyl-1H-pyrrole-2-carboxylic acid ethyl ester (entry 1, Table 1)*: ^{1}H NMR ($CDCl_3$, 600.1 MHz) δ 1.35 (t, 3H, $J = 7.2$ Hz), 2.01 (s, 3H,), 2.27 (s, 3H), 4.31 (q, 2H, $J = 7.2$ Hz), 6.67 (s, H_2); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ (9.8, 10.2), 14.4, 59.8, 119.1, 120.4, 120.3, 126.5, 162.0. *3,4-Diethyl-1H-pyrrole-2-carboxylic acid ethyl ester (entry 2, Table 1)*: ^{1}H NMR ($CDCl_3$, 600.1 MHz) δ 1.14 (t, 3H, $J = 7.4$ Hz), 1.19 (t, 3H, $J = 7.7$ Hz), 1.35 (t, 3H, $J = 7.2$ Hz), 2.45 (q, 2H, $J = 7.4$ Hz), 2.75 (q, 2H, $J = 7.3$ Hz), 4.31 (q, 2H, $J = 7.1$ Hz), 6.67 (d, $J = 2.6$ Hz); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ (14.5, 14.9, 15.5), (18.0, 18.1), 59.8, 118.7, 119.2, 126.8, 132.5, 161.6. *3,4-Dipropyl-1H-pyrrole-2-carboxylic acid ethyl ester (entry 3, Table 1)*: ^{1}H NMR ($CDCl_3$, 600.1 MHz) δ 0.96 (t, 6H, $J = 7.4$ Hz), 1.34 (t, 3H, $J = 7.1$ Hz), 1.55 (m, 4H), 2.39 (t, 2H, $J = 7.7$ Hz), 2.69 (t, 2H, $J = 7.7$ Hz), 4.30 (q, 2H, $J = 7.1$ Hz), 6.67 (d, $J = 2.8$ Hz); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ (14.0, 14.1, 14.3), (23.6, 24.3), (26.9, 26.9), 59.7, 118.8, 119.9, 125.2, 131.0, 161.7. *3-Ethyl-4-methyl-1H-pyrrole-2-carboxylic acid ethyl ester (entry 4, Table 1)*: ^{1}H NMR ($CDCl_3$, 600.1 MHz) δ 1.16 (t, 3H, $J = 7.2$ Hz), 1.35 (t, 3H, $J = 7.1$ Hz), 2.28 (s), 2.42 (q, 2H, $J = 7.4$ Hz), 4.31 (q, 2H, $J = 7.2$ Hz), 6.68 (d, $J = 2.8$ Hz); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 10.1 (14.4, 14.4), 18.1, 59.8, 119.1, 119.3, 127.3, 162.0. *4-Ethyl-3-propyl-1H-pyrrole-2-carboxylic acid ethyl ester (entry 5, Table 1)*: ^{1}H NMR ($CDCl_3$, 600.1 MHz) δ 0.95 (t, 3H, $J = 7.2$ Hz), 1.18 (t, 3H, $J = 7.6$ Hz), 1.35 (t, 3H, $J = 7.2$ Hz), 1.54 (m, 2H), 2.44 (q, 2H, $J = 7.4$ Hz), 2.70 (t, 2H, $J = 7.9$ Hz), 4.30 (q, 2H, $J = 7.2$ Hz), 6.68 (d, $J = 3.0$ Hz); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ (14.2, 14.4, 14.7), 18.0 (24.3, 26.9), 59.7, 118.9, 119.1, 127.2, 130.8, 161.7. *4-Methyl-3-propyl-1H-pyrrole-2-carboxylic acid ethyl ester (entry 6, Table 1)*: ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ 0.96 (t, 3H, $J = 7.4$ Hz), 1.37 (t, 3H, $J = 7.1$ Hz), 1.56 (m, 2H, $J = 7.5$ Hz), 2.04 (s, 3H), 2.72 (t, 2H, $J = 7.6$ Hz), 4.32 (q, 2H, $J = 7.1$ Hz), 6.67 (d, 1H, $J = 2.9$ Hz), 8.77 (br, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 10.0, 14.1, 14.5, 23.9, 26.9, 59.8, 119.0, 120.2, 120.2, 131.5, 161.6. *3-Methyl-1H-pyrrole-2,4-dicarboxylic acid diethyl ester (entry 1, Table 2)*: ^{1}H NMR (600.13 MHz, CD_3OD): δ 1.32 (t, $J = 7.2$ Hz, 3H), 1.35 (t, $J = 7.2$ Hz, 3H), 2.54 (s, 3H), 4.25 (q, $J = 7.2$ Hz, 2H), 4.31 (q, $J = 7.2$ Hz, 2H), 7.43 (s, 1H); ^{13}C NMR (100.6 MHz, CD_3OD): δ 11.5, 14.7 (×2), 60.7, 61.2, 117.1, 121.9, 128.7, 130.9, 162.7, 166.6. *1H-Pyrrole-2,4-dicarboxylic acid diethyl ester (entry 2, Table 2)*: ^{1}H NMR (600.13 MHz, CD_3OD): δ 1.24 (t, $J = 7.2$ Hz, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 4.18 (q, $J = 7.2$ Hz, 2H), 4.24 (q, $J = 7.2$ Hz, 2H), 7.04 (dd, $J = 2.0$, 2.0 Hz, 1H), 7.54 (dd, $J = 1.6$, 3.2, 1H), 12.51 (s, 1H, *NH*); ^{13}C NMR (100.6 MHz, CD_3OD): δ 14.2 (×2), 59.4, 60.1, 115.1, 116.6, 123.4, 127.8, 159.9, 163.2. *3-Phenyl-1H-pyrrole-2,4-dicarboxylic acid diethyl ester (entry 3, Table 2)*: ^{1}H NMR (600.13 MHz, DMSO-d_6): δ 1.00 (t, $J = 7.2$ Hz, 3H), 1.03 (t, $J = 7.2$ Hz, 3H), 3.99 (q, $J = 7.2$ Hz, 2H), 4.03 (q, $J = 7.2$ Hz, 2H), 7.21–7.28 (m, 5H), 7.56 (s, 1H), 12.44 (s, 1H, *NH*); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 13.7, 13.9, 59.0, 59.6, 115.5, 120.4, 126.5, 126.6 (×2), 127.6, 130.2 (×2), 131.5, 134.0, 160.0, 163.0. *3-Propyl-1H-pyrrole-2,4-dicarboxylic acid diethyl ester (entry 4, Table 2)*: ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 0.86 (t, $J = 7.5$ Hz, 3H), 1.24 (t, $J = 7.0$ Hz, 3H), 1.28 (t, $J = 7.0$ Hz, 3H), 1.48 (sextet, $J = 7.5$ Hz, 2H), 2.98 (t, $J = 7.5$ Hz, 2H), 4.17 (q, $J = 7.0$ Hz, 2H), 4.24 (q, $J = 7.0$ Hz, 2H), 7.42 (d, $J = 2.6$ Hz, 1H), 12.08 (s, 1H, *NH*); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 13.9, 14.2 (×2), 24.0, 26.4, 59.0, 59.6, 114.7, 120.0, 127.7, 133.4, 160.5, 163.6. *3-Ethyl-1H-pyrrole-2,4-dicarboxylic acid diethyl ester (entry 5, Table 2)*: ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 1.15 (t, $J = 7.1$ Hz, 3H), 1.18 (t, $J = 7.1$ Hz, 3H), 1.31 (t, $J = 7.5$ Hz, 3H), 2.99 (q, $J = 7.5$ Hz, 2H), 4.18 (q, $J = 7.1$ Hz, 2H), 4.28 (q, $J = 7.1$ Hz, 2H), 7.42 (d, $J = 2.6$ Hz, 1H), 12.04 (br s, 1H, *NH*); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 15.01, 14.1 (×2), 27.62, 59.9, 60.53, 115.3, 120.5, 128.54, 136.2, 161.3, 164.44.

Acknowledgements

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References and notes

1. The program was aimed at giving the BS/MS level students exposure to pharmaceutical process R&D in an academic setting. *Chemical and Engineering News*; Education Concentrate, **2001**, p 41.
2. (a) Barton, D. H. R.; Kervagore, J.; Zard, S. *Tetrahedron* **1990**, *21*, 7587–7598; (b) Barton, D. H. R.; Zard, S. *J. Chem. Soc., Chem. Commun.* **1985**, 1098–1100; (c) Ono, N.; Maruyama, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4470–4472; (d) Sessler, J. L.; Mozattari, A.; Johnson, M. *Org. Syn.* **1991**, *70*, 68–77.
3. Kisanga, P. B.; Verkade, J. G. *Tetrahedron* **2001**, *57*, 467–475, and references cited therein.
4. Bhattacharya, A.; Purohit, V. C.; Rinaldi, F. *Org. Proc. Res. Dev.* **2003**, *7*, 254–258.
5. Ono, N.; Maruyama, K. *Chem. Lett.* **1988**, 1511–1514.
6. Mahn, W. J. *Academic Laboratory Chemical Hazards Guidebook*; Nostrand Reinhold: New York, 1990.
7. For radical character in cycloaddition processes, see: Firestone, R. A. *Tetrahedron* **1977**, *33*, 3009–3039.
8. The reaction was scaled up to provide initial supply of materials.
9. For silver acetate catalyzed cycloaddition of isocyanoacetates, see: (a) Grigg, R.; Lansdell, M. I.; Thornton-Pett, M. *Tetrahedron* **1999**, *55*, 2025–2044, and references cited therein; (b) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *Tetrahedron Lett.* **2005**, *46*, 2563–2566.

10. Adding trace amounts (100 ppm) of BHT to MTBE in this case also resulted in low yield of the product.
11. KH, purchased as a suspension in mineral oil, was washed repeatedly with hexanes and dried under vacuum.
12. For all the known compounds, GCMS analysis (Shimadzu QP5050A) in the EI mode provided similarity index match of >90% compared to the authentic samples in the NIST-98 database.