2-Cyano-4-nitro-*N*,*N*-dimethylaniline (2a): NMR ($CDCl_3$) δ 3.37 (s, 6 H), 6.80 (d, J = 10 Hz, 1 H), 8.17 (d of d, J = 10 Hz, J = 2 Hz, 1 H), 8.40 (d, J = 2 Hz, 1 H); IR ($CHCl_3$) 2880, 2800, 2200, 1600, 1500, 1330, 910, 810 cm^{-1}; mass spectrum, m/e 191 (M^+).

2-Nitro-*N*,*N*-dimethylaniline (2b): NMR ($CDCl_3$) δ 2.72 (s, 6 H), 6.60–7.87 (m, 4 H); IR (thin film) 2880, 2770, 1600, 1500, 1340, 1290, 1155, 1040, 740 cm^{-1}; mass spectrum, m/e 166 (M^+).

3-Nitro-*N*,*N*-dimethylaniline (2c). The preparation of this compound was determined not to be synthetically useful and the percent yield (15%) was estimated by NMR analysis of the crude reaction mixture.

4-Nitro-*N*,*N*-dimethylaniline (2d): NMR ($CDCl_3$) δ 3.10 (s, 6 H), 6.60 (d, J = 10 Hz, 2 H), 8.15 (d, J = 10 Hz, 2 H); IR ($CHCl_3$) 1590, 1510, 1480, 1320, 1110 cm^{-1}; mass spectrum, m/e 166 (M^+).

2-Nitro-4-methyl-*N*,*N*-dimethylaniline (2e): NMR ($CDCl_3$) δ 2.28 (s, 3 H), 2.80 (s, 6 H), 6.92 (d, J = 8 Hz, 1 H), 7.22 (d of d, J = 8 Hz, J = 2 Hz, 1 H), 7.55 (d, J = 2 Hz, 1 H); IR (thin film) 1620, 1520, 1340, 1280, 910, 790 cm^{-1}.

2-Cyano-*N*,*N*-dimethylaniline (2f): NMR ($CDCl_3$) δ 2.90 (s, 6 H), 6.68–6.93 (m, 2 H), 7.20–7.56 (m, 2 H); IR (thin film) 2840, 2800, 2200, 1590, 1280, 1160, 1040, 750 cm^{-1}; mass spectrum, m/e 146 (M^+).

3-Cyano-*N*,*N*-dimethylaniline (2g). The preparation of this compound was determined not to be synthetically useful and the percent yield (trace) was estimated by NMR analysis of the crude reaction mixture.

4-Cyano-*N*,*N*-dimethylaniline (2h): NMR ($CDCl_3$) δ 3.07 (s, 6 H), 6.65 (d, J = 8 Hz, 2 H), 7.46 (d, J = 8 Hz, 2 H); IR ($CHCl_3$) 2860, 2810, 2200, 1600, 1360, 1060, 1000, 810 cm^{-1}; mass spectrum, m/e 146 (M^+).

4-(Trifluoromethyl)-*N*,*N*-dimethylaniline (2i): NMR ($CDCl_3$) δ 3.02 (s, 6 H), 6.74 (d, J = 9 Hz, 2 H), 7.50 (d, J = 9 Hz, 2 H); IR (Nujol) 1620, 1370, 1330, 1100, 1070, 820 cm^{-1}; mass spectrum, m/e 189 (M^+).

4-(Dimethylamino)phenyl 4-chlorophenyl sulfone (2j): NMR ($CDCl_3$) δ 3.00 (s, 6 H), 6.70 (d, J = 10 Hz, 2 H), 7.41 (d, J = 8 Hz, 2 H), 7.78 (d, J = 10 Hz, 2 H), 7.88 (d, J = 8 Hz, 2 H); IR (Nujol) 1600, 1320, 1150, 780 cm^{-1}; mass spectrum, m/e 295 (M^+).

4-Chloro-*N*,*N*-dimethylbenzamide (2k): NMR ($CDCl_3$) δ 3.06 (s, 6 H), 7.45 (br s, 4 H); IR (Nujol) 1625, 1100, 850, 760 cm^{-1}; mass spectrum, m/e 185 (M^+).

3,6-Dimethyl-2-(dimethylamino)pyrazine (2o): NMR ($CDCl_3$) δ 2.40 (s, 3 H), 2.50 (s, 3 H), 2.92 (s, 6 H), 7.90 (s, 1 H); IR (thin film) 1540, 1450, 1380, 1360, 1300, 1180, 1140, 770 cm^{-1}; mass spectrum, m/e 151 (M^+).

5-(Dimethylamino)-1-phenyltetrazole (2p): NMR ($CDCl_3$) δ 2.90 (s, 6 H), 7.60 (s, 5 H); IR (Nujol) 1580, 1565, 1080, 1060, 940, 775, 700 cm^{-1}; mass spectrum, m/e 189 (M^+).

2-(Dimethylamino)benzothiazole (2q): NMR ($CDCl_3$) δ 3.05 (s, 6 H), 6.88–7.78 (m, 4 H); IR (Nujol) 1580, 1550, 1530, 1440, 1400, 1390, 1280, 1120, 740, 720 cm^{-1}; mass spectrum, m/e 178 (M^+).

2-(Dimethylamino)-4-methylquinoline (2r): NMR ($CDCl_3$) δ 2.40 (s, 3 H), 3.04 (s, 6 H), 6.54 (s, 1 H), 7.00–7.91 (m, 4 H); IR (thin film) 1580, 1525, 1480, 1370, 1160, 820, 740 cm^{-1}; mass spectrum, m/e 186 (M^+).

2-(Dimethylamino)quinoline (2s): NMR ($CDCl_3$) δ 3.18 (s, 6 H), 6.78 (d, J = 9 Hz, 1 H), 7.00–7.90 (m, 5 H); IR (Nujol) 1675, 1630, 1560, 1400, 820, 765 cm^{-1}; mass spectrum, m/e 172 (M^+).

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Registry No. **1a**, 16588-02-6; **1b**, 88-73-3; **1c**, 121-73-3; **1d**, 100-00-5; **1e**, 89-60-1; **1f**, 873-32-5; **1g**, 766-84-7; **1h**, 623-03-0; **1i**, 98-56-6; **1j**, 80-07-9; **1k**, 74-11-3; **1l**, 134-85-0; **1m**, 99-91-2; **1n**, 89-98-5; **1o**, 95-89-6; **1p**, 14210-25-4; **1q**, 615-20-3; **1r**, 634-47-9; **1s**, 612-62-4; **2a**, 17417-10-6; **2b**, 610-17-3; **2c**, 619-31-8; **2d**, 100-23-2; **2e**, 52262-63-2; **2f**, 20925-24-0; **2h**, 1197-19-9; **2i**, 329-17-9; **2j**, 86471-08-1; **2k**, 14062-80-7; **2o**, 13134-42-4; **2p**, 57020-33-4; **2q**, 4074-74-2; **2r**, 20173-80-2; **2s**, 21154-18-7; HMPA, 680-31-9; 1-fluoro-2-nitrobenzene, 1493-27-2; 1,2-dinitrobenzene, 528-29-0; 1-bromo-2-nitrobenzene, 577-19-5; 1-iodo-2-nitrobenzene, 609-73-4.

Amidoalkylation Reactions of Anilines. A Direct Synthesis of Benzodiazepines

George A. Kraus* and Stephen Yue

Department of Chemistry, Iowa State University, Ames, Iowa 50011

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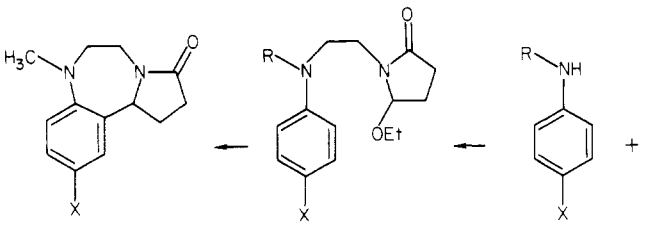
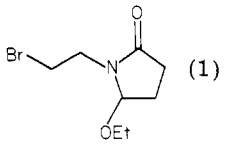
Intermolecular amidoalkylation reactions on aromatic rings constitute an effective strategy for the construction of heterocyclic compounds.[1] A variety of substituents, including nitro groups, can be accommodated on the aromatic ring. However, anilines or acetanilides react with acyl iminium ions to afford mixtures of products in only modest yields.[2] Moreover, the reactions with both *o*- and *p*-toluidine yield products wherein the position of substitution of the electrophile is directed by the methyl group.[3] This reactivity profile is due to deactivation by the iminium salt that is produced either by protonation in an acid-catalyzed reaction or by complexation with the Lewis acid catalyst.

As part of our study of the synthetic utility of the amidoalkylation reaction,[4] we examined the preparation of benzodiazepine **1** (see eq 1). In view of the aforementioned



1 **2a**, R = CH_3CO; **b**, R = CH_3 **3a**, R = CH_3CO; **b**, R = CH_3



(1)

4

X = H, Cl, OCH_3

problems, we decided to effect an intramolecular amidoalkylation reaction. Although a few examples of intramolecular amidoalkylation reactions on acetanilide analogues have been reported,[5] we are not aware of any reactions using anilines. We report herein an unexpectedly

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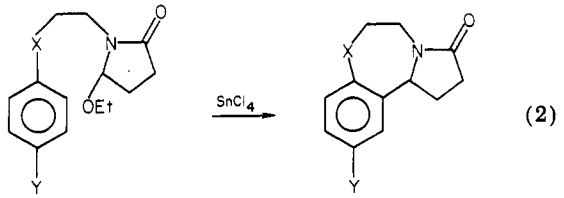
(2) Ota, M.; Kaneyuki, H.; Matsui, K. *J. Chem. Soc. Jpn., Pure Chem. Sect.* **1960**, 81, 1849. Haworth, R. D.; MacGillivray, R.; Peacock, D. H. *J. Chem. Soc.* **1950**, 1493.
(3) Buc, S. R. U.S. Patent 2 593 840; *Chem. Abstr.* **1952**, *46*, 6844. Ota, M.; Kaneyuki, H.; Matsui, K. *J. Chem. Soc. Jpn., Pure Chem. Sect.* **1960**, *81*, 1849.
(4) Kraus, G. A.; Neuenschwander, K. *Tetrahedron Lett.* **1980**, *21*, 3841. Kraus, G. A.; Neuenschwander, K. *J. Chem. Commun.* **1982**, 134.
(5) Hoover, F. W.; Stevenson, H. B.; Rothrock, H. S. *J. Org. Chem.* **1963**, *28*, 1825.

facile synthesis of the benzodiazepine skeleton which occurred *during alkylation of the aniline*. The reaction is apparently *catalyzed by the amine hydrobromide* produced in the reaction of **3b** with bromo lactam **4**.[6]

The intermolecular amidoalkylation reaction of **4** with either *N*-methylacetamide or *N*-methylaniline with Lewis acids ($AlCl_3$ or $SnCl_4$, 0 °C, CH_2Cl_2) led only to the destruction of **4**. Heating the bromo lactam **4** with the sodium salt of acetanilide in DMF failed to produce **2a**. The only isolable product was 5-ethoxy-*N*-vinylpyrrolidinone. Treatment of 2 equiv of *N*-methylaniline with 1 equiv of **4** at 70 °C for 12 h provided benzodiazepine **1** in 65% yield after silica gel chromatography. In the same manner benzodiazepines **1** (X = Cl) and **1** (X = OCH_3) were prepared in 76% and 66% yields, respectively. The structure of **1** (X = Cl) was confirmed by X-ray crystallography.[7] Surprisingly, neither aniline nor *p*-methoxyaniline yielded a benzodiazepine. The reaction with aniline afforded a mixture of products. The main product after chromatography was one wherein aniline had displaced both the bromide and the ethoxyl group. Efforts to transform this product into a benzodiazepine by way of further heating or Lewis acid catalysis were unsuccessful. Aromatic ether **5** and sulfide **6** also participate in an amidoalkylation reaction (eq 2). Cyclization is best effected with $SnCl_4$ in



(2)

5, X = O; Y = OCH_3
6, X = S; Y = H

7, X = O; Y = OCH_3
8, X = S; Y = H

methylene chloride at ambient temperature. The heterocycles **7** and **8** are produced in 26% and 60% yields, respectively.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Dichloromethane was distilled from P_2O_5. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM360 60-MHz instrument. Carbon-13 NMR spectra were determined on a JOEL FX-90Q Fourier transform instrument. Both proton and carbon chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. High-resolution mass spectra were recorded on an AEI MS-902 high-resolution mass spectrometer.

General Procedure for the Formation of 1. Lactam **4** (1 equiv) and 2 equiv of the aniline were heated at 70 °C without solvent. For the preparation of **1** (X = H), **1** (X = Cl), and **1** (X = OCH_3) the reactions were heated for 12, 14, and 2 h, respectively. The crude product was purified by chromatography on silica gel.

1 (X = H): mp 88.5–89.5 °C; NMR ($CDCl_3$) δ 2.15–2.55 (m, 4 H), 2.85 (s, 3 H), 2.75–3.2 (m, 2 H), 3.3–3.65 (m, 2 H), 4.90 (br t, *J* = 6 Hz, 1 H), 6.75–7.30 (m, 4 H); IR (Nujol) 1675 cm^{-1}; mass spectrum, *m/e* calcd for $C_{13}H_{16}N_2O$ (m^+) 216.126 27, found 216.126 19.

1 (X = Cl): m 81–83 °C; ^1H NMR ($CDCl_3$) δ 2.15–2.50 (m, 4 H), 2.85 (s, 3 H), 2.6–3.23 (m, 2 H), 3.23–3.60 (m, 2 H), 4.5–4.9 (m, 1 H), 6.83 (dd, *J* = 2, 5 Hz, 1 H), 7.0–7.3 (m, 2 H[; ^{13}C NMR ($CDCl_3$) δ 24.71, 30.50, 39.60, 41.68, 54.63, 58.98, 119.07, 125.83, 126.48, 128.24, 131.95, 149.92, 173.31; mass spectrum, *m/e* calc for $C_{14}H_{18}N_2O_2$ (m^+) 246.136 83, found 246.136 37.

5-Ethoxy-1-[2-(4-methoxyphenoxy)ethyl]pyrrolidin-2-one (5). To a suspension of sodium hydride (0.195 g, 4.07 mmol), from which the mineral oil had been removed, in 8 mL of the dry dimethylformamide (DMF) was added *p*-methoxyphenol (0.505 g, 407 mmol). After the evolution of hydrogen was complete, a solution of **4** (0.800 g, 3.39 mmol) in 2 mL DMF was added, and the solution was stirred at room temperature for 18 h. The DMF was removed in vacuo. Ether and 1 N NaOH were added. The aqueous layer was extracted with ether. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was chromatographed on silica gel with 2:1 ethyl acetate/hexane to afford 0.390 g (41%) of **5**: ^1H NMR ($CDCl_3$) δ 1.20 (t, *J* = 7 Hz, 3 H), 1.80–2.67 (m, 4 H), 3.54 (q, *J* = 7 Hz, 2 H), 3.76 (s, 3 H), 3.97–4.22 (m, 2 H), 5.03–5.20 (m, 1 H), 6.83 (s, 4 H); IR (film) 1670, 1495 cm^{-1}.

5-Ethoxy-1-[2-(phenylthio)ethyl]pyrrolidin-2-one (6). Sodium thiophenoxide was prepared from sodium hydride (0.214 g, 4.45 mmol) and thiophenol (0.489 g, 4.45 mmol) in 12 mL of DMF. A solution of **4** (1.00 g, 4.23 mmol) in 2 mL of DMF was added, and the solution was stirred at room temperature for 1 h. After removal of the DMF in vacuo, a 1 H NaOH solution was added. The aqueous layer was extracted with ether. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was chromatographed on silica gel with 2:1 ethyl acetate/hexane to afford 0.822 g (73%) of **6**: ^1H NMR ($CDCl_3$) δ 1.18 (t, *J* = 6 Hz, 3 H), 1.67–2.60 (m, 4 H), 2.97–3.90 (m, 6 H), 4.82–5.03 (m, 1 H), 6.97–7.4 (m, 5 H); IR (film) 1685, 1450 cm^{-1}.

General Procedure for the Formation of 7 and 8. To a 0.2 M solution of lactam **5** or **6** in dichloromethane was added one equivalent of $SnCl_4$. The solution was stirred at room temperatue for 24 h. The solution was then diluted with dichloromethane, washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was chromatographed on silica gel to provide the pure product.

7: 26% yield; NMR ($CDCl_3$) δ 2.10–2.50 (m, 4 H), 3.40–4.50 (m, 4 H), 3.75 (s, 3 H), 4.70–5.00 (m, 1 H), 6.60–7.10 (m, 3 H); IR (Nujol) 1675, 1495, 1205, 1060, 1030 cm^{-1}; mass spectrum, *m/e* calcd for $C_{13}H_{15}NO_3$ (m^+) 233.105 20, found 233.105 77.

8: 60% yield; NMR ($CDCl_3$) δ 2.20–3.70 (m, 7 H), 4.25 (dt, *J* = 4,13 Hz, 1 H), 5.00–5.30 (m, 1 H), 7.10–7.45 (m, 3 H), 7.45–7.73 (m, 1 H); IR (Nujol) 1690, 1445, 1420, 750, 725 cm^{-1}; mass spectrum, *m/e* calcd for $C_{12}H_{13}NOS$ (m^+) 219.071 79, for 219.071 66.

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Registry No. **1** (X = H), 86436-51-3; **1** (X = Cl), 86436-52-4; **1** (X = OCH_3), 86436-53-5; **3b** (X = H), 100-61-8; **3b** (X = Cl), 932-96-7; **3b** (X = OCH_3), 5961-59-1; **4**, 82259-06-1; **5**, 86436-54-6; **6**, 86436-55-7; **7**, 86436-56-8; **8**, 86436-57-9; $SnCl_4$, 7646-78-8; *p*-methoxyphenol, 150-76-5; thiophenol, 108-98-5.

(6) The lactam (see ref 4) is produced by the method of Speckamp and co-workers: Speckamp, W. M.; Schoemaker, H. E. *Tetrahedron Lett.* **1978**, 4841.

(7) Significant distances and angles are consistent with expected values within a standard deviation. Unit cell dimensions: a = 8.098 Å, b = 12.047 Å, c = 6.264, α = 96.290°, β = 80.730°, γ = 89.840°; space group, $P\bar{1}$; R = 0.085.