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Regioselective Bromination of 3, 4-Dimethoxytoluene with N-Bromosuccinimide

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Abstract: The selective brominations of 3, 4-dimethoxytoluene with N-bromosuccinimide were reported. The nuclear and side-chain brominated products were obtained under different reaction conditions. The mechanism was also discussed.

Keywords: Bromination, 3, 4-dimethoxy toluene, N-bromosucinimide, regioselective bromination.

The benzylisoquinoline alkaloids play an important role in alkaloid chemistry and act as the biosynthetic precursors to many naturally occurring isoquinolines including pavines, morphinans, protoberberines and aporphines. 1-Benzylisoquinolines can be prepared from tetrahydroisoquinoline and alkylating agent – benzyl bromide by an asymmetric route[1]. The free-radical side-chain bromination of 3, 4-dimethoxytoluene could be a possible route to the synthesis of benzyl bromide. From the known brominating reagents, N-bromosuccinimide (NBS), an available and popular reagent employed mostly in free radical allylic and benzylic brominations was selected. When 3, 4-dimethoxy toluene was brominated with NBS in CCl_4, however, the experimental results were rather unexpected. Three products **1**, **2** and **3** were obtained respectively under different reaction conditions (**Scheme 1**). The structures of products were confirmed by ^1H NMR and MS spectra[2].

Experimental

*Synthesis of compound **1***

To a stirred solution of 0.760 g (5 mmol) 3, 4-dimethoxy toluene in 25 mL of CCl_4 was added 0.890 g (5 mmol) NBS, the mixture was heated to reflux for 8 hrs, the reaction mixture was cooled to room temperature, succinimide was filtered and washed with CCl_4, the solvent was evaporated under reduced pressure to yield the crude **1**, recrystallization from the mixture of hexane-diethyl ether afforded 0.632 g (54.7%) of **1** as white needles. mp: 51.0-52.1°C (lit[3]. mp: 50-51°C).

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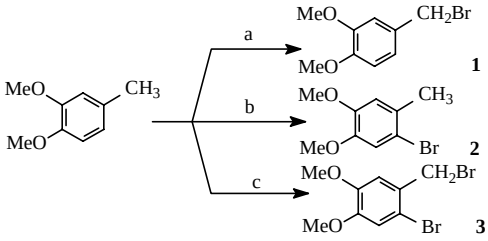
*Synthesis of compound **2***

(1) To a solution of 0.152 g (1 mmol) 3, 4-dimethoxytoluene in 5 mL of CCl_4 was added 0.196 g (1.1 mmol) NBS, the mixture was stirred at room temperature for 35 hrs. Then succinimide was filtered and washed with CCl_4, and the solvent was evaporated under reduced pressure to yield the crude **2**. Recrystallization from hexane afforded 0.197 g (85.3%) of **2** as slightly yellowish needles. mp: 30.0-31.2°C.

(2) To a stirred solution of 0.761 g (5 mmol) 3, 4-dimethoxytoluene in 25 mL of CH_3CN was added 0.979 g (5.5 mmol) NBS. After the mixture was stirred for 2 hrs, the solvent was evaporated under reduced pressure and 20 mL CCl_4 was added. The solid was filtered and washed with CCl_4, and the solvent was evaporated to yield the crude **2**, recrystallization from hexane afforded 0.987 g (85.5%) of **2**.

Scheme 1



a: NBS, CCl_4, reflux, 8 hrs; b: NBS, CCl_4, rt., 35 hrs; c: NBS, CCl_4, reflux, 26 hrs

*Synthesis of compound **3***

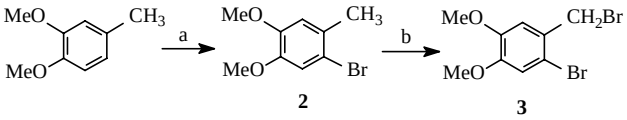
To a stirred solution of 0.152 g (1 mmol) 3, 4-dimethoxytoluene in 5 mL of CCl_4 was added 0.356 g (2 mmol) NBS, the mixture was heated to reflux for 26 hrs. Then work up as compound **1**. Recrystallization of the crude **3** from hexane afforded 0.118 g (38.1%) of **3** as white needles. mp: 84.0-85.5°C (lit[4]. mp: 82-84°C).

Results and Discussion

When the ratio of the amount of NBS and 3, 4-dimethoxytoluene was 1:1, the dominant product was benzyl bromide **1**. But the yield was unsatisfactory. When the ratio was increased to 2:1, the sole product containing two bromine atoms was isolated. The product structure was confirmed to be **3**. When benzoyl peroxide was added, the reaction time was shortened, but the yield of compound **3** was still poor. When the reaction of 3, 4-dimethoxytoluene and NBS was carried out at room temperature, the nuclear bromination product **2** was achieved in a high yield. The nuclear bromination reaction also took place in a polar solvent. When the reaction was carried out in aceto-nitrile at room temperature, ring bromination product **2** was obtained only after 2 hrs with good yield. In terms of reaction times, ring bromination with NBS was faster in CH_3CN than in CCl_4. Compound **2** can further react with 1 equiv. NBS in CCl_4 under

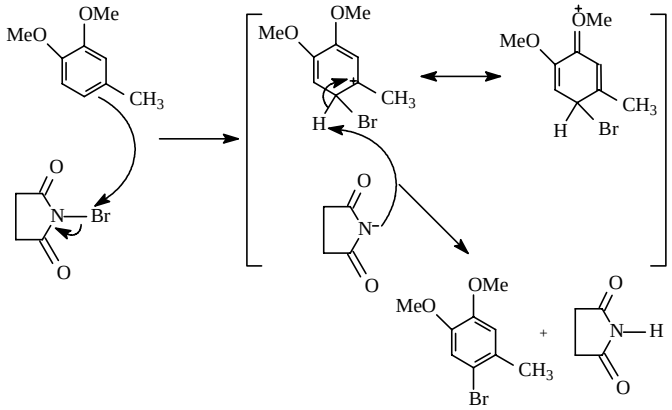
reflux to afford **3** with or without benzoyl peroxide (**Scheme 2**). Compound **3** can also be obtained in one-pot reaction through the intermediate monobrominated compound **2** in a good yield. After 3, 4-dimethoxytoluene reacted with NBS for 2 hrs in acetonitrile at room temperature, acetonitrile was removed and CCl_4 was added. Without isolating the reaction product **2**, the reaction mixture was heated under reflux 5 hrs to give product **3**.

Scheme 2



a: NBS, CH_3CN, rt., 2 hrs; b: NBS, CCl_4, reflux, 5 hrs

Scheme 3



In accordance with previous work on the use of NBS for bromination of activated aromatic rings[5, 6, 7], the presence of the methoxy group is a prerequisite for nuclear bromination. The methoxy group activates the aromatic nucleus at the para position. The side-chain bromination follows a radical pathway, while nuclear bromination is probably an electrophilic substitution reaction (**Scheme 3**). Low temperature and polar solvent facilitate the latter, while high temperature and non-polar solvent facilitate the former.

References and Notes

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2. Spectral data:
   1: ^{1}H NMR ($CDCl_3$, 300MHz, δppm) 3.883 (s, 3H, -OCH_3); 3.901 (s, 3H, -OCH_3); 4.507(s, 2H, -CH_2Br); 6.811 (d, 1H, Ar-H, J=8.1Hz); 6.919 (d, 1H, Ar-H, J=1.8Hz); 6.958 (dd, 1H, Ar-H, J=8.1, 1.8Hz). EI-MS (*m/z*): 230:232 (1:1) (M+); 151 (base); 107.
   2: ^{1}H NMR ($CDCl_3$, 300MHz, δppm) 2.327 (s, 3H, -CH_3); 3.843 (s, 3H, -OCH_3); 3.847 (s, 3H, -OCH_3); 6.731 (s, 1H, Ar-H); 7.000 (s, 1H, Ar-H). EI-MS (*m/z*): 230:232 (1:1) (M+, base);

215:217 (1:1); 108.
3: ^{1}H NMR ($CDCl_3$, 300MHz, δppm) 3.876 (s, 3H, -OCH_3); 3.883 (s, 3H, -OCH_3); 4.589 (s, 2H, -CH_2Br); 6.927 (s, 1H, Ar-H); 7.016 (s, 1H, Ar-H). EI-MS (*m/z*): 308:310:312 (1:2:1) (M+); 229:231 (1:1) (base).

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