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Bromination of Deactivated Aromatics: A Simple and Efficient Method

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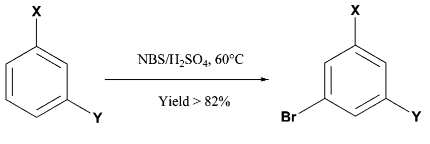

X, Y = Electron Withdrawing Groups

Highly deactivated aromatic compounds were smoothly monobrominated by treatment with *N*-bromosuccinimide (NBS) in concentrated H_2SO_4 medium affording the corresponding bromo derivatives in good yields. Mild reaction conditions and simple workup provides a practical and commercially viable route for the synthesis of bromo compounds of deactivated aromatics.

Brominated benzene compounds have received wide attention as precursors in the synthesis of a variety of active pharmaceutical ingredients, for example, Citalopram,[1] Bromperidol,[2] Bromindione,[3] Ambroxol,[4] Tramadol,[5] etc. Also the bromarenes have been extensively used in the aromatic bond formation reactions such as Heck arylation,[6] Suzuki,[7] Buchwald,[8] Negishi,[9] and Stille[10] couplings, etc., for the synthesis of biaryls some of which are the precursors for a few of the antihypertensive agents.[11] Bromoaromatic compounds find application in the synthesis of dendrimers.[12] Several procedures are available for the synthesis of deactivated bromoarenes.[13−29] However, most of these methods involve the use of moisture-sensitive Lewis acid,[24] long reaction time,[26,28] and poor yields.[14,25,26,28]

In one of our programs in medicinal chemistry wherein we need to synthesize a highly deactivated brominated aromatic compound, we came across the report of Lambert et al.[27] on the bromination of nitrobenzene by use of NBS in an aqueous

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SCHEME 1. Bromination of Deactivated Aromatic Compounds

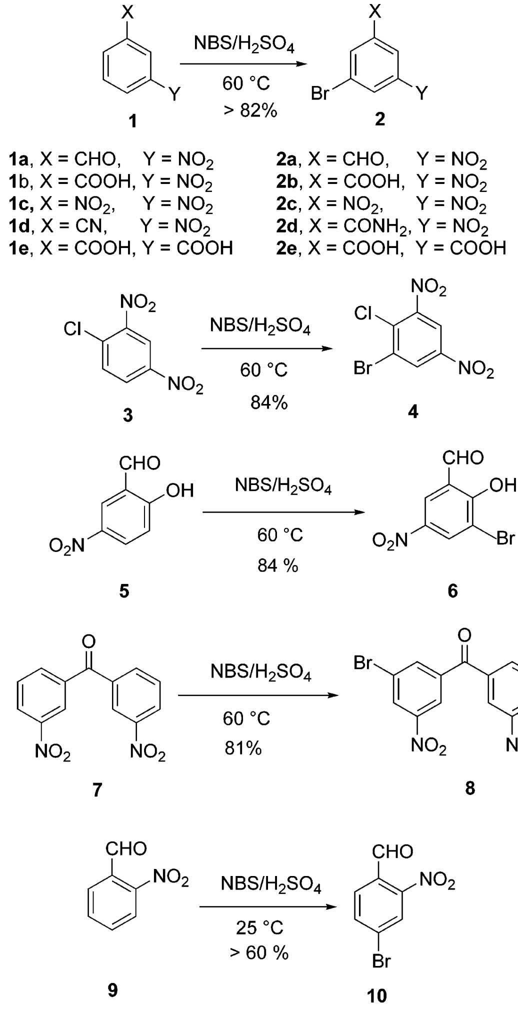

TABLE 1. Bromination of Deactivated Aromatic Compounds with NBS/H_2SO_4[a]

entry	substrate	time (h)	yield (%)	product	mp, °C (lit.)
1	**1a**	1.5	92	**2a**	97−99 (100)[30]
2	**1b**	1.5	83	**2b**	161−162 (161)[30]
3	**1c**	2.5	87	**2c**	75−76 (75−76)[26]
4	**1d**	1.5	86	**2d**	189−191 (187−192)[31]
5	**1e**	1.5	86	**2e**	275−277 (281−283)[32]
6	**3**	2	84	**4**	61−62 (63)[33]
7	**5**	2	84	**6**	148−149 (149−150)[34]
8	**7**	2	81	**8**	110−112
9	**9**	3	60	**10**	95−96 (97−98)[35]

[a] For entries 1−8, reactions were performed at 60 °C and for entry 9 at 25 °C due to byproduct formation at higher temperatures.

TABLE 2. Bromination of Deactivated Aromatic Compounds with TFA/H_2SO_4 (0.4 v/v, 50 mL/100 mmol) at 60 °C

entry	substrate	time (h)	conversion[a] (%)
1	**1c**	2.5	<10
2	**1d**	2	<10
3	**3**	2	<10

[a] Approximate conversion by ^1H NMR.

H_2SO_4 medium. But bromination of 1,3-dideactivated aromatic compounds has not been studied under these conditions. Dolbier[28] reported a new method for the bromination of deactivated aromatics using NBS in trifluoroacetic acid (TFA) as solvent medium and H_2SO_4 as catalyst. However, the method suffers from disadvantages such as slow reaction times (30−48 h), large volumes[36] of TFA and H_2SO_4 used, etc. Attempted bromination of *m*-nitrobenzaldehyde using potassium bromate as elucidated by Harrison et al.[15] resulted only in the formation of 3-nitrobenzoic acid and not 3-bromo-5-nitrobenzaldehyde (**2a**). Also there was no reaction in the case of 1,3-dinitrobenzene under this condition.

In this Note, we wish to report a modified and efficient method for the bromination of deactivated aromatic compounds by using NBS in concentrated H_2SO_4 as medium (Scheme 1). Thus the bromination of 3-nitrobenzaldehyde (**1a**) with NBS in H_2SO_4 at 60 °C afforded 3-bromo-5-nitrobenzaldehyde (**2a**) in good yield (Table 1, entry 1). The reaction was completed in 1.5 h and the product was isolated by a simple workup procedure. A similar observation was noticed in the case of aromatic substrates bearing two deactivating groups like 1,3-dinitrobenzene (**1c**). The reaction was completed in less than 3 h furnishing 5-bromo-1,3-dinitrobenzene (**2c**) in 87% yield (Table 1, entry 3). In contrast a very low conversion was observed when bromination was carried out for 2−2.5 h under the conditions of Dolbier (Table 2) while there was virtually no reaction under the conditions of Lambert.

In the present method the reaction proceeds to completion in a short period with less quantity of concentrated H_2SO_4 affording good to excellent yield of the monobrominated product. The generality of this approach was established on a series of deactivated aromatics as presented in Table 1. Bromination of bis-(3-nitrophenyl)methanone (**7**) proceeded smoothly in 2 h with 2.2 equiv of NBS to afford the dibromo compound **8** in 81% yield.

Regioselective bromination was observed in the case of 2-nitrobenzaldehyde (**9**) to give 4-bromo-2-nitrobenzaldehyde (**10**) in 60% yield (Table 1, entry 9). This bromination method exhibits a high tolerance for the aldehyde group as observed in the case of a few other aromatic aldehydes such as 5-nitrosalicylaldehyde (**5**), which was smoothly brominated to give 3-bromo-5-nitrosalicylaldehyde (**6**) in 84% yield. However, when the bromination of 3-nitrobenzaldehyde (**1a**) was carried out under the conditions of Dolbier we have observed that the aldehyde was oxidized to the acid with the formation of the 3-bromo-5-nitrobenzoic acid in very small amounts. Bromination of the 3-nitrobenzonitrile (**1d**) under our protocol yielded 3-bromo-5-nitrobenzamide (**2d**) due to concomitant hydration of the nitrile (Table 1, entry 4).

Jian and Tour[29] reported bromination of 1,3-dinitrobenzene using bromine in concentrated HNO_3−concentrated H_2SO_4 medium. When we attempted this method for the bromination of 3-nitrobenzaldehyde (**1a**), the reaction was not clean and furnished a 9:1 mixture of 3-bromo-5-nitrobenzoic acid (**2b**)

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(36) 50 mL of TFA and 20 mL of concentrated H_2SO_4 for 100 mmol of highly deactivated aromatic compound like 1,3-dinitrobenzene.

and 3,5-dinitrobenzoic acid.[37] This observation demonstrates the incompatibility of the aldehyde functionality under the conditions of both Dolbier and Jian in comparison with that of NBS in H_2SO_4 acid medium.

In summary, we report a simple and efficient method for the bromination of highly deactivated aromatic substrates, which contain at least two electron-deactivating substituents, using NBS in H_2SO_4 medium. The relatively high rate of reaction, the simple procedure, regioselectivity, and moderate to excellent yields make this method a unique one for the bromination of highly deactivated aromatic compounds.

Experimental Section

General Experimental Procedure for the Synthesis of Compounds 2a−e, 4, 6, 8, and 10. 3-Nitrobenzaldehyde (**1a)** (10 g, 66 mmol) was taken up in concentrated H_2SO_4 (30 mL) and heated to 60 °C. To this was added NBS (14.13 g, 79 mmol, 1.2 equiv[38]) in three portions each in 15 min. When the reaction was considered complete as determined by TLC analysis, the mixture was poured into crushed ice (100 g) to precipitate the solids. The precipitated solids were filtered, washed with water (60 mL) then with 40 mL of *n*-hexane, and finally dried to obtain 3-bromo-5-nitrobenzaldehyde (**2a**) (14.03 g, 61 mmol, 92%). Mp 97−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.63 (s, 1H), 8.66 (s, 1H), 10.08 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.0, 124.1, 131.6, 137.5, 138.4, 149.2, 188.4. MS *m*/*z* calculated for $C_7H_4{}^{79}BrNO_3$ [M^+] 229, found 229.

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Supporting Information Available: Spectral data for all the compounds described in Table 1 (^{1}H NMR, ^{13}C NMR, and mass spectra for **2a**, **2b**, and **4**; ^{1}H NMR and ^{13}C NMR for **2c**, **2e**, **6**, and **10**; and ^{1}H NMR, ^{13}C NMR, mass, and IR spectra for **2d** and **8**). This material is available free of charge via the Internet at http://pubs.acs.org.

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[37] The ratio of 3-bromo-5-nitrobenzoic acid and 5-bromo-1,3-dinitro benzene was estimated from ^{1}H NMR spectral data and HPLC analysis.

[38] 2.2 equiv of NBS was added for the bromination of compound **7**.