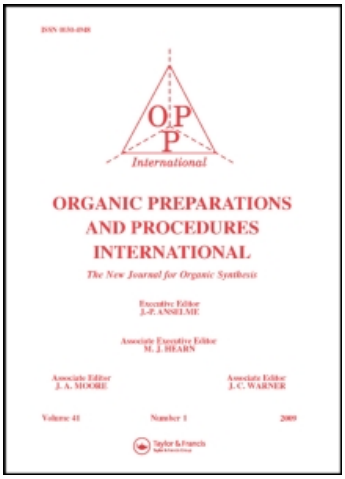

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N-(NITROPHENYL) BENZAMIDE AND BENZENESULFONAMIDE DERIVATIVES BY NUCLEOPHILIC AROMATIC SUBSTITUTION

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N-(NITROPHENYL) BENZAMIDE AND BENZENESULFONAMIDE DERIVATIVES BY NUCLEOPHILIC AROMATIC SUBSTITUTION

Submitted by (8/09/04)

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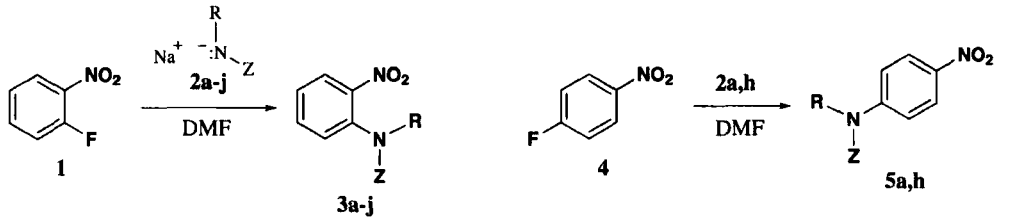
One of our current projects required a series of *N*-(3-butenyl)-*N*-(2-nitrophenyl) amide derivatives as precursors for a new synthesis of 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines.[1] Two other approaches to these targets—alkylation of 2-nitroacetanilide with a homoallylic iodide and nucleophilic aromatic substitution of 2-fluoro-1-nitrobenzene with a 3-butenylamine derivative followed by *N*-acylation—failed to give adequate yields of the desired products. We, therefore, sought a direct approach whereby we could install the entire pre-fabricated amide side chain onto the aromatic ring by reaction of an *N*-(3-butenyl)benzamide anion with 2-fluoro-1-nitrobenzene. Buchwald and co-workers[2] have recently reported a general method for the amidation of aromatic halides by primary and secondary carboxamides using a copper(I) iodide/*N*,*N*'-dimethyl-1,2-diamine catalyst system. Beyond this, however, there exist relatively few protocols for substituting amides onto aromatic rings.[3] Though sulfonamides have been added to activated aromatic substrates by nucleophilic aromatic substitution,[4] this method has not been extended to benzamides since *N*-(2-nitrophenyl)benzamides are available by nitration of *N*-phenylbenzamides[5] or by *N*-benzoylation of 2-nitroanilines.[6] The syntheses of our required targets, specifically **1e** and **1f**, do not readily lend themselves to these earlier approaches. Thus, we have explored the nucleophilic substitution of 2- and 4-fluoro-1-nitrobenzene by primary and secondary benzamides and primary benzenesulfonamides, and report here a procedure for accomplishing this transformation.

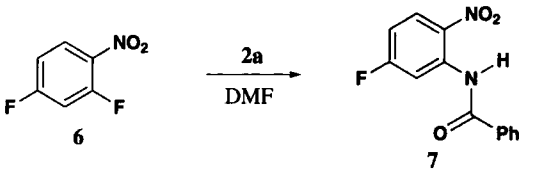
The results of our study are summarized in the *Scheme*. The amide derivatives were deprotonated at 40°C for 2 hours using 1.1 equivalents of NaH in anhydrous DMF. Best results



a) Z = C_6H_5CO, R = H; b) Z = 4-$CH_3C_6H_4CO$, R = H; c) Z = 4-ClC_6H_4CO, R. = H; d) Z = C_6H_5CO, R = CH_3; e) Z = C_6H_5CO, R = $CH_2CH_2CH{=}CH_2$; f) Z = C_6H_5CO, R = $CH_2CH_2C(CH_3){=}CH_2$; g) Z = $C_6H_5SO_2$, R = H; h) Z = 4-$CH_3C_6H_4SO_2$, R = H; i) Z, R = phthalimidoyl; j) Z, R = succinimidoyl

in the substitution reaction were achieved using a 2:1 mole ratio of the amide to the aromatic substrate and reaction times of 36-48 hours. A number of the amide anions were insoluble in DMF, but these eventually redissolved once the fluoronitrobenzene was added. Following reaction, workup with NH_4Cl and purification by crystallization or flash column chromatography gave the substitution products in pure form; if necessary, the excess amide could be recovered at this stage.

The reaction proceeded in reasonable yields for primary benzamides (60-75%) and secondary benzamides (50-60%) reacting with 2-fluoro-1-nitrobenzene. Additions to 4-fluoro-1-nitrobenzene, however, were less reliable as attempts to add phthalimide to this system failed. A previous report[7] using potassium ethylthiolate on 2,4-dihalobenzamides demonstrated that nucleophilic aromatic substitution occurs more readily at C2 than at C4. Indeed, when we reacted anion **2a** with 2,4-difluoro-1-nitrobenzene (**6**) under our standard conditions, the exclusive amide substitution product was **7** resulting from addition-elimination at C2.



6 7

Finally, we attempted to extend this reaction to add non-aromatic amides to 2-fluoro-1-nitrobenzene. In the case of acetamide, the reaction proceeded, but yields were lower (30-40%) and there were more side products generated—2-nitrophenol from water present in the amide and *N*,*N*-dimethyl-2-nitroaniline from dimethylamine produced on extended heating of DMF. More hindered aliphatic amides, such as *N*-methylacetamide, gave negligible yields.

In conclusion, we have optimized a procedure for the nucleophilic aromatic substitution of 2- and 4-fluoronitrobenzene by benzamide and benzenesulfonamide derivatives. It uses readily available, inexpensive reagents and gives good yields of the addition products. Purification can be readily accomplished using crystallization or flash chromatography. The current procedure complements earlier approaches for the synthesis of *N*-(nitrophenyl)benzamides and allows for the preparation of several less accessible targets.

EXPERIMENTAL SECTION

DMF (EM Science, GR grade), from a freshly opened bottle, was dried over 4Å molecular sieves under nitrogen and transferred by syringe into each reaction. All reactions were performed under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates. Preparative separations were carried out using flash column chromatography[8] on silica gel (grade 62, 60-200 mesh) mixed with UV active phosphor (Sorbent Technologies UV-5); band elution was monitored using a hand-held UV lamp. Melting points are uncorrected. IR spectra were run as thin films on NaCl disks and were referenced to polystyrene. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, and referenced to internal TMS; coupling constants (J) are given in Hz.

Benzamide and succinimide were recrystallized from 1,2-dichloroethane, and phthalimide was recrystallized from ethanol prior to use.[9] Other commercial amides were used as received. Amide precursors to **2e** and **2f** were prepared by Schotten-Baumann benzoylation of 3-buten-1-amine and 3-methyl-3-buten-1-amine using the procedure of Dewar and co-workers.[10]

Typical Procedure for Nucleophilic Aromatic Substitution of 2- and 4-Fluoro-1-nitrobenzene by Aromatic Amides. *N*-(2-Nitrophenyl)benzamide (3a).- In a 250 mL, three-necked round-bottomed flask equipped with an addition funnel, a magnetic stir bar and a condenser, 0.44 g of 60% NaH in mineral oil (11.0 mmol) was washed with hexane (3x) and suspended in 15 mL of DMF. Stirring was started and a solution of 1.21 g (10.0 mmol) of benzamide in 15 mL of DMF was added dropwise at room temperature. The mixture was stirred for 2 h at room temperature to give anion **2a** as a thick white suspension. A solution of 0.71 g (5.0 mmol) of **1** in 2 mL of DMF was then added dropwise. The reaction became warm and turned yellow-brown in color. The reaction was stirred for 1 h at room temperature and for 36 h at 50°C, then added to saturated aqueous NH_4Cl and extracted with ether (3x). The combined ether layers were washed with water and saturated NaCl, dried ($MgSO_4$) and concentrated under vacuum. The crude product was flash chromatographed on a 40 cm x 2 cm silica gel column eluted with 10-20% ether in hexanes to afford 0.83 g (68%) of **3a** as a light yellow solid, mp 93-94°C (EtOH), *lit*[6a] mp 93-94°C (EtOH). The spectral data matched those reported.[6a]

***N*-(2-Nitrophenyl)-4-methylbenzamide (3b).**- 0.86 g (67%) as a light yellow solid, mp 111-112°C (EtOH), *lit*[11] mp 109-110°C (no solvent given); IR: 3379, 1687, 1508, 1338 cm^{-1}; ^1H NMR: δ 10.8 (br s, 1 H), 8.97 (dd, 1 H, J = 8.7, 1.3), 8.26 (dd, 1 H, J = 8.4, 1.5), 7.72 (ddd, 1 H, J = 8.7, 7.2, 1.6), 7.61 (m, 1 H), 7.42 (m, 1 H), 7.35-7.28 (complex, 2 H), 7.23 (ddd, 1 H, J = 8.5, 7.2, 1.3), 2.57 (s, 3 H); ^{13}C NMR: δ 168.3, 137.3, 136.0, 135.1, 131.7, 131.1, 127.0, 126.3, 125.9, 123.4, 122.1, 20.2; MS *m/z*: 256 (M^+).

Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.63; H, 4.69; N, 10.94. Found: C, 65.58; H, 4.74; N, 10.89

***N*-(2-Nitrophenyl)-4-chlorobenzamide (3c).**- 0.90 g (65%) as a light yellow solid, mp 161-162°C; IR: 3344, 1691, 1504, 1341 cm^{-1}; ^1H NMR: δ 11.4 (br s, 1 H), 8.98 (dd, 1 H, J = 8.5, 1.3), 8.29 (dd, 1 H, J = 8.4, 1.5), 7.95 (d, 2 H, J = 8.7), 7.73 (ddd, 1 H, J = 8.5, 7.2, 1.3), 7.52 (d, 2 H, J = 8.7), 7.25 (ddd, 1 H, J = 8.5, 7.2, 1.3); ^{13}C NMR: δ 164.7, 139.1, 136.3, 135.1, 132.4, 131.7, 129.3, 128.8, 126.0, 123.5, 122.1; MS *m/z*: 276, 278 (M^+, M^++2)

Anal. Calcd for $C_{13}H_9ClN_2O_3$: C, 56.42; H, 3.25; N, 10.13. Found: C, 56.55; H, 3.32; N, 10.01

***N*-Methyl-*N*-(2-nitrophenyl)benzamide (3d).**- 0.67 g (52%) as a light yellow solid, mp 82-83°C ($CHCl_3$), *lit*[5] mp 83-84°C ($CHCl_3$); IR: 1656, 1530, 1351 cm^{-1}; ^1H NMR: (uncoalesced) δ 7.83 (br s, 1 H), 7.53 (br s, 1 H), 7.50-7.20 (br m, 6 H), 7.17 (br s, 1H), 3.45 (br s, 3 H); ^{13}C NMR: δ 170.3, 145.9, 138.8, 134.8, 134.1, 131.0, 130.0, 128.2 (2), 127.9, 125.5, 37.8; MS *m/z*: 256 (M^+).

Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.63; H, 4.69; N, 10.94. Found: C, 65.77; H, 4.75; N, 10.83

***N*-(3-Butenyl)-*N*-(2-nitrophenyl)benzamide (3e).**- 0.86 g (58%) as a yellow oil; IR: 1657,

1528, 1348, 994, 918 cm^{-1}; ^1H NMR: (uncoalesced) δ 7.83 (br s, 1 H), 7.50 (br s, 1 H), 7.43-7.20 (br m, 6 H), 7.16 (br s, 1 H), 5.79 (br s, 1 H), 5.09 (br d, 1 H, J = 16.1), 5.05 (br d, 1 H, J = 9.6), 4.32 (br s, 1 H), 3.55 (m, 1 H), 2.47 (br s, 2 H); ^{13}C NMR: δ 165.6, 146.0, 137.5, 134.9, 133.7, 131.8, 129.9, 128.2 (2), 127.9 (2), 125.7, 117.1, 49.1, 32.1; MS *m/z*: 296 (M^+).

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.92; H, 5.41; N, 9.46. Found: C, 69.10; H, 5.49; N, 9.33

***N*-(3-Methyl-3-butenyl)-*N*-(2-nitrophenyl)benzamide (3f)**.- 0.84 g (54%) as a light yellow solid, mp 65-66°C; IR: 1653, 1529, 1348, 894 cm^{-1}; ^1H NMR: (uncoalesced) δ 7.84 (br s, 1 H), 7.51 (br s, 1 H), 7.45-7.23 (br m, 6 H), 7.14 (br s, 1 H), 4.79 (br s, 1 H), 4.73 (br s, 1 H), 4.38 (br s, 1 H), 3.59 (m, 1 H), 2.41 (br s, 2 H), 1.75 and 1.73 (2 s, 3 H); ^{13}C NMR: δ 168.4, 145.8, 142.6, 135.3, 133.7, 131.9, 130.0, 128.2 (2), 128.0 (2), 125.7, 112.1, 49.1, 35.4, 22.5; MS *m/z*: 310 (M^+).

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.68; H, 5.81; N, 9.03. Found: C, 69.79; H, 5.87; N, 8.96

***N*-(2-Nitrophenyl)phenylsulfonamide (3g)**.- 0.96 g (69%) as a light yellow solid, mp 100-102°C (*i*-PrOH), *lit*[5] mp 101-102°C (EtOH); IR: 3278, 1528, 1348, 1172 cm^{-1}; ^1H NMR: δ 9.87 (br s, 1 H), 8.10 (dd, 1 H, J = 8.5, 1.6), 7.85 (m, 3 H), 7.59 (m, 2 H), 7.47 (tm, 2 H, J = 7.9), 7.16 (ddd, 1 H, J = 8.5, 7.4, 1.4); ^{13}C NMR: δ 147.4, 138.6, 137.2, 135.9, 133.7, 129.4, 127.1, 126.1, 123.9, 121.0; MS *m/z*: 278 (M^+).

Anal. Calcd for $C_{12}H_{10}N_2O_4S$: C, 51.80; H, 3.60; N, 10.07. Found: C, 52.01; H, 3.68; N, 9.95

***N*-(2-Nitrophenyl)-4-methylphenylsulfonamide (3h)**.- 0.99 g (68%) as a light yellow solid, mp 111-113°C (*i*-PrOH), *lit*[6b] mp 112-114°C (EtOH); IR: 3284, 1527, 1344, 1168 cm^{-1}; ^1H NMR: δ 9.85 (br s, 1 H), 8.10 (dd, 1 H, J = 8.5, 1.6), 7.83 (dd, 1 H, J = 8.5, 1.4), 7.73 (d, 2 H, J = 8.5), 7.58 (ddd, 1 H, J = 8.7, 7.1, 1.6), 7.26 (dm, 2 H, J = 8.5), 7.15 (ddd, 1 H, J = 8.7, 7.4, 1.4), 2.39 (s, 3 H); ^{13}C NMR: δ 144.8, 140.6, 135.8, 135.6, 133.9, 130.0, 127.2, 126.1, 123.7, 120.9, 21.6; MS *m/z*: 292 (M^+).

Anal. Calcd for $C_{13}H_{12}N_2O_4S$: C, 53.42; H, 4.11; N, 9.59. Found: C, 53.58; H, 4.19; N, 9.40

***N*-(2-Nitrophenyl)phthalimide (3i)**.- 1.01 g (75%) as a light yellow solid, mp 201-203°C (*i*-PrOH), *lit*[12] mp 203°C (no solvent given); IR: 1732, 1718, 1526, 1378 cm^{-1}; ^1H NMR: δ 8.20 (dd, 1 H, J = 8.2, 1.5), 7.97 (m, 2 H), 7.90-7.75 (complex, 3 H), 7.63 (ddd, 1 H, J = 8.2, 7.5, 1.5), 7.54 (dd, 1 H, J = 8.0, 1.5); ^{13}C NMR: δ 166.3, 145.7, 134.7, 134.3, 134.1, 130.8, 129.7, 125.8, 124.2, 123.6; MS *m/z*: 268 (M^+).

Anal. Calcd for $C_{14}H_8N_2O_4$: C, 62.69; H, 2.99; N, 10.45. Found: C, 62.76; H, 3.02; N, 10.38

***N*-(2-Nitrophenyl)succinimide (3j)**.- 0.53 g (48%) as a tan solid, mp 157-158°C (*i*-PrOH), *lit*[13] mp 156°C (EtOH-H_2O); IR: 1718, 1532, 1353 cm^{-1}; ^1H NMR: δ 8.19 (dd, 1 H, J = 8.2, 1.3), 7.78 (td, 1 H, J = 7.7, 1.5), 7.62 (ddd, 1 H, J = 8.2, 7.7, 1.5), 7.39 (dd, 1 H, J = 7.7, 1.5), 2.96 (ABm, 4 H); ^{13}C NMR: δ 175.3, 143.3, 135.6, 134.3, 130.4, 130.1, 125.9, 28.7; MS *m/z*: 220 (M^+).

Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.67; N, 12.73. Found: C, 54.71; H, 3.75; N, 12.58

***N*-(4-Nitrophenyl)benzamide (5a)**.- 0.80 g (66%) as a light yellow solid, mp 199-200°C (EtOAc), *lit*[14] mp 199-200°C (EtOAc-hexane). The spectral data matched those reported.[14]

***N*-(4-Nitophenyl)-4-methylphenylsulfonamide (5h)**.- 0.97 g (66%) as a light yellow powder, mp 191-192°C (*i*-PrOH), *lit*[15] mp 189-190°C (EtOH). The spectral data matched those reported.[15]

***N*-(2-Nitro-5-fluorophenyl)benzamide (7)**.- 0.83 g (64%) as a yellow powder, mp 116-117°C (*i*-PrOH); IR: 3346, 1692, 1504, 1336 cm^{-1}; ^1H NMR: δ 11.6 (br s, 1H), 8.87 (dd, 1 H, J = 11.5, 2.7), 8.35 (dd, 1 H, J = 9.3, 5.7), 7.99 (m, 2 H), 7.63-7.52 (complex, 3 H), 6.91 (ddd, 1 H, J = 9.3, 6.5, 2.7); ^{13}C NMR: δ 166.7 ($^1J_{CF}$ = 258.2), 165.7, 137.9, 137.8, 133.5, 132.9, 129.1, 128.7 ($^3J_{CF}$ = 11.5), 127.3, 110.8 ($^2J_{CF}$ = 24.0), 108.6 ($^2J_{CF}$ = 30.0); MS *m/z*: 260 (M^+).

Anal. Calcd for $C_{13}H_9FN_2O_3$: C, 60.00; H, 3.46; N, 10.77. Found: C, 60.22; H, 3.52; N, 10.59

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A NOVEL AND CONVENIENT SYNTHESIS OF 4-HALOBUTYRALDEHYDE ACETALS

Submitted by John A. Hyatt†
(08/02/04)

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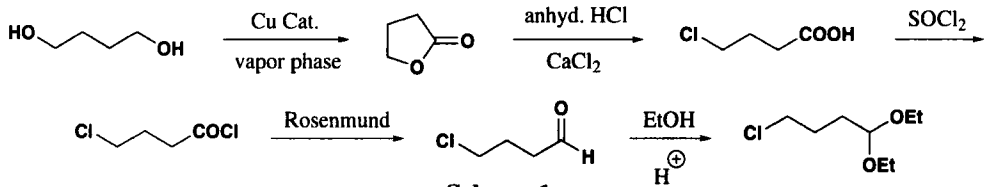
The dimethyl and diethyl acetals of 4-chlorobutyraldehyde and 4-bromobutyraldehyde (1,1-dimethoxy- and 1,1-diethoxy-4-chlorobutane and 1,1-dimethoxy- and 1,1-diethoxy-4-bromobutane) are valuable synthetic intermediates. In particular, these acetals are useful in the Fischer indole synthesis of substituted tryptophols and tryptamines and in the synthesis of natural products.[1] Despite their utility and structural simplicity, there appears to be only one commercial source which makes available small quantities of one of the acetals.[2] The published chemistry for the preparation of these compounds, illustrated for chlorobutyraldehyde diethyl acetal, is rather lengthy and involves a poorly reproducible Rosenmund reduction.[3] Furthermore, in our hands the



Scheme 1