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NOVEL BROMINATION REAGENTS[1]. HEXABROMOCYCLOPENTADIENE: BROMINATION OF ACTIVATED SATURATED SITES

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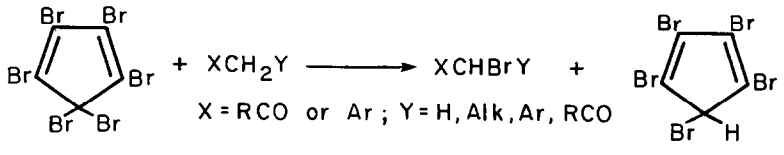
Abstract. Hexabromocyclopentadiene (HBC) readily brominates α-keto and benzylic sites, apparently by bromonium ion transfer.

We have recently shown[1] that hexabromocyclopentadiene (HBC)(1) is a new and useful aromatic bromination reagent in that it performs site-selective electrophilic bromination of activated (electron rich) aromatic compounds. This was postulated to occur by bromonium ion release by virtue of aromatic stabilization of the cyclopentadienide counterpart which ends up as pentabromocyclopentadiene (2).

We wish to report now that HBC(1) readily brominates ketones in α-position and alkyl aromatics in benzylic position, as shown in the Scheme and detailed in the Table. We tried aliphatic-(entries 1-7), aromatic-(8-12), alicyclic-(13-17), β-dicarbonyl(18-21) and α,β-unsaturated(22,23) ketones and a small number of α-methylene aromatics (entries 24-27) using varying amounts of HBC. As before[1], the reactions were strongly dependent on solvent polarity; we worked in acetonitrile solutions at two temperatures: 70°C at which analytical/kinetical runs were performed and monitored by NMR (in MeCN-d_3) and at reflux (82°C) with subsequent work-up and analysis of the crude reaction mixture and occasional isolation of the pure products.

The α-bromination of ketones is a well documented reaction[2-18] and continuously pursued because of its synthetic significance and mechanistic interest. In both these contexts one is particularly concerned with the site- and/or stereoselectivity of the processes. From this point of view, HBC(1) usually provides the thermodynamically stable bromo-derivative although kinetically controlled products have been observed, i.e. the electronic and steric features of the substrate can be product determining. Thus, simple but asymmetric ketones are brominated at the more substituted α-carbon (entries 1-4) but terminal bromination products were also observed before undergoing isomerization (cf. footnote d in the Table). Additional bromines enter anyway the terminal position (entries 5,6) and, moreover, α,α,α-tribromoketones can be readily obtained (entries 7,12).



1 2

Table 1. Bromination of active (α-keto and benzylic) sites with hexabromocyclopentadiene (HBC) (1)[a]

Entry	Ketone	[HBC]/[ketone]	Product	Temp.,°C	Time,hrs	Yield,%[b]([c])	Ref.
1	$CH_3CH_2COCH_3$	1	$CH_3CHBrCOCH_3$[d]	70	17.5	82	6
2	- " -	1	- " -	82	2	100 (30)	
3	$PhCH_2COCH_3$	1	$PhCHBrCOCH_3$	70	32	63	7
4	- " -	1	- " -	82	10	90 (45)	
5	- " -	2	$PhCHBrCOCH_2Br$	82	20	100 (70)	8
6	$PhCHBrCOCH_2Br$	1	$PhCHBrCOCHBr_2$	82	62	83 (80)	
7	$PhCHBrCOCHBr_2$	1	$PhCHBrCOCBr_3$	82	65	65 (60)	
8	$PhCOCH_3$	1	$PhCOCH_2Br$	70	14	64	3,9
9	- " -	1	- " -	82	16	80	
10	- " -	2	$PhCOCHBr_2$	70	60	60	10
11	$PhCOCH_2Br$	1	- " -	82	16	70 (60)	
12	$PhCOCHBr_2$	3.5	$PhCOCBr_3$	70	240	30	11
13	$CH_2CH_2CH_2CH_2CH_2C{=}O$	1	$CH_2CH_2CH_2CH_2\underset{Br}{C}HC{=}O$	82	4	53 (40)	12
14	$CH_2CH_2\underset{CMe_3}{C}HCH_2CH_2C{=}O$	1	$CH_2CH_2\underset{CMe_3}{C}HCH_2\underset{Br}{C}HC{=}O$[e]	70	23	67	13
15	- " -	1	- " -	82	4	66 (40)	
16	- " -	2	$\underset{Br}{C}HCH_2\underset{CMe_3}{C}HCH_2\underset{Br}{C}HC{=}O$	82	8	90 (54)	14
17	3-cholestanone	1	2α-bromocholestanone	82	15	90 (77)	15
18	$CH_3COCH_2CO_2Et$	1	$CH_2BrCOCH_2CO_2Et$[f]	70	23	70	16
19	- " -	1	- " -	82	20	100 (42)	
20	$CH_3COCH_2COCH_3$	1	$CH_2BrCOCH_2COCH_3$	82	4	70	17
21	- " -	1	$CH_3COCH_2BrCOCH_3$[g]	70	6[g]	20	
22	$(CH_3)_2C{=}CHCOCH_3$	1	$(CH_3)_2C{=}CBrCOCH_3$	82	2	100	18
23	$PhCH{=}CHCOCH_3$	1	$PhCH{=}CHCOCH_2Br$	70	8	85 (70)	3-5
24	$PhCH_3$	1	$PhCH_2Br$	82[h]	160	66	20
25	Ph_2CH_2	1	Ph_2CHBr	82[h]	336	64	21
26	Fluorene	1	9-Bromofluorene	82	186	88	22
27	- " -	1	- " -	70	600	80	

a) Brominations were performed either in MeCN-d_3 in NMR tubes at 70°C or in refluxing MeCN (82°C) followed by analysis; products were authenticated by spectroscopy[b] or isolation[c].

b) Determined by NMR measurement of the reaction mixture at 70° or of the crude product from 82°.

c) Isolated by fractional crystallization or by chromatography on silica gel (in many cases appreciable decomposition took place on the column); no optimization experiments were performed.

d) At first a mixture of isomeric 1-bromo- and 3-bromo-derivatives was observed (e.g. after 4 hrs the ratio is 3:10, respectively) but complete isomerization to the latter occurred eventually.

e) Mixture of trans and cis isomers (1:1). At longer reaction times, dehydrobromination set in.

f) Small amounts of 2-bromo derivative were observed at low conversion but rearranged rapidly.

g) At 70°C the bromination of (9) took place very slowly at position 3 and only after long induction times, during which the starting ketone (9) completely disappeared but could be brought back by acidification (TFA).

h) At 70°C the reaction proceeded very slowly.

Cyclic ketones behave normally (entries 13-17) but prolongation of the reaction in cases 13-15 reduces the yield because of dehydrobromination. An additional experiment is worth mentioning: 2-methylcyclohexanone in pure acetonitrile at 70°C is brominated by HBC in position 2 but in acetonitrile/methanol (10%) the 6-bromo derivative was the only product (as observed by NMR). This behaviour is analogous to the solvent effect reported for molecular bromine[19], only more specific.

The case of β-dicarbonyl compounds is interesting (entries 18-21): the terminally brominated derivatives are always the end-product but in the first stage the methylene position is preferentially attacked. This is particularly clearly observed with acetylacetone at 70° where the centrally brominated compound slowly appears after an induction period of ca. two hours during which virtually all the NMR signals of the starting material disappeared. It is suggested that a (charge-transfer) complex between HBC(1) and the enol form of acetylacetone is formed before site-selective Br^+ transfer to the central position with eventual rearrangement to the terminal methyl group. We believe, in fact, that HBC-enol complexation (of variable strength) precedes any of the observed bromination processes.

The bromination of α,β-unsaturated ketones presents an apparent discrepancy (entries 22,23). Mesityl oxide is brominated exclusively in the vinylic, α position, but benzalacetone in the terminal α position. We tend to invoke charge density arguments to account for this different yet high specificity.

Finally, the bromination of toluene, diphenylmethane and fluorene in their benzylic positions is, to our knowledge the first instance of uncatalyzed halogenations at non-enolisable saturated sites. In contrast to published procedures[20-22] no radical initiation was necessary and no competitive attack on the aromatic nucleus occurred, but the reactions were very slow (entries 24-27) and the mechanism of this electrophilic bromination at saturated, benzylic sites is still to be worked out.

In all above described cases, pentabromocyclopentadiene(2) is formed and in some cases even carries on the bromination albeit at a much lower rate. This, however, is left to be discussed in a forthcoming report.

To conclude, the apparently esoteric compound HBC(1) has many advantages for use as a bromination reagent in α-keto or benzylic positions: it is readily available, solid and relatively non-corrosive and performs slow and selective bromination in good to excellent yields.

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References

1. Bromo-organics. 4. Part 3: B. Fuchs, Y. Belsky, E. Tartakovsky, J. Zizuashvili and S. Weinman, J. Chem. Soc., Chem. Commun., 1982, 778.
2. A. Roedig in Houben-Weyl "Methoden der Organischen Chemie-Halogen Verbindungen" (E. Müller, Ed.), Vol. V/4, p. 171, Georg Thieme, Stuttgart, 1960.
3. R. Bloch, Synthesis, 1978, 140.
4. V. Calo, L. Lopez, G. Pesce and P.E. Todesco, Tetrahedron, 1973, 29, 1625.
5. D.V.C. Awang and S. Wolfe, Can. J. Chem., 1969, 47, 706.
6. a) C. Rappe and R. Kumar, Arkiv Kemi, 1965, 23, 475.
   b) C. Rappe, ibid, 1965, 23, 81 and references cited there.
   c) C. Rappe in "The Chemistry of the Carbon-Halogen Bond (S. Patai, Ed.), p. 1074, Wiley, New York, 1973.
7. H. Brederek and C. Gompper, Chem. Ber., 1954, 87, 700.
8. A.J. Fry and J. J. O'Dea, J. Org. Chem., 1975, 40, 3625.
9. R.M. Cowper and L.H. Davidson, Org. Synth. Coll. Vol. II, 1943, 480.
10. W. Taylor, J. Chem. Soc., 1937, 304.
11. J.G. Aston, J.D. Newkirk, J. Dorsky and D.M. Jenkins, J. Am. Chem. Soc., 1942, 64, 1413.
12. H. Schmid and P. Karrer, Helv. Chim. Acta, 1946, 29, 573.
13. R.H. Prager and P.A. Reece, Austr. J. Chem., 1975, 28, 1775.
14. F.G. Bordwell and K.M. Wellman, J. Org. Chem., 1966, 31, 351.
15. I. Malunowicz, J. Fajkos and F. Sorm, Coll. Czech. Chem. Commun., 1960, 25, 1359.
16. A. Svendsen and P.M. Boll, Tetrahedron, 1973, 29, 4251.
17. D.F. Tavares, W.I. O'Sullivan and C.R. Hauser, J. Org. Chem.,1962, 27, 1251 and references cited there.
18. H. Moureu and P. Chovin, Bull. Soc. Chim., France, 1953, 586 and other papers in the series.
19. a) E.W. Garbisch, Jr., J. Org. Chem., 1965, 30, 2109 but see also:
   b) M. Gaudry and A. Marquet, Bull. Soc. Chim., France, 1969, 4178.
20. V. Veijola, Suomen Kemistilehti, 1953, 26A, 272.
21. S. Leiv and I. Songstad, Acta Chem. Scand., 1970, 24 ,356.
22. A.H. Wragg, T.S. Stevens and D.M. Ostle, J. Chem. Soc., 1958, 4057.

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