Benzylic Brominations with *N*-Bromosuccinimide in (Trifluoromethyl)-benzene

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Abstract: A variety of benzylic brominations were performed by using *N*-bromosuccinimide in (trifluoromethyl)benzene with photochemical activation in the presence of 2,2′-azobisisobutyronitrile, 1,1′-azobis(cyclohexanecarbonitrile), or benzoyl peroxide as the radical initiator. This system provides clean, rapid, and high-yielding reactions with replacement of conventional solvents, such as tetrachloromethane, by less-toxic (trifluoromethyl)benzene.

Key words: benzylic bromination, (trifluoromethyl)benzene, free radical, *N*-bromosuccinimide, azobisisobutyronitrile

In a project aimed at the synthesis of artificial receptors, we needed to effect monobromination of each of two or more methyl groups attached to benzenoid rings. Especially important target molecules were the tribromides 1-{1,1-bis[3-(bromomethyl)phenyl]ethyl}-4-(bromomethyl)benzene (**2a**) and 1-{1,1-bis[4-(bromomethyl)phenyl]ethyl}-3-(bromomethyl)benzene (**2b**), derived from 1-[1,1-bis(3-methylphenyl)ethyl]-4-methylbenzene (**1a**) and its isomer 1-[1,1-bis(4-methylphenyl)ethyl]-3-methylbenzene (**1b**), respectively. A variety of functional-group interconversions can be applied to **2a** and **2b**, thus allowing the attachment of amino acid moieties to the trityl cores; compounds **2a** and **2b** are also potential starting materials for the synthesis of dendrimers. To access **2a** and **2b**, we explored benzylic brominations of the methyl groups of **1a** and **1b**, with the expectation that it would be difficult to avoid polybromination.

Radical-mediated bromination is frequently used to achieve selective activation of a methyl group in an appropriate organic molecule. This reaction is normally carried out by using *N*-bromosuccinimide (NBS) in tetrachloromethane with various radical initiators.[1] This solvent, however, presents a relatively high toxicity, including possible carcinogenicity, which restricts its use.[2] Tetrachloromethane can be replaced by other solvents, e.g. methyl acetate, in light- and microwave-assisted benzylic brominations.[3] To avoid the use of tetrachloromethane, we explored the use of NBS in (trifluoromethyl)benzene (α,α,α-trifluorotoluene, benzotrifluoride) as a solvent for benzylic brominations because of its favorable physical properties, chemical inertness, and low toxicity.[4] We found that brominations of mono-, di-, or trimethylated aromatic and heterocyclic systems occur efficiently under photochemical conditions with NBS in the presence of 2,2′-azobisisobutyronitrile (AIBN), 1,1′-azobis(cyclohexanecarbonitrile) (ACCN), or benzoyl peroxide (BP) as a radical initiator in (trifluoromethyl)benzene.

A variety of reaction conditions were examined with **1a** as a substrate by a multiparallel protocol using a Radleys Carousel,[5] which led to the preferred procedure described below. The conditions were optimized for the production of the tribromo compound 1,1′-{1-[4-(bromomethyl)phenyl]ethane-1,1-diyl}bis[3-(bromomethyl)benzene] (**2a**). (Trifluoromethyl)benzene was chosen as a solvent, not only because of its inertness and low toxicity, but also on account of its relatively low refractive index (n_D 1.4149),[6] a property known to be important for achieving efficient photoinduced brominations with NBS.[7] The trimethyl substrates **1a** and **1b** and the dimethyl substrate **1c**[8] provided a good test of the robustness of the procedure because of the opportunities for polybromination. The preferred procedure that we developed gave very acceptable yields of the desired products **2a**–**c** (see Table 1). As expected, there was no detectable bromination of the non-benzylic methyl group in compounds **1a** and **1b**. A study of mono- and dimethyl aromatic compounds (**1d**–**h**) and mono- and dimethyl heterocyclic compounds (**1i**–**o**) was also made, and good yields of products **2d**–**o** were likewise obtained (Table 1), which are comparable to the best results in the literature.[9–15]

Variants of the classical NBS procedures use bromine or bromine-generating systems in the presence of water.[16,17] For one example (**1o**), we found that bromination can, alternatively, be accomplished efficiently by using bromine in a two-phase 1:1 (v/v) mixture of water and (trifluoromethyl)benzene.

Chemicals were AnalaR or laboratory grade from reputable suppliers and were used directly. (Trifluoromethyl)benzene was 99.9+% (water < 0.001%). Petroleum ether (PE) used was the fraction boiling in the range 40–60 °C. Silica gel 60 (35–70 μm) was used for medium-pressure (flash) chromatography. TLC was performed on silica gel plates (Kieselgel 60 F_{254}, 0.2 mm) with spot detection by UV (254, 365 nm) or aq $KMnO_4$. ^1H and ^{13}C NMR spectra were recorded at the frequencies stated, using residual protons of the deuterated solvents as internal standards. For bromomethyl compounds **2d**–**o**, the NMR data (^{13}C data not given) either agreed with literature values or were consistent with their assigned structures.

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Table 1 Mono-, Di- and Tri-Benzylic Bromination Using *N*-Bromosuccinimide in (Trifluoromethyl)benzene

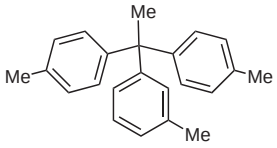
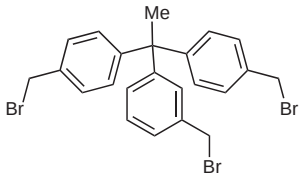
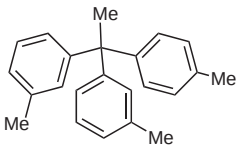
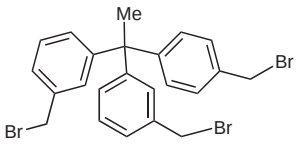
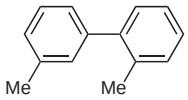
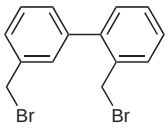
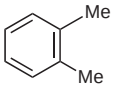
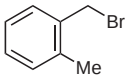
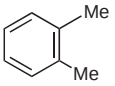
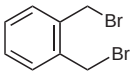
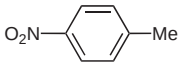
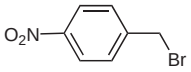
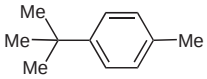
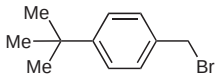
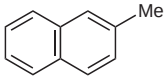
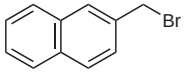
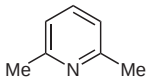
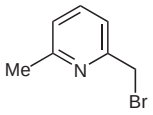
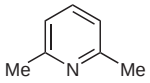
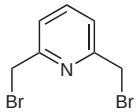
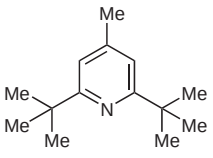
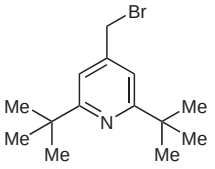
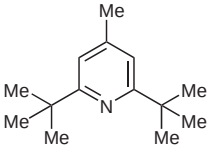
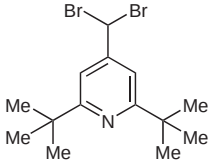
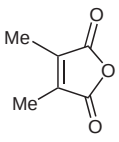
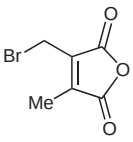
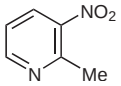
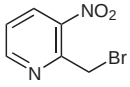
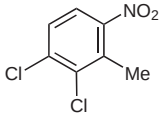
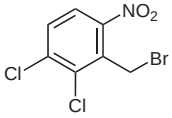
	Substrate	Time (h)	Product	Yield (%)
1a		3	**2a**		54
1b		3	**2b**		59
1c		3	**2c**		71[a] (57[b])
1d		3	**2d**		59 (47[b])
1e		4	**2e**		54[a]
1f		6.5	**2f**		60
1g		2.5	**2g**		88
1h		3	**2h**		85
1i		7.5	**2i**		50
1j		8	**2j**		45
1k		7	**2k**		61
1l		7	**2l**		55
1m		3.5	**2m**		60

Table 1 Mono-, Di- and Tri-Benzylic Bromination Using *N*-Bromosuccinimide in (Trifluoromethyl)benzene (continued)

	Substrate	Time (h)		Product	Yield (%)
1n		6	**2n**		37[b]
1o[c]		6	**2o**		70

[a] 1,1′-Azobis(cyclohexanecarbonitrile) catalyst.
[b] Benzoyl peroxide catalyst.
[c] Photobromination with Br_2 (details below).

Brominated Compounds (2a–n): General Procedure

NBS (1.1 equiv for each required Br substitution) and AIBN, 1,1′-azobis(cyclohexanecarbonitrile), or BzOOBz (0.11 equiv) were suspended in dry (trifluoromethyl)benzene (~2.5–3.5 mL/mmol NBS) under N_2 in a two-necked round-bottomed flask fitted with a condenser and N_2 bubbler. A soln of the substrate (1 equiv) in (trifluoromethyl)benzene (2–3 mL per mmol substrate) was added to the mixture, and a 200 W tungsten lamp was positioned so that it was almost touching the flask. The irradiated reaction mixture was stirred and refluxed while the reaction was monitored by TLC using an appropriate eluent (e.g., 20% CH_2Cl_2–PE or 15% EtOAc–PE). When the reaction was complete, the mixture was allowed to cool to r.t. and then filtered. The solvent was removed in vacuo and the crude product was taken up in the minimum volume of (trifluoromethyl)benzene (~20 mL). The organic phase was washed with aq $Na_2S_2O_5$ (2 × 20 mL), dried ($MgSO_4$), and concentrated. The residual material was purified by flash chromatography (PE–EtOAc or PE–CH_2Cl_2); the fractions that contained product were combined and the solvent was removed to give the pure product.

1-{1,1-Bis[4-(bromomethyl)phenyl]ethyl}-3-(bromomethyl)benzene (2a)

Prepared from 1-[1,1-bis(4-methylphenyl)ethyl]-3-methylbenzene (**1a**); white solid; yield: 54%; mp 91–93 °C; R_f = 0.22 (CH_2Cl_2–PE, 1:4).

IR (KBr): 3045, 2895, 1524, 775, 610 (C–Br) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08 (s, 3 H, Me), 4.33 (s, 2 H, *m*-CH_2Br), 4.39 (s, 4 H, 2 × *p*-CH_2Br), 6.9–7.2 (m, 12 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.83 (Me), 33.71 (*p*-CH_2Br), 34.32 (*m*-CH_2Br), 52.74 (C_q), 126.43, 127.04, 128.62, 129.05, 129.42, 129.76, 135.74, 137.69, 146.87, 149.84 (all Ar C atoms).

MS (EI, 70 eV): *m/z* (%) = 540 [M^+], 538 (18) [M^+], 536 (20) [M^+], 534 [M^+], 525, 523 (68), 521 (72), 519, 459, 457 (100), 455.

Anal. Calcd for $C_{23}H_{21}Br_3$: C, 51.39; H, 3.91. Found: C, 51.25; H, 3.78.

1-{1,1-bis[3-(bromomethyl)phenyl]ethyl}-4-(bromomethyl)benzene (2b)

Prepared from 1-[1,1-bis(4-methylphenyl)ethyl]-3-methylbenzene (**2a**); colorless oil; yield: 59%; R_f = 0.25 (CH_2Cl_2–PE, 1:4).

IR (film): 3046, 2895, 1601, 778, 608 (C–Br) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.12 (s, 3 H, Me), 4.36 (s, 4 H, *m*-Ar–CH_2Br), 4.42 (s, 2 H, *p*-Ar–CH_2Br), 6.76–7.25 (m, 12 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.99 (Me), 33.63 (*p*-CH_2Br), 34.19 (*m*-CH_2Br), 52.79 (C_q), 126.41, 126.99, 128.00, 128.90, 129.04, 129.72, 135.70, 137.62, 146.72, 149.72 (all Ar C atoms).

MS (EI, 70 eV): *m/z* (%) = 540 [M^+], 538 (22) [M^+], 536 (24) [M^+], 534 [M^+], 525 (30), 523 (90), 521 (96), 519 (28), 459, 457 (100), 455.

Anal. Calcd for $C_{23}H_{21}Br_3$: C, 51.39; H, 3.91. Found: C, 51.05; H, 3.72.

2,3′-Bis(bromomethyl)biphenyl (2c)

Prepared from 2,3′-dimethylbiphenyl;[8] white solid; yield: 71%; mp 44–46 °C (PE); R_f = 0.25 (CH_2Cl_2–PE, 1:19).

IR (KB): 3040, 2850, 1599, 796, 604 (C–Br) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.45 (s, 2 H, CH_2Br), 4.57 (s, 2 H, CH_2Br), 7.15–7.51 (m, 8 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.97 (CH_2Br), 33.20 (CH_2Br), 128.37, 128.50, 129.02, 129.39, 129.71, 130.02, 130.63, 131.31, 135.12, 135.33, 138.34, 140.71, 141.32 (all Ar C atoms).

MS (EI, 70 eV): *m/z* (%) = 342 (9%) [M^+], 340 (19) [M^+], 338 (10) [M^+], 259 (56), 179 (100).

Anal. Calcd for $C_{14}H_{12}Br_2$: C, 49.45; H, 3.56. Found: C, 49.28; H, 3.39.

1-(Bromomethyl)-2-methylbenzene (2d)

Prepared from *o*-xylene; colorless liquid; yield: 59%; R_f = 0.5 (100% PE).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, CH_3), 4.58 (s, 2 H, CH_2Br), 7.21–7.39 (m, 4 H, Ar).

1,2-Bis(bromomethyl)benzene (2e)

Prepared from *o*-xylene; white solid; yield: 54%; mp 88–90 °C (Lit.[9] 92–93 °C); R_f = 0.38 (PE).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.59 (s, 4 H, 2 × CH_2Br), 7.18–7.31 (m, 4 H, Ar).

1-(Bromomethyl)-4-nitrobenzene (2f)

Prepared from 4-nitrotoluene; white solid; yield: 60%; mp 86–90 °C (Lit.[10] 94–96 °C); R_f = 0.30 (CH_2Cl_2–PE, 2:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.45 (s, 2 H, CH_2Br), 7.58 (d, 2 H, *J* = 6 Hz, Ar), 8.23 (d, 2 H, *J* = 6, Ar).

1-(Bromomethyl)-4-*tert*-butylbenzene (2g)

Prepared from 1-*tert*-butyl-4-methylbenzene; colorless oil; yield: 88%; R_f = 0.58 (CH_2Cl_2–PE, 1:9).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 9 H, 3 × Me), 4.53 (s, 2 H, CH_2Br), 7.35 (m, 4 H, Ar).

MS (EI, 70 eV): *m/z* (%) = 228 (<1) [M^+], 213 (25), 147 (100), 132 (23), 117 (17), 91 (8).

2-(Bromomethyl)naphthalene (2h)
Prepared from 2-methylnaphthalene; pale brown solid; yield: 85%; mp 50–52 °C (Lit.[12] 51–53 °C); R_f = 0.34 (CH_2Cl_2–PE, 1:9).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.61 (s, 2 H, CH_2Br), 7.43 (m, 3 H, Ar), 7.82 (m, 4 H, Ar).

2-(Bromomethyl)-6-methylpyridine (2i)
Prepared from 2,6-lutidine; pale brown solid; yield: 50%; mp 35–37 °C; R_f = 0.42 (EtOAc–PE, 3:7).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.55 (s, 3 H, Me), 4.51 (s, 2 H, CH_2Br), 7.06 (d, 1 H, *J* = 9, Ar), 7.25 (d, 1 H, *J* = 6, Ar), 7.65 (m, 1 H, Ar).

MS (EI, 70 eV): *m/z* (%) = 185 (<1) [M^+], 122 (10), 106 (100), 79 (28).

2,6-Bis(bromomethyl)pyridine (2j)
Prepared from 2,6-lutidine; white solid; yield: 45%; mp 80–82 °C (lit.[13] 83–86 °C); R_f = 0.48 (EtOAc–PE, 2:8).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.47 (s, 4 H, CH_2Br), 7.30 (d, 2 H, *J* = 6 Hz, Ar), 7.64 (m, 1 H, Ar).

4-(Bromomethyl)-2,6-di-*tert*-butylpyridine (2k)
Prepared from 2,6-di-*tert*-butyl-4-methylpyridine; colorless oil at r.t.; yield: 61%; R_f = 0.58 (hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 18 H, Me), 4.30 (s, 2 H, CH_2Br), 7.01 (s, 2 H, Ar).

4-(Dibromomethyl)-2,6-di-*tert*-butylpyridine (2l)
Prepared from 2,6-di-*tert*-butyl-4-methylpyridine; white solid; yield: 55%; mp 72–74 °C; R_f = 0.63 (hexane).

IR (KBr): 3045, 2895, 1524, 604 (C–Br) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (s, 18 H, Me), 6.46 (s, 1 H, $CHBr_2$), 7.18 (s, 2 H, Ar).

MS (EI, 70 eV): *m/z* (%) = 365 [M^+], 363 (50%) [M^+], 361 [M^+], 350 (55), 348 (100), 346 (61).

Anal. Calcd for $C_{14}H_{21}NBr_2$: C, 46.31; H, 5.83; N, 3.86. Found: C, 46.35; H, 5.85; N, 3.91.

3-(Bromomethyl)-4-methyl-2,5-furandione (2m)
Prepared from 3,4-dimethylfuran-2,5-dione; pale yellow oil; yield: 60%; R_f = 0.46 (Et_2O–PE, 4:6).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.12 (s, 3 H, Me), 4.12 (s, 2 H, CH_2Br).

2-(Bromomethyl)-3-nitropyridine (2n)
Prepared from 2-methyl-3-nitropyridine;[18] yellow oil; yield: 37%; R_f = 0.27 (CH_2Cl_2–PE, 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.90 (s, 2 H, CH_2Br), 7.45 [m, 1 H, pyridine C(4)H], 8.32 [d, 1 H, pyridine C(5)H], 8.75 [d, 1 H, pyridine C(3)H].

2-(Bromomethyl)-3,4-dichloro-1-nitrobenzene (2o)
2,3-Dichloro-6-nitrotoluene (5.0 g, 24.3 mmol) was stirred vigorously in $PhCF_3$ (50 mL) and H_2O (50 mL) under N_2 (no catalyst). The mixture was illuminated with a 150 W tungsten bulb, and Br_2 (16.0 g, 100 mmol, 5.1 mL) was slowly added. Workup was performed as described in the general procedure above: pale yellow solid; yield: 70%; R_f = 0.50 (PE–Et_2O, 4:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.84 (s, 2 H, CH_2), 7.55 (d, *J* = 8.9 Hz, 1 H, ArH), 7.79 (d, *J* = 8.9 Hz, 1 H, ArH).

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