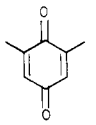
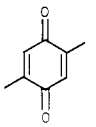
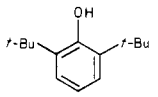
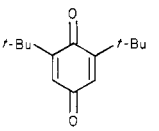
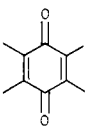
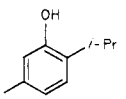
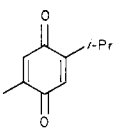
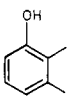
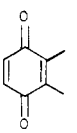
Table I

| substrate | product | isolated yield,[a] % |
|---|---|---|
|  1 |  2 | 84 |
|  3 |  4 | 57 |
|  5 |  6 | 52 |
|  7 |  8 | 59 |
|  9 |  10 | 46 |
|  11 |  12 | 30 |

[a] All compounds were characterized by comparison of their physical and spectral properties with literature values.

we have adopted is a modified two-phase Jones oxidation procedure (ether/aqueous chromic acid) which enables us to routinely prepare 30–60 g of alkyl quinones in a one-pot reaction. Although the yields obtained range from modest to very good (see Table I), the process itself is quite simple to carry out and far less expensive than the previously discussed procedures. The bonus associated with this method is that quinones of reasonably high purity are virtually always obtained by simple extraction procedures; i.e., *chromatographic purifications are rarely required.*

This method does not work well with 2-methoxyphenol, presumably due to competitive *o*-quinone formation and subsequent polymerization.

## Experimental Section

**General Methods.** Melting points were determined with a Thomas-Hoover Uni-Melt capillary melting point apparatus. Infrared spectra were determined with Perkin-Elmer Model 257, 457, and 727 spectrophotometers. Nuclear magnetic resonance spectra were recorded by using Varian T-60, EM-360, and EM-390 spectrometers, and chemical shifts are reported in parts per million ($\delta$) relative to an internal tetramethylsilane reference. Nominal mass spectra were recorded by using a Finnigan 4000 GC/MS system and a Varian Associates M-66 spectrometer.

**General Procedure for the Conversion of Phenols to Quinones.** This procedure will be illustrated by using 2,6-dimethylphenol. The other phenol oxidations listed in Table I can be accomplished by using exactly the same procedure. 2,6-Dimethylphenol (30 g, 0.25 mol) was dissolved in 350 mL of ether and placed in a 2-L round-bottomed flask fitted with an overhead stirrer and an addition funnel. The reaction vessel was immersed in an ice-water bath, and the addition funnel was charged with Jones reagent, produced from $Na_2Cr_2O_7{\cdot}2H_2O$ (165 g, 0.5534 mol), 105 mL of 96% $H_2SO_4$, and 235 mL of $H_2O$. Addition required approximately 2.5 h. After the addition, the reaction mixture was allowed to stir for at least 24 h. The reaction mixture was washed with ether (4 × 200 mL), and the combined ether extracts were washed with saturated $NaHCO_3$ solution (2 × 100 mL) and with water (200 mL). The ether layer was dried over $MgSO_4$ and concentrated in vacuo to yield 2,6-dimethylbenzoquinone: 28.1 g (84%); mp 44–46 °C (lit. mp 45–47 °C); $^1H$ NMR ($CDCl_3$) 6.55 (s, 2), 2.00 (s, 6); mass spectrum, *m/e* 136.

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**Registry No.** 1, 576-26-1; 2, 527-61-7; 3, 95-87-4; 4, 137-18-8; 5, 128-39-2; 6, 719-22-2; 7, 527-35-5; 8, 527-17-3; 9, 89-83-8; 10, 490-91-5; 11, 526-75-0; 12, 526-86-3; 2-methoxyphenol, 90-05-1.

# Reaction of Activated Aryl and Heteroaryl Halides with Hexamethylphosphoramide[1]

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*Received October 25, 1982*

The use of hexamethylphosphoramide (HMPA) to effect N,N-dimethylation of an aromatic substrate via aromatic nucleophilic substitution has captured the interest of several groups of workers.[1-4] For example, the reaction of HMPA with substituted nitro-[1-3] and cyanobenzenes[1,3] and the reaction of HMPA with several activated halo-heteroaryl compounds[4] have been reported. Because of the synthetic usefulness demonstrated by these various reports, we have extended our investigation[1] of the aromatic nucleophilic substitution reaction of HMPA and report here our findings of the effect of various aryl and heteroaryl activating groups as well as the effect of various leaving groups. The activated aryl and heteroaryl substrates that we have studied to date are reported in Tables I and II, respectively.

As indicated in entries **a**–**h** in Table I, the nitro and cyano groups are very effective in activating the benzene ring toward reaction with HMPA. Ortho or para substitution appears to be necessary to make such transformations synthetically useful. Electron-releasing groups appear to deactivate this reaction as exemplified by the higher reaction temperature and longer reaction time required for the conversion of 1-chloro-4-methyl-2-nitrobenzene (entry **e**, Table I) to 2-nitro-4-methyl-*N*,*N*-dimethylaniline.

Another group that effects such a transformation is the trifluoromethyl (entry **i**, Table I), albeit in low yield. The reaction is, however, very clean and the starting material can be easily separated from the product by acid extrac-

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(2) Ishikawa, N.; Kuroda, K. *Chem. Abstr.* **1968**, *68*, 114192y. Ishikawa, N. *Ibid.* **1971**, *75*, 63381u.
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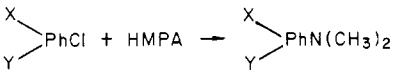
0022-3263/83/1948-2933$01.50/0 

Table I. Reaction of Aryl Halides with HMPA[a]




1a-n 2a-n

| entry | X | Y | rctn temp, °C | time, h | % yield | bp or mp, °C (ref) |
|---|---|---|---|---|---|---|
| a | 2-CN | 4-$NO_2$ | 150 | 24 | 94 | 110-111 (110) (13) |
| b | 2-$NO_2$ | H | 150 | 20 | 68 | 78-92 (0.08 mm) [85 (0.08 mm)] (14) |
| c | 3-$NO_2$ | H | 200 | 5 | 15 | |
| d | 4-$NO_2$ | H | 150 | 24 | 84 | 168-170 (165) (15) |
| e | 2-$NO_2$ | 4-$CH_3$ | 200 | 48 | 62 | 85-88 (0.08 mm) [85 (0.08 mm)] (16) |
| f | 2-CN | H | 200 | 48 | 64 | 58-65 (0.06 mm) [54 (0.06 mm)] (17) |
| g | 3-CN | H | 180 | 48 | trace | |
| h | 4-CN | H | 200 | 48 | 84 | 80-81 (76) (18) |
| i | 4-$CF_3$ | H | 200 | 40 | 17 | 73-74 (70) (19) |
| j | 4-(4-ClPh$SO_2$) | H | 200 | 12 | 63 | 179-180 |
| k | 4-COOH | H | 200 | 6 | 73 | 59-60 (59) (20) |
| l | 4-COPh | H | 150 | 40 | | |
| m | 4-$COCH_3$ | H | 150 | 15 | | |
| n | 2-CHO | H | 150 | 15 | | |

[a] All of the product compounds were purified by distillation or recrystallization and were found to be greater than 90% pure as determined by thin-layer chromatography on silica gel 7GF with chloroform as eluant ($R_f$ values between 0.2 and 0.8).

tion. Bis(*p*-chlorophenyl) sulfone (entry **j**, Table I) also reacts with HMPA with replacement of a single chlorine atom. Apparently, the *p*-dimethylamino group deactivates the sulfone from further reaction, which further substantiates the effect of lower reactivity for compounds containing an electron releasing group.

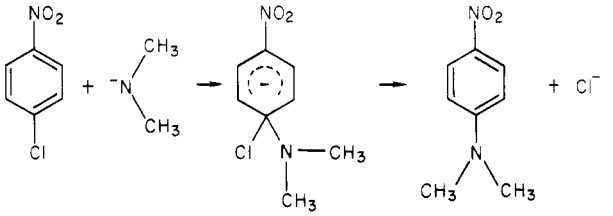
*p*-Chlorobenzoic acid (entry **k**, Table I) reacts with HMPA to produce *p*-chloro-*N*,*N*-dimethylbenzamide in good yield. The conversion of carboxylic acids to amides via HMPA has been previously reported[5] in the literature. This experiment did, however, point out that acid amides were not suitable activating groups for such a reaction. Diaryl ketones, aryl alkyl ketones, and aromatic aldehydes (entries **l**–**n**, Table I) were found to be unsuitable substrates for this reaction, and in these cases a complex mixture of products was formed. This is consistent with the findings of Monson[6] who has shown that acetophenones react with HMPA to give 1,3,5-triphenylbenzenes in low yield.

A variety of chlorinated heterocycles (Table II) have been studied and in all cases replacement of the chloro group by the dimethylamino group was observed. Pyrazines, tetrazoles, thiazoles, and quinolines were sufficiently reactive to produce a clean substitution. 2-Chloro-4-methylquinoline (entry **r**, Table II) is an interesting example in light of the previously mentioned deactivating effect of a methyl group. Apparently, the deactivating group as well as the activating group has to be either ortho or para to the leaving group to exert an effect on the reactivity of the substrate.

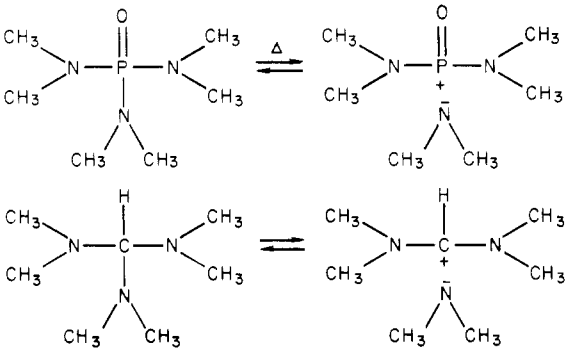
To further investigate the nature of this transformation, we have also studied the effect of various leaving groups (Table III).

The following relative order of reactivity of the leaving group was observed: F, $NO_2$ >> Cl, Br > I. This same order of reactivity has been observed by other groups[7] for the reaction of amines with 1-halo-2,4-dinitrobenzenes. The ability to displace a nitro group with a dimethylamino group is particularly interesting. Kornblum[8] has previously shown that activated nitrobenzenes can undergo similar substitution reactions with anionic nucleophiles.

Scheme I




Scheme II




In all of the reactions studied, irrespective of the nature of the leaving group or activating group, there was no indication that regioisomeric substitution products were being formed. Consequently, on the basis of (1) the nature and positional requirements of the activating groups and deactivating groups, (2) the relative reactivity of the leaving groups, and (3) the lack of regioisomeric products, an SnAr mechanism[9] is implicated (Scheme I).

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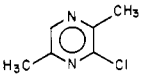
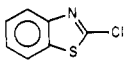
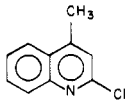
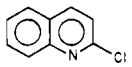
Table II. Reaction of Heteroaryl Halides with HMPA[a]

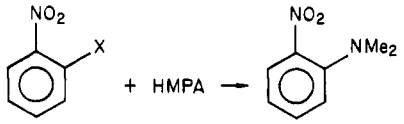
RCl + HMPA → $RN(CH_3)_2$

1o-s 2o-s

| entry | RCl | rctn temp, °C | time, h | % yield | bp or mp, °C (ref) |
|---|---|---|---|---|---|
| o |  | 150 | 15 | 49 | 52-53 (1.0 mm) [50 (1 mm)] (21) |
| p |  | 150 | 15 | 50 | 109-111 (110) (22) |
| q |  | 150 | 15 | 64 | 85-88 (87) (23) |
| r |  | 150 | 15 | 89 | 95-97 (0.4 mm) [100 (0.01 mm)] (24) |
| s |  | 150 | 19 | 76 | 78-81 (71) (24) |

[a] All of the product compounds were purified by distillation or recrystallization and were found to be greater than 90% pure as determined by thin-layer chromatography on silica gel 7GF with chloroform as eluant ($R_f$ values between 0.2 and 0.8).

Table III. Reaction of Ortho-Substituted Nitrobenzenes with HMPA (Leaving Group Effect)



| X | temp, °C | rctn time, h | % conv[a] | % yield[b] | total time, h |
|---|---|---|---|---|---|
| F | 150 | 5 | 83 (84) | 83 | 15 |
| $NO_2$ | 150 | 5 | 86 (93) | 66 | 23 |
| Cl | 150 | 5 | 40 (41) | 68 | 20 |
| Br | 150 | 5 | 46 (44) | 63 | 36 |
| I | 150 | 5 | 32 | 78 | 36 |

[a] The percent conversion was determined by working up the reactions after heating 5 h at 150 °C. The values not in parentheses are from NMR analysis and the values in parentheses are from gas chromatographic analysis on a 6 ft × 1/8 in column containing 3% SE-30 on chromosorb W. In the case of *o*-iodonitrobenzene a GC analysis is not reported due to the similar retention times of the substrate and product. The difference in the GC and NMR values for the *o*-dinitrobenzene substrate is attributed to small amounts of byproducts in this reaction mixture that were not taken into account in the GC analysis. [b] These are crude yields and all reaction products gave NMR and IR spectra identical with product **2b** in Table I (*o*-nitro-*N*,*N*-dimethylaniline).

On the basis of this postulate, we believe that HMPA may have some ionic character at elevated temperatures that in principle is similar to the behavior of the trisaminomethanes[10] (Scheme II).

There may, however, be other equally viable mechanisms to explain such a process.

In conclusion, HMPA offers a clean, simple, and efficient method for the conversion of activated aryl or heteroaryl halides to the corresponding dimethylamino derivative.

When conducting reactions in HMPA at elevated temperatures, one should, therefore, be aware of potential reactions with the solvent.

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## Experimental Section[11]

The following procedure is typical of the experimental conditions used for the reaction of activated halo compounds with HMPA.

**General Procedure.** The activated halo compound (0.025 mol) is placed in a three-necked flask equipped with a condenser, thermometer, and magnetic stirrer. HMPA (25 mL) is added and the system flushed with nitrogen before the temperature is raised to 150 °C[12] and held there for 24 h. The mixture is then cooled to room temperature and poured into 100 mL of water. This mixture is extracted with ether (3 × 75 mL), and the combined ether extracts are washed with water (2 × 100 mL) and dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated in vacuo. This material can be further purified, if desired, by dissolving the product in ether (50 mL) and extracting the ether with 18% (w/w) aqueous hydrochloric acid (3 × 20 mL). The hydrochloric acid phase is separated and the pH is adjusted to 11 by addition of 10% aqueous sodium hydroxide with cooling. The resulting material is isolated by filtration or extraction and dried in vacuo.

(11) Infrared spectra were recorded on a Perkin-Elmer Model 457 infrared spectrophotometer or a Nicolet MX-S FT-IR spectrophotometer. Samples were run as thin films, Nujol mulls, or $CHCl_3$ or $CCl_4$ solutions. NMR spectra were obtained in $CCl_4$, $CDCl_3$, or $Me_2SO$-$d_6$ solutions [$(CH_3)_4Si$ as internal standard] at 60 Mz with a Varian EM-360A spectrometer. All boiling points and melting points are uncorrected and melting points were recorded on a Fisher-Johns melting point apparatus. Preliminary results of an inhalation toxicity study of HMPA released by DuPont showed the development of nasal tumors in rats exposed to 400 and 4000 ppb of HMPA daily after 8 months. Although there is no data available on the toxic effects of HMPA in humans, it is recommended that HMPA be handled with the precautions appropriate for a potential carcinogen.

(12) It is important not to let the reaction temperature exceed 200 °C for an extended length of time since an emulsion forms under these conditions that is very difficult to workup.

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(15) Remington, W. *J. Am. Chem. Soc.* **1945**, *67*, 1838.
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(22) Viehe, H.; George, P. *Chimia* **1975**, *29*, 209.
(23) Viehe, H. *Angew. Chem.* **1973**, 446.
(24) Pedersen, E.; Lawesson, S. *Tetrahedron* **1974**, *30*, 875.

**2-Cyano-4-nitro-*N*,*N*-dimethylaniline (2a)**: NMR ($CDCl_3$) $\delta$ 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 ($CDCl_3$) $\delta$ 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 ($CDCl_3$) $\delta$ 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 ($CDCl_3$) $\delta$ 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 ($CDCl_3$) $\delta$ 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 ($CDCl_3$) $\delta$ 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 ($CDCl_3$) $\delta$ 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 ($CDCl_3$) $\delta$ 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 ($CDCl_3$) $\delta$ 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 ($CDCl_3$) $\delta$ 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 ($CDCl_3$) $\delta$ 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 ($CDCl_3$) $\delta$ 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 ($CDCl_3$) $\delta$ 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 ($CDCl_3$) $\delta$ 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

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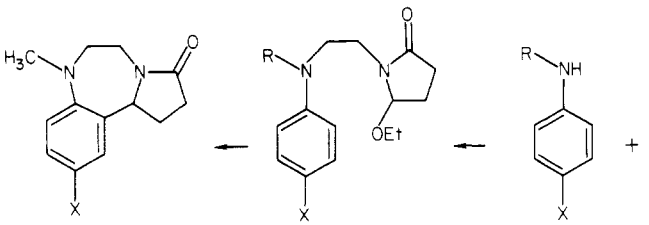
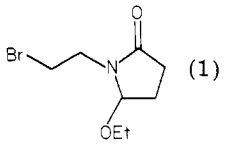
Intermolecular amidoalkylation reactions on aromatic rings constitute an effective strategy for the construction of heterocyclic compounds.[1] A variety of substituents, including nitro groups, can be accommodated on the aromatic ring. However, anilines or acetanilides react with acyl iminium ions to 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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