Tetrahedron. Vol. 31, pp. 231 to 233. Pergamon Press 1975. Printed in Great Britain

2-BROMO-2-CYANO-N,N-DIMETHYLACETAMIDE AS A NEW BROMINATING AGENT

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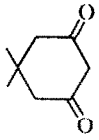
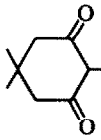
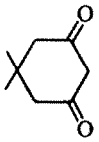
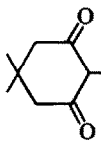
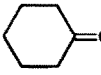
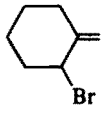
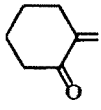
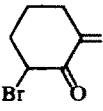
(*Received in Japan* 3 *July* 1974; *Received in UK for publication* 7 *October* 1974)

Abstract—It has been found that 2-bromo-2-cyano-N,N-dimethylacetamide is effective for monobromination at α-carbon of ketones with high selectivity. Effects of solvent and of radical initiator and scavenger are suggestive of radical mechanism.

After development of the preparation of 2-bromo-2-cyano-N,N-dimethylacetamide[1] (BCDA) we wish to report the value of this compound as a new brominating agent. BCDA is effective for bromination at α-carbon of ketones with high selectivity. Normally the bromination was carried out by refluxing the benzene solution of BCDA and the substrate in 1:1 molar proportion. Results of the experiments are summarized in Table 1.

Benzylideneacetone was brominated into 1-bromo-4-phenyl-3-buten-2-one under the above condition in 56% yield. In place of benzene the use of chloroform and isopropanol gave lower yields, 44% and 15%, respectively. This selective monobromination at methyl of benzylideneacetone has not been achieved by known brominating agents other than pyrrolidone hydrotribromide.[2] Further six ketones were brominated using benzene as solvent and, as shown in Table 1, the corresponding monobrominated ketones were obtained in

Table 1. Bromination* of ketones with 2-bromo-2-cyano-N,N-dimethylacetamide (BCDA) and with 2-bromomalononitrile (BMN)

Run No	Substrate	Brominating agent	Reaction time (hr)	Product	Yield (%)
1	$C_6H_5CH{=}CHCOCH_3$	BCDA	4	$C_6H_5CH{=}CHCOCH_2Br$ **1**	56
2		BCDA	6	 **2**	90
3		BMN	5	 **2**	90
4	$C_6H_5COCH_3$	BCDA	8	$C_6H_5COCH_2Br$ **3**	66
5	$C_6H_5COCH_3$	BMN	8	$C_6H_5COCH_2Br$ **3**	52
6	$CH_3COCH_2CH_3$	BCDA	6	$CH_3COCHBrCH_3$ **4**	46
7	$CH_3COCH_2CH_3$	BMN	17	$CH_3COCHBrCH_3$ **4**	5
8	$C_6H_5CH_2COCH_3$	BCDA	6	$C_6H_5CHBrCOCH_3$ **5**	62
9		BCDA	0·7	 **6**	62
10		BCDA	2	 **7**	88

*Substrate: 0·05 mole; brominating agent: 0·05 mole; solvent: benzene, 50 ml; reaction temp.: refluxing.

good yields. From these results it can be said that the bromination is characterized by the selectivity at α-carbon of the ketones in the side favorable to enolization. Allyl carbon and α-carbon of carboxylate was not affected by BCDA, as demonstrated by noting inertness to the compounds such as crotononitrile, methyl crotonate, ethyl phenylacetate, ethyl malonate, N,N-dimethylbarbituric acid, cyclohexene, *p*-nitrotoluene and phenol. In view of these facts BCDA appears to offer high selective bromination of α-carbon of ketones which is not feasible by the analogous brominating agents such as 2,2,2-tribromoacetophenone[3] or 2,2-dibromomalononitrile[4] and the other known agents.

In the bromination BCDA was converted into debrominated 2-cyano-N,N-dimethylacetamide, most of which was easily isolated during product isolation. This is an additional benefit, as this can be utilized by conversion into BCDA.

The α-bromoketone products exhibited IR and NMR spectra consistent with their structures. Some of them which were fuming were identified as thiazole derivatives by reacting with thiourea.

In order to know whether the reaction proceeds through a radical path, preliminary mechanistic examination was undertaken to see the effect of a radical initiator and scavenger. Control experiments by using benzylideneacetone as a substrate showed that the presence of 2,2'-azobisisobutyronitrile, as shown in Table 2, shortened the reaction period and the presence of *p*-benzoquinone entirely restrained the bromination. These facts in addition to the solvent effect shown in the foregoing suggest a radical mechanism.

Further experiments were carried out to test 2-bromomalononitrile as a brominating agent. Under the same conditions, benzylideneacetone did not react with 2-bromomalononitrile and the three ketones selected as the substrates (Table 1) were brominated in the yields lower than those in the BCDA bromination. This lower reactivity of 2-bromomalononitrile and difficulty in the isolation of the debrominated malononitrile make this method practically useless for bromination as compared with the BCDA method.

Table 2. Bromination[a] of benzylideneacetone with 2-bromo-2-cyano-N,N-dimethylacetamide (BCDA)

$C_6H_5CH{=}CHCOCH_3 \xrightarrow{BCDA} C_6H_5CH{=}CHCOCH_2Br$

Solvent	Additive	Reaction time (hr)	Yield (%)
Benzene	—	4	56
Chloroform	—	10	44
Isopropanol	—	26	14
Benzene	AIBN[b]	2	50
Benzene	BQ[c]	8	0

[a] Benzylideneacetone: 0·05 mole; BCDA: 0·05 mole; solvent: 50 ml; reaction temp.: refluxing.
[b] 2,2'-Azobisisobutyronitrile, 0·004 mole.
[c] *p*-Benzoquinone, 0·01 mole.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Spectra reported herein were determined with a Hitachi ESP-3T UV spectrophotometer, a Hitachi EPI-G2 IR spectrophotometer, and a JEOL JNM-C-60H NMR spectrometer using TMS as internal standard. The following abbreviations are used: d = doublet, m = multiplet, q = quartet, s = singlet, t = triplet.

General procedure for bromination with 2-bromo-2-cyano-N,N-dimethylacetamide (BCDA). For the bromination the substrates used were benzylideneacetone, dimedone, acetophenone, 2-butanone, phenylacetone (b.p. 118–122° (35 mmHg)), cyclohexanone and 2-benzylidenecyclohexanone (m.p. 53–54°).

A soln of 0·05 mole of the substrate and 9·5 g (0·05 mole) of BCDA (m.p. 53–54°)[1] in 50 ml benzene was refluxed with stirring. The reaction times recorded in Table 1 were decided by noting disappearance of BCDA on TLC. Process of the reaction was also indicated by noting shift of UV absorption maximum of the soln in the runs of the reaction of benzylideneacetone with BCDA for examination of the effect of solvent and of radical initiator and scavenger (Table 2). The reaction soln was concentrated under reduced pressure, and the resulting residue was submitted to extraction with light petroleum (isopropyl ether in the runs with benzylideneacetone). The insoluble residual crystals, m.p. 65–66°, were shown to be 2-cyano-N,N-dimethylacetamide, which were nearly quantitative in most runs. After removal of the solvent, the residue was fractionally distilled under reduced pressure to give the monobrominated product. In the run 10 in Table 1 the crystalline product **7** was obtained by concentration of the light petroleum extract. In the run 2 in Table 1 most of the product **2** was deposited in the reaction soln on cooling.

Yield of the brominated product in each run is recorded in Tables 1 and 2. Physical and analytical data are described below. In the runs 6, 7, 8, 9 and 10 in Table 1 α-bromoketone products (among them **4**, **5** and **6** were unstable fuming liquids) were identified by conversion into hydrobromides of 2-aminothiazole derivatives by refluxing with equimolar amount of thiourea in EtOH.

1-Bromo-4-phenyl-3-buten-2-one (**1**), b.p. 108–115° (0·03 mmHg), m.p. 44–46° (lit.[2] m.p. 46–47°); IR(KBr) ν cm^{-1}: 1670 (CO); UV(EtOH) λ_{max} mμ(ϵ): 225 (10500), 299 (24100); NMR($CDCl_3$) τ: 2·32–2·68 (5H, m, aromatic protons), 2·30 (1H, d, J = 16 Hz, –CH=CHCO–), 3·10 (1H, d, J = 16 Hz, –CH=CHCO–), 5·93 (2H, s, CH_2). (Found: C, 53·38; H, 4·08; Br, 35·57. $C_{10}H_9OBr$ requires: C, 53·36; H, 4·03; Br, 35·50%).

2-Bromodimedone (**2**), needles from benzene, m.p. 174–175° (dec) (lit.[5] m.p. 175–176° (dec)); IR(KBr) ν cm^{-1}: 1678 (CO); NMR(CF_3CO_2H) τ: 7·32 (4H, s, $2CH_2$), 8·81 (6H, s, $2CH_3$). (Found: C, 43·41; H, 5·00; Br, 36·73. $C_8H_{11}O_2Br$ requires: C, 43·86; H, 5·06; Br, 36·48%).

2-Bromoacetophenone (**3**), b.p. 135–136° (18 mmHg), m.p. 49–50° (lit.[6] m.p. 49–51°); IR(KBr) ν cm^{-1}: 1697 (CO). (Found: C, 45·07; H, 3·71; Br, 42·58. C_7H_7OBr requires: C, 44·95; H, 3·71; Br, 42·72%).

2-Bromobutan-3-one (**4**), b.p. 79–82° (110 mmHg) (lit.[7] b.p. 80° (110 mmHg)); IR(liquid) ν cm^{-1}: 1724 (CO); NMR ($CDCl_3$) τ: 5·64 (1H, q, J = 7 Hz, CH), 7·69 (3H, s, CH_3CO), 8·32 (3H, d, J = 7 Hz, CH_3). 2-Amino-4,5-dimethylthiazole hydrobromide: prisms from EtOH, m.p. 283–284°; IR(KBr) ν cm^{-1}: 1622. (Found: C, 29·14; H, 4·44; N, 13·49; S, 15·76; Br, 38·49. $C_5H_9N_2SBr$ requires: C, 28·71; H, 4·33; N, 13·39; S, 15·33; Br, 38·21%).

1-Bromo-1-phenylpropan-2-one (**5**), b.p. 117–125° (6 mmHg) (lit.[8] b.p. 122–126° (8 mmHg)); IR(liquid) ν cm^{-1}: 1714 (CO); NMR($CDCl_3$) τ: 2·63–2·87 (5H, m, aromatic protons), 4·60 (1H, s, CH), 7·79 (3H, s, CH_3). 2-Amino-4-methyl-5-phenylthiazole hydrobromide: needles from EtOH, m.p. 212–214° (lit.[8] m.p. 213–215°); IR(KBr) ν cm^{-1}: 1634. (Found: C, 44·25; H, 4·12; N, 10·61; S, 12·26; Br, 29·78. $C_{10}H_{11}N_2SBr$ requires: C, 44·29; H, 4·08; N, 10·32; S, 11·83; Br, 29·46%).

2-Bromocyclohexanone (**6**), b.p. 89–94° (4 mmHg) (lit.[9] b.p. 112–113° (20 mmHg)). 2-Amino-4,5,6,7-tetrahydrobenzothiazole hydrobromide: prisms from H_2O, m.p. 232–234° (lit.[10] m.p. 235–236°); IR(KBr) ν cm^{-1}: 1618. (Found: C, 36·19; H, 4·78; N, 12·03; S, 14·04; Br, 34·15. $C_7H_{11}N_2SBr$ requires: C, 35·75; H, 4·71; N, 11·91; S, 13·64; Br, 33·98%).

2-Bromo-6-benzylidenecyclohexanone (**7**). Prisms from light petroleum, m.p. 82–84°; IR(KBr) ν cm^{-1}: 1678 (CO); UV(EtOH) λ_{max} mμ(ϵ): 226 (7500), 298·5 (14900); NMR($CDCl_3$) τ: 2·48 (1H, t, J = 1·5 Hz, $\rangle$C=CH–), 2·64 (5H, s, aromatic protons), 5·34 (1H, t, J = 5·0 Hz, –CHBr–), 6·67–8·24 (6H, m, $3CH_2$). (Found: C, 58·70; H, 4·99; Br, 30·66. $C_{13}H_{13}OBr$ requires: C, 58·88; H, 4·94; Br, 30·13%). 2-Amino-4-benzylidene-4,5,6,7-tetrahydrobenzothiazole hydrobromide: prisms from aq.EtOH, m.p. 229–231°; IR(KBr) ν cm^{-1}: 1622; UV(EtOH) λ_{max} mμ(ϵ): 268 (14100), 297 (21290). (Found: C, 52·24; H, 4·67; N, 8·40; S, 10·11; Br, 24·55. $C_{14}H_{15}N_2SBr$ requires: C, 52·01; H, 4·67; N, 8·66; S, 9·71; Br, 24·71%).

Procedure for bromination with 2-bromomalononitrile

Three ketones, dimedone, acetophenone and 2-butanone, were subjected to the bromination with 2-bromomalononitrile (m.p. 63–65°).[11] The brominations were worked up by the same manner as for those with BCDA. Results are recorded in Table 1. In the run 3 the monobrominated product crystallized out of the soln and in the other runs was obtained by fractional distillation of the residue under reduced pressure after concentration of the reaction soln. The distillation residue was composed of malononitrile and 2-bromomalononitrile, separation of which was laborious.

Acknowledgement—We wish to thank Mr. K. Narita and the other members of the Analysis Center of this college for microanalysis and NMR measurement.

REFERENCES

[1]J. Suzuki, K. Suzuki and M. Sekiya, *Chem. Pharm. Bull. Tokyo* **22**, 965 (1974)
[2]D. V. C. Awang and S. Wolfe, *Can. J. Chem.* **47**, 706 (1969)
[3]F. Kröhnke and K. Ellegast, *Chem. Ber.* **86**, 1556 (1953); B. I. Stepanov and V. F. Traven, *Zh. Org. Khim.* **5**, 387 (1969); V. A. Smrchek, V. F. Traven and B. I. Stepanov, *Ibid.* **8**, 1766 (1972)
[4]T. Hata, *Bull. Chem. Soc. Japan* **37**, 547 (1964)
[5]E. R. Blout, V. W. Eager and D. C. Silverman, *J. Am. Chem. Soc.* **68**, 566 (1948)
[6]Org. Synth. Coll. Vol. II, 480 (1943)
[7]J. R. Catch, D. F. Elliott, D. H. Hey and E. R. H. Jones, *J. Chem. Soc.* 272 (1948)
[8]A. C. B. Smith and W. Wilson, *Ibid.* 1342 (1955)
[9]P. Z. Bedoukian, *J. Am. Chem. Soc.* **67**, 1430 (1945)
[10]N. K. Kucherova and K. A. Kocheshkov, *J. Gen. Chem. USSR* **16**, 1701 (1946)
[11]P. Bouldt, L. Schulz and J. Etzemüller, *Chem. Ber.* **100**, 1281 (1967)