Synthesis of 3-(*N*-Alkylamino)acetophenones *via* a Benzyne Intermediate

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Reaction of 2-(2-bromophenyl)-2-methyl-1,3-dioxolane with lithium (1,1-dimethylethyl)amide, lithium (2,2-dimethylpropyl)amide, lithium (1,1-dimethylpropyl)amide gave the corresponding *N*-(alkyl)-3-(2-methyl-1,3-dioxolan-2-yl)benzenamines in moderate yields. 1-[3-[(1,1-Dimethylethyl)amino]phenyl]ethanone (**4**) was prepared in over 80% yield from 2-(2-bromophenyl)-2-methyl-1,3-dioxolane (**2**).

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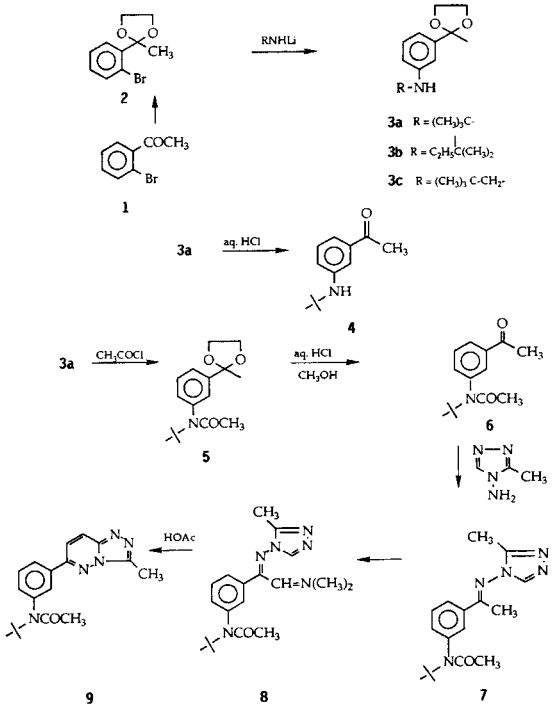
As part of an investigation on anxiolytic agents [1], such as *N*-alkyl-*N*-[3-(3-methyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)phenyl]alkanamides [2], 1-[3-[(1,1-dimethylethyl)amino]-phenyl]ethanone (**4**) was needed as a starting material. The synthesis of **4** has been reported in the literature (32% yield) by *N*-alkylation of 3-aminoacetophenone *via* oxidative coupling with lithium *tert*-butyl copper amide [3]. Our attempt to prepare **4** by this oxidative coupling method (tetrahydrofuran solvent) resulted in a detonation on quenching with ammonium hydroxide as described for this procedure [3].

We therefore sought an alternative method for the preparation of **4** and report a high yield synthesis *via* a benzyne intermediate. 2-Bromoacetophenone (**1**) was converted to the 1,3-dioxolane **2** with *p*-toluenesulfonic acid and ethylene glycol. Reaction of **2** with lithium (1,1-dimethylethyl)amide gave the desired *N*-(1,1-dimethylethyl)-3-(2-methyl-1,3-dioxolan-2-yl)benzenamine (**3a**) (93%). Hydrolysis (aqueous hydrochloric acid) of the ketal group gave **4** in over 85% yield from **2**. Acylation of **3a** with acetyl chloride afforded the *N*-*tert*-butyl-*N*-acetyl derivative **5**, which on mild hydrolysis (aqueous hydrochloric acid in methanol) gave *N*-(3-acetylphenyl)-*N*-(1,1-dimethylethyl)-acetamide (**6**). The benzyne procedure can also be used to synthesize regioselectively other 3-aminoacetophenones containing a hindered *N*-alkyl group. For example, reaction of **2** with lithium 1,1-dimethylethylpropylamide or lithium 2,2-dimethylpropylamide gave the derivatives **3b** (27%) and **3c** (51%), respectively.

Following our previously described procedure for the synthesis of 6-phenyl-1,2,4-triazolo[4,3-*b*]pyridazines [4], *N*-(3-acetylphenyl)-*N*-(1,1-dimethylethyl)acetamide (**6**) was reacted with 3-methyl-1,2,4-triazole to give **7** (94%). Reaction of **7** with *t*-butoxybis(dimethylamino)methane and cyclization with acetic acid afforded *N*-(1,1-dimethylethyl)-*N*-[3-(3-methyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)phenyl]acetamide (**9**) in high overall yield.



EXPERIMENTAL

All melting points were determined on a Mel-Temp apparatus and are uncorrected. Thin layer chromatography was performed with Merck silica gel 60 F254 0.25 mm plates. Proton nuclear magnetic resonance spectra (nmr) were recorded on either a Nicolet NT-300 WB or a General Electric QE-300 Fourier transform nuclear magnetic resonance spectrometer. Chemical shifts are reported as δ in units of parts per million relative to an internal standard of tetramethylsilane in deuteriochloroform. Coupling constants are reported in Hertz (Hz). Multiplicities are as follows: s, singlet; d, doublet; t, triplet; m, multiple; br, broad.

N-(1,1-Dimethylethyl)-3-(2-methyl-1,3-dioxolan-2-yl)benzenamine (**3a**). Procedure I.

To a flame dried flask (with stirring bar) was added 200 ml of dry distilled tetrahydrofuran under argon. After cooling to −78°, 45 ml (0.43 mole) of 1,1-dimethylethylamine (distilled from calcium hydride) was added. To the mixture was added 120 ml of *tert*-butyllithium (0.204 mole) in pentane (1.7 *M*) over 15 minutes (exothermic reaction). The tan solution was stirred at −78° for 30 minutes and 13.104 g (53.9 mmoles) of 2-(2-bromophenyl)-2-methyl-1,3-dioxolane (**2**) [5] in 25 ml of tetrahydrofuran added over 10 minutes. The mixture was stirred 1 hour at −78° and then allowed to warm with times and temperatures as follows: (1

hour −70°; 2 hours −53°; 3 hours −23°; 4 hours +2°; 5 hours +12°). Water (10 moles) was added slowly (gas evolution with warming) and the mixture concentrated under vacuum. The residue plus 100 ml of water was extracted with ether (100 ml) and then with three 15 ml portions of ether. The combined extract was dried (magnesium sulfate) and the solvent removed. The solid was triturated with 12 ml of hot hexane, cooled to 0°, filtered and the solid washed with hexane to give 9.48 g (75%) of tan solid, mp 62-65°. Chromatography of the mother liquors on silica gel with hexane-ethyl acetate-triethylamine (6.9:1:0.045) as solvent gave an additional 2.33 g of solid, mp 61-65°. Recrystallization of a sample from hexane gave white crystals, mp 65-66°; ^{1}H nmr (deuteriochloroform): δ 1.34 (s, 9H), 1.64 (s, 3H), 3.70 (m, 2H), 4.02 (m, 2H), 6.68 (m, 1H), 6.86 (m, 2H), 7.13 (m, 1H).

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.35; H, 8.97; N, 5.81.

N-(1,1-Dimethylpropyl)-3-(2-methyl-1,3-dioxolan-2-yl)benzenamine (**3b**). Procedure II.

A flame dried flask (flushed with argon) with 40 ml of tetrahydrofuran and a stirring bar was cooled to −78° and 5.5 ml of 1,1-dimethylpropylamine (distilled from calcium hydride) added. A solution (11.2 ml) of *n*-butyllithium (47 mmoles) in hexane (2.14 *M*) was added over 5 minutes. After stirring 30 minutes at −78°, 1.456 g (5.99 mmoles) of 2-(2-bromophenyl)-2-methyl-1,3-dioxolane (**2**) in 4 ml of tetrahydrofuran was added over 8 minutes. The solution was stirred at −78° for 1 hour and allowed to warm to 10° over 5 hours. Water was added slowly and the mixture concentrated under vacuum. The residue was partitioned between 40 ml of water and 40 ml of ether, the ether layer separated and the aqueous layer extracted with ether (3 x 6 ml). The combined extract was dried (magnesium sulfate) and the solvent removed. The solid was chromatographed on silica gel with hexane containing 10% ethyl acetate and 0.57% triethylamine to give 0.40 g (27%) of light tan solid. A sample was recrystallized from hexane to give white crystals, mp 46-48°; ^{1}H nmr (deuteriochloroform): δ 0.90 (t, 3H), 1.28 (s, 6H), 1.64 (s, 3H), 1.67 (q, 2H), 3.80 (m, 2H), 4.01 (m, 2H), 6.64 and 6.66 (q, 1H), 6.82 (m, 2H), 7.11 (m, 1H).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 71.98; H, 9.22; N, 5.57.

N-(2,2-Dimethylpropyl)-3-(2-methyl-1,3-dioxolan-2-yl)benzenamine (**3c**).

As described in Procedure II, 5.5 ml of 2,2-dimethylpropylamine and 47 mmoles of *n*-butyllithium was reacted with 1.456 g of 2-(2-bromophenyl)-2-methyl-1,3-dioxolane (**2**) and the product chromatographed to give 0.76 g (51%) of tan crystals, mp 49-52°. A sample was recrystallized from hexane to give off white needles, mp 53-55°; ^{1}H nmr (deuteriochloroform): δ 1.0 (s, 9H), 1.65 (s, 3H), 2.9 (s, 2H), 3.80 (m, 2H), 4.02 (m, 2H), 6.53-6.56 (m, 1H), 6.74-6.80 (m, 2H), 7.11-7.16 (m, 1H).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.3; H, 9.3; N, 5.60. Found: C, 72.8; H, 9.1; N, 5.5.

1-[3-[1,1-Dimethylaminophenyl]ethanone (**4**).

To a solution of 0.56 g (2.36 mmoles) of *N*-(1,1-dimethylethyl)-3-(2-methyl-1,3-dioxolan-2-yl)benzenamine (**3a**) in 35 ml of methanol was added 7 ml of water and 3.5 ml of concentrated hydrochloric acid. After 0.5 hour, 5 g of solid sodium bicarbonate was added in small portions and the mixture was concentrated, diluted with water and extracted with ether. The extract was dried (magnesium sulfate) and the solvent removed to give 0.45 g (99%) of a tan oil; ^{1}H nmr (deuteriochloroform): δ 1.37 (s, 9H), 2.56 (s, 3H), 6.9-6.95 (m, 1H), 7.19-7.33 (m, 3H).

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.4; H, 8.96; N, 7.3. Found: C, 75.1; H, 8.74; N, 7.3.

N-(3-Acetylphenyl)-*N*-(1,1-dimethylethyl)acetamide (**6**).

To a solution of 1.28 g (5.42 mmoles) of *N*-(1,1-dimethylethyl)-3-(2-methyl-1,3-dioxolan-2-yl)benzenamine (**3a**) and 2.31 ml of diisopropylethylamine in 10 ml of dichloromethane, cooled to 0°, was added dropwise 0.66 ml (9.3 mmoles) of acetyl chloride in 4 ml of dichloromethane. The solution was stirred at room temperature for 3 hours, 1 ml of methanol added and the solvent removed under vacuum. To the residue was added 40 ml of ethyl acetate and 40 ml of saturated sodium bicarbonate. The organic layer was separated and the aqueous layer extracted with ethyl acetate (5 x 6 ml). The combined organic layer and extracts were dried (magnesium sulfate) and the solvent removed to give 1.56 g of an oil. Chromatography on silica gel with 30% ethyl acetate in hexane gave 1.38 g (92%) of *N*-(1,1-dimethylethyl)-*N*-[3-(2-methyl-1,3-dioxolan-2-yl)phenyl]acetamide (**5**) as an oil. To the proceeding oil (1.52 g, 5.47 mmoles) was added 75 ml of methanol, 15 ml of water and 7.5 ml of concentrated hydrochloric acid. After stirring 30 minutes, 12.7 g of solid sodium bicarbonate was added in small portions. The mixture was concentrated, diluted with 100 ml of water and extracted with ether. The ether extracts were dried (magnesium sulfate) and the solvent removed to give 1.23 g (96%) of product as a solid. Recrystallization from hexane gave 0.91 g of yellow needles, mp 75-76°; ^{1}H nmr (deuteriochloroform): δ 1.37 (s, 9H), 1.660 (s, 3H), 1.666 (s, 3H), 3.76 (m, 2H), 4.07, (m, 2H), 7.22-7.51 (m, 4H).

Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.3; H, 8.4; N, 5.1. Found: C, 69.0; H, 8.7; N, 4.9.

(*E*)-*N*-(1,1-Dimethylethyl)-*N*-[3-[1-[(3-methyl-4*H*-1,2,4-triazol-4-yl)-imino]ethyl]phenyl]acetamide (**7**).

A mixture of 1.23 g (5.29 mmoles) of *N*-(3-acetylphenyl)-*N*-(1,1-dimethylethyl)acetamide (**6**), 0.815 g (8.31 mmoles) of 4-amino-3-methyl-1,2,4-triazole, 0.097 g (0.56 mmole) of *p*-toluenesulfonic acid in 65 ml of toluene was refluxed for 30 hours with azeotropic removal of water. The solvent was removed and saturated sodium bicarbonate added. The mixture was extracted with dichloromethane and the extracts dried (magnesium sulfate) and the solvent removed. The residue was chromatographed on silica gel with 5% methanol in dichloromethane as solvent to give 1.57 g (94%) of a white foam. A 0.5 g sample was crystallized from diethyl ether to give 0.37 g of white crystals, mp 118.5-121°; ^{1}H nmr (deuteriochloroform): δ 1.41 (s, 9H), 1.72 (s, 3H), 2.41 (s, 3H), 2.45 (s, 3H), 7.33-8.0 (m, 4H), 8.14 (s, 1H).

Anal. Calcd. for $C_{17}H_{23}N_6O$: C, 65.2; H, 7.4; N, 22.4. Found: 65.2; H, 7.4; N, 22.6.

(*E,E*)-*N*-[3-[3-(Dimethylamino)-1-[(3-methyl-4*H*-1,2,4-triazol-4-yl)-imino]-2-propenyl]phenyl]-*N*-(1,1-dimethylethyl)acetamide (**8**).

A solution of 1.52 g (4.83 mmoles) of (*E*)-*N*-(1,1-dimethylethyl)-*N*-[3-[1-[(3-methyl-4*H*-1,2,4-triazol-4-yl)imino]ethyl]phenyl]acetamide (**7**) and 2.4 ml of *t*-butoxybis(dimethylamino)methane in 10 ml of tetrahydrofuran was stirred at 23° for 3 hours. Water (10 ml) was added and the solvent removed under vacuum. The residue was chromatographed on silica gel with 5% methanol in dichloromethane as solvent to give 1.72 g (97%) of a yellow foam.

Crystallization from diethyl ether gave 0.77 g of white crystals, mp 155-157°.

Anal. Calcd. for $C_{20}H_{28}N_6O$: C, 65.2; H, 7.7; N, 22.8. Found: C, 65.4; H, 7.6; N, 23.0.

N-(1,1)-dimethylethyl)-*N*-[3-(3-methyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)phenyl]acetamide (**9**).

A solution of 1.54 g (4.19 mmoles) of (*E,E*)-*N*-[3-[3-(dimethylamino)-1-[(3-methyl-4*H*-1,2,4-triazol-4-yl)imino]-2-propenyl]phenyl]-*N*-(1,1-dimethylethyl)acetamide (**8**) in 40 ml of glacial acetic acid was refluxed for 18 hours and the solvent removed under vacuum. To the residue was added 20 ml of water and 20 ml of saturated sodium bicabonate and the mixture extracted with dichloromethane. The extract was dried with magnesium sulfate and the solvent removed. The residue was chromatographed on silica gel with 5% methanol in dichloromethane to give 1.26 g (92%) of a yellow foam. A 0.96 g sample was crystallized from 5 ml of hexane to give 0.72 g of tan crystals, mp 176-178°; ^{1}H nmr (deuteriochloroform): δ 1.44 (s, 9H), 1.76 (s, 3H), 2.90 (s, 3H), 7.26-8.21 (m, 6H).

Anal. Calcd. for $C_{18}H_{21}N_5O$: C, 66.9; H, 6.5; N, 21.7. Found: C, 67.1 H, 6.6; N, 21.6.

REFERENCES AND NOTES

[1] J. D. Albright, D. B. Moran, W. B. Wright, Jr., J. B. Collins, B. Beer, A. S. Lippa and E. N. Greenblatt, *J. Med. Chem.*, **24**, 591 (1981).

[2] J. D. Albright, D. W. Powell and J. P. Dusza, U.S. Patent 4,892,873 (1990).

[3] H. Yamamoto and K. Maruoka, *J. Org. Chem.*, **45**, 2739 (1980).

[4] D. F. Lieberman and J. D. Albright, *J. Heterocyclic Chem.*, **25**, 827 (1988).

[5] R. Beugelmans, M. Bois-Choussy and Q. Tang, *J. Org. Chem.*, **52**, 3882 (1987); G. P. Schiemenz and H. Kaack, *Liebigs Ann. Chem.*, 1480 (1973).