Tetrahedron Letters 50 (2009) 831–833

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A novel simple and efficient bromination protocol for activated arenes

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ARTICLE INFO

Article history:
Received 27 October 2008
Revised 25 November 2008
Accepted 3 December 2008
Available online 7 December 2008

Keywords:
Bromination
Oxidation
Redox
Chemoselectivity
Green chemistry
Electrophilic substitution

ABSTRACT

An efficient, high yielding, and environmentally benign bromination using an alkali metal bromide as the bromine source is disclosed. Investigation of the protocol revealed that the method operates for activated arenes producing the corresponding monobrominated products in good to excellent yields.

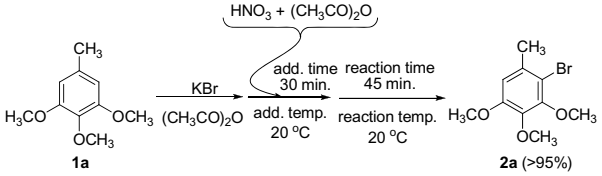
Methoxyphenyl moieties constitute essential parts of a large number of biologically active compounds, natural products, and pharmaceutical chemicals, and thus represent an important synthetic building block for the synthesis of such compounds. For this purpose, the corresponding methoxyphenyl bromides are frequently utilized as substrates.

Aryl bromides can be prepared by means of the classical Sandmeyer reaction.[1] In addition, regioselective nuclear bromination of activated aromatic and heteroaromatic compounds can also be performed by means of *N*-bromosuccinimide with tetrabutylammonium bromide present as a phase-transfer catalyst[2] or using dioxane dibromide.[3] Selective monobromination of electron-rich arenes has also been reported using $CuBr_2$[4] or alkali metal bromides in the presence of concentrated H_2SO_4[5] or various oxidants,[6] sometimes in the presence of acids[7] and/or catalysts.[8] Several of these methods are, however, saddled with various drawbacks making them environmentally unfriendly and unsuitable for large-scale industrial use due to (1) low atom economy as the large *N*-succinimide molecular fragment is used as the bromine carrier, (2) the requirement of auxiliary reagents, (3) toxic solvents as the reaction medium, and (4) harsh reaction conditions.

A current project in our laboratory is dedicated to the design and development of new synthetic pathways to phenol-based antioxidants and their intermediates,[9,10] which also comprises the discovery of new pathways toward coenzyme Q_{10}. For this purpose, we needed access to 2-bromo-3,4,5-trimethoxy-1-methylbenzene **2a**, Scheme 1.

Our general plan for the investigation and development of new synthetic pathways embraces the requirement that the processes should be environmentally benign as well as applicable for large-scale syntheses. These requirements eliminate most of the commonly used reagents for bromination, for example, *N*-bromosuccinimide.

It is known that nitric acid can oxidize bromide ions with formation of molecular bromine and nitrous acid, Scheme 2. This reaction was thoroughly investigated and revealed to be an equilibrium directed strongly toward the bromide ion ($K_1 = 1.6 \times 10^{-6}\ M^{-4}$).[12] The small positive value of the difference between the standard reduction potentials[13] ($\Delta E = E_2 - E_1 = 0.147$ V) of the two half-reactions of the overall redox process suggests that a reaction equilibrium shifted toward the bromide ion rather than bromine, which is in full agreement with the experimentally determined value of K_1.[13] Thus, the observed result of this redox process is that a very small quantity of Br_2 is present in the reaction mixture at the reaction equilibrium.



Scheme 1. An efficient high yielding bromination process.[11]

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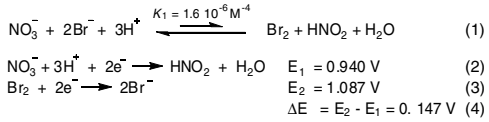
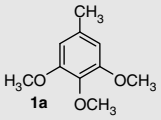
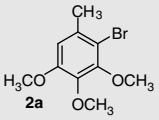
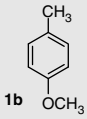
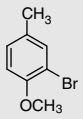
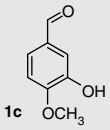
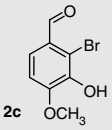
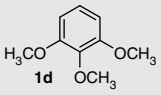
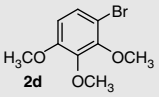
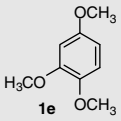
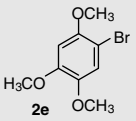
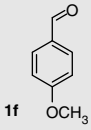
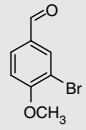
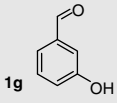
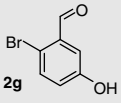
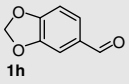
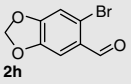
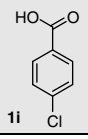
doi:10.1016/j.tetlet.2008.12.016



Scheme 2. Nitric acid-bromide reaction and the reverse nitrous acid-bromine reaction.

Table 1
Results of the bromination of a series of arenes **1a–i**

Entry	Substrate**1**	Product**2**	Yield[e] (%)
1[a]	 **1a**	 **2a**	>95
2	 **1b**	 **2b**	92
3	 **1c**	 **2c**	86
4	 **1d**	 **2d**	82
5	 **1e**	 **2e**	77
6[b]	 **1f**	 **2f**	39
7[c]	 **1g**	 **2g**	39
8	 **1h**	 **2h**	36
9[d]	 **1i**	—	—

[a] Isolated yield.
[b] A by-product was also obtained (~25%), the structure of which was not identified.
[c] 3-Hydroxy-4-nitrobenzaldehyde was obtained (~35%) as a side-product.
[d] Unconverted **1i** was the only compound present (~15%) in the reaction mixture.
[e] Yield % determined by GC using an internal standard and a purified sample of the synthesized and isolated product.

We believed that this reaction equilibrium could be used for a controlled production of molecular bromine, in which a telescoped subsequent step could take part in a selective bromination and thus promote the redox process to operate toward the production of more Br_2. This reaction sequence could be continued until the bromide source or the substrate **1** was consumed.

We designed a protocol for this purpose using the easily handled potassium bromide as the bromine source. The substrate, 1,2,3-trimethoxy-5-methylbenzene **1a**, and KBr were mixed in acetic anhydride. In an effort to accomplish better control of the production of Br_2 and thus the selectivity, the nitric acid oxidant was added dropwise as a solution in acetic anhydride. The addition of the oxidant was conducted at 20 °C, and the reaction mixture was kept at the same temperature throughout the bromination reaction. Details regarding the bromination process are provided in Scheme 1 and in note[11]. It is important to emphasize the environmentally benign aspects of the disclosed bromination protocol: (1) a very small quantity of molecular bromine is present throughout the whole reaction, (2) the quantity of nitric acid is also low at any time during the reaction, (3) the oxidant is used only in a stoichiometric quantity, (4) the solvent is acceptable even for large-scale use, and (5) the reaction is performed at room temperature.

In order to investigate the generality of this bromination protocol, a series of substituted arenes (Table 1) were submitted to the bromination conditions described in Scheme 1.

The obtained results (Table 1) show that the bromination protocol operates excellently with activated arenes (see **1a**–**1e**). Our original target product, 2-bromo-3,4,5-trimethoxy-1-methylbenzene **2a**,[14] was obtained in a yield of >95%. Benzene derivatives substituted only with electron-withdrawing groups such as 4-chlorobenzoic acid **1i** did not react. In general, the yields of the various brominated products increase with the number of electron-donating groups (**1a** > **1c** > **1f**). Moreover, the regioselectivity of the reactions is in agreement with the known directing ability of the substituent groups.

Taken as a whole, the results strongly suggest that the bromination operates according to an electrophilic substitution by means of the Br^+ ion.[15] Br is a deactivating group, thus monobrominated arenes are considerably less reactive compared to the starting arene. This fact explains the high selectivity of the novel bromination protocol disclosed herein.

In conclusion, a new, simple, efficient, and cheap bromination protocol is disclosed. Moreover, the process can be considered to be 'green' compared to other procedures. The method involves reagents that can be handled easily even on large scale making it suitable also for industrial scale applications.

Acknowledgments

Economic support from Denomega AS, the Nutrition research program at the University of Bergen, Fluens Synthesis AS, and the Research Council of Norway (G.O) is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.016.

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11. *General procedure*: (2-Bromo-3,4,5-trimethoxy-1-methylbenzene **2a** [72326-72-8]). Nitric acid (65%, 1.6 mmol, 0.11 mL) was added to acetic anhydride (5.0 mL). This mixture was, by means of a syringe-pump, added dropwise over a period of 30 min to a mixture of 3,4,5-trimethoxytoluene (1.5 mmol) and KBr (2.0 mmol) in acetic anhydride (2.5 mL). After complete addition of the oxidant, the reaction mixture was stirred for another 45 min at 20 °C. Water (10 mL) was added to the reaction mixture, which was stirred for another 30–40 min at room temperature. The quenched reaction mixture was extracted with diethyl ether (3 × 10 mL). The organic layers were combined and washed with saturated brine solution, dried over sodium sulfate, filtered, and the solvent was then removed under reduced pressure to afford 2-bromo-3,4,5-trimethoxy-1-methylbenzene **2a** in a yield of >95% (colorless — yellowish oil). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.34 [s, 3H], 3.81 [s, 3H], 3.83 [s, 3H], 3.86 [s, 3H], 6.57 [s, 1H]. MS (EI) *m*/*z* (%): M^+ 262 (100), 260 (99), 217 (25), 202 (40), 166 (20), 151 (25), 138 (47), 123 (38), 108 (12), 77 (20), 63 (15), 51 (27). TLC system: hexane/ethyl acetate = 11:1, R_f = 0.45 on a silica gel plate with fluorescent indicator at λ = 254 nm.
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