Pergamon

Tetrahedron Letters, Vol. 38, No. 25, pp. 4415-4416, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00943-X

1,3-Dibromo-5,5-Dimethylhydantoin, a useful Reagent for Aromatic Bromination

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Abstract: 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) is a useful and easy to handle reagent for bromination of various aromatic derivatives substituted with electron donating groups. In the presence of trimethylsilyltrifluoromethanesulfonate, DBDMH showed increased reactivity, and in one case, the reaction followed another pathway, suggesting an alternative mechanism. © 1997 Elsevier Science Ltd.

During the course of the total synthesis of the *Lycopodium* alkaloid Huperzine A[1], we investigated several reaction conditions for the selective bromination at C5 of 2-methoxy-6-methylpyridine. Direct bromination with bromine-potassium bromide-potassium hydroxide or bromine-sodium hydrogenophosphate[2] gave respectively a mixture of 5-bromo and 3,5-dibromo derivatives or 5-bromo and 3-bromo derivatives. These mixtures need to be purified in both cases. The use of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) overcame the problem of regioselective bromination and selectively gave 5-bromo-2-methoxy-6-methylpyridine in high yield (85%) after distillation[1]. We present in this paper our further studies with this cheap, easy to handle brominating reagent in various aromatic brominations under mild conditions. DBDMH has been already used in aromatic bromination in the presence of a strong acid such as trifluoromethanesulfonic acid (TfOH), generating the bromonium cation which reacted with aromatics having electron donating or withdrawing substituents[3]. Various methoxy substituted benzoic acids were also brominated with DBDMH in aqueous sodium hydroxide[4].

Two sets of experiments have been developped with DBDMH alone and with mixtures of DBDMH and TMSOTf. With the first neutral system, aryl derivatives susbstituted with a strong donating group such as a hydroxy group, one or two methoxy groups, or substituted amino groups reacted smoothly in THF (typically after overnight reaction), affording the expected bromo derivatives (Table, entries 4, 6, 10-12 and 14). Rapid treatment of phenols with only one half equivalent of DBDMH gave rise to a mixture of mono and dibromoderivatives (entry 5). Ethers (entries 10-12) afforded in good yields monobromo and dibromo derivatives, depending on the stoichiometry of DBDMH. Toluene, *ortho*-anisaldehyde and 2-picoline (entries 1, 8 and 13) proved to be inert under these reaction conditions, while *meta*-xylene and quinoline (entries 3 and 16) gave only poor yields, showing the limit of this neutral system.

The mixture DBDMH-TMSOTf in methylene chloride proved to be more reactive, affording brominated compounds with toluene and *ortho*-anisaldehyde (entries 2 and 9). A striking difference of behaviour between the two reagents was observed with 2-allylphenol (entries 6 and 7). DBDMH alone

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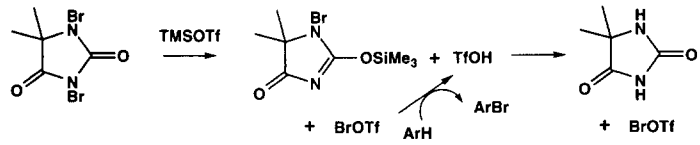
afforded the expected arylic bromination, whereas DBDMH-TMSOTf gave rise to a dihydrobenzofuran derivative resulting from a nucleophilic attack of phenol group on the side chain bromonium intermediate.

The difference of reactivity and chemoselectivity between the two systems could be explained by the formation of a bromonium triflate as reactive intermediate. After electrophilic substitution, one equivalent of triflic acid was released. This strong acid reacting with the silylenol intermediate could give rise to 5,5-dimethylhydantoin (DMH) and a second equivalent of bromonium triflate (Scheme).



In order to compare with the DBDMH-TfOH reagent previously described[3], bromination of methyl benzoate was also examined (entries 17 and 18). The lack of reactivity observed in our case showed that in the presence of a strong acid, the reaction followed probably a different pathway.

Table

Entry	Substrate	Molecular ratio (Susbtrate/Reagent) DBDMH	DBDMH +TMSOTf	Reaction condition: Time	Products % (ratio)
1	Toluene	1/0.5		18 h	Starting material
2	Toluene		1/0.5/0.5	12 h	2-Bromotoluene:4-Bromotoluene 80 (1.4:1)
3	1,3-Dimethyl benzene	"		18 h	1-Bromo-2,4-dimethyl benzene 20
4	2-Methylphenol	1/1		"	4-Bromo-2-methylphenol: 4,6-Dibromo-2-methylphenol 75 (1:4)
5	2-Allylphenol	1/0.5		2 h	4-Bromo-2-allylphenol 8 4,6-Dibromo-2-allylphenol 13 Starting material 79
6	"	1/1		18 h	4,6-Dibromo-2-allylphenol 85
7	"		"	2 h	3-Bromomethyl-2,3-dihydrobenzofuran 50
8	*o*-Anisaldehyde	1/0.5		18 h	Starting material
9	"		"	2 h	3-Bromo-*o*-anisaldehyde 86
10	Anisole	"		18 h	4-Bromo-anisole 85
11	1,3-Dimethoxy benzene	"		"	1-Bromo-2,4-dimethoxy benzene 98
12	"	1/1		"	1,3-Dibromo-2,4-dimethoxy benzene 85
13	2-Picoline	"	"	"	Starting material
14	4-Dimethylamino pyridine	1/0.5		"	3-Bromo-4-dimethylamino pyridine 80
15	2-Methoxy-6-methyl pyridine	1/1		"	5-Bromo-2-methoxy-6-methyl pyridine 85
16	Quinoline	"		"	3-Bromo quinoline 20
17	Methyl benzoate		"	2 h	Starting material
18[3]	"		0.5/0.1(TfOH)	"	3-Bromo methyl benzoate 77

Acknowledgement: We thank Daphné Monteux for helpful suggestions.

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(*Received in France* 7 *April* 1997; *accepted* 9 *May* 1997)