A Convenient Method for the Monobromination of Active Methylene Compounds

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A general procedure for the conversion of active methylene compounds to the corresponding monobromoderivatives consists in treating the active methylene compounds with bromine. Numerous examples, however, show that a mixture of dibromo- and monobromo-derivatives is yielded even by the equimolar reaction of the active methylene compounds and bromine.

Although dibromocyanoacetamide was prepared by Hesse[1] as early as 1896, the monobromoderivative was not prepared until 1922 by Gupta and Thorpe.[2] They prepared monobromocyanoacetamide in a 55% yield by the partial debromination of dibromocyanoacetamide with dimethylaniline. Later, Wideqvist[3] reported that monobromocyanoacetamide was obtained in a high yield when an equimolar amount of cyanoacetamide and dibromocyanoacetamide was heated in an aqueous solution. In a previous paper,[4] it was shown that

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[1] B. C. Hesse, *Am. Chem. J.*, **18**, 723 (1896).

[2] B. M. Gupta and J. F. Thorpe, *J. Chem. Soc.*, **121**, 1896 (1922).

[3] S. Wideqvist, *Acta. Chem. Scand.*, **7**, 696 (1953).

[4] T. Hata and T. Mukaiyama, This Bulletin, **35**, 1108 (1962).

monobromocyanoacetamide was also obtained in a high yield by the reaction of cyanoacetamide and dibromocyanoacetamide in 95% ethanol.

In the present experiment, the proportionation procedure was extended to the preparation of *N*-ethyl monobromocyanoacetamide and *N*-cyclohexyl monobromocyanoacetamide, which were obtained in 84% and 90% yields respectively, according to the following equation:

$$\mathrm{NCCH_2CONHR + NCCBr_2CONHR}$$
$$\rightarrow \mathrm{2\ NCCHBrCONHR}$$
$$\mathrm{R:\ C_2H_5\ or\ C_6H_{11}}$$

Similarly, monobromomalonitrile was obtained in a 60% yield by the proportionation reaction of malonitrile and dibromomalonitrile in the presence of a catalytic amount of boron trifluoride.

$$\mathrm{CH_2(CN)_2 + CBr_2(CN)_2 \xrightarrow{BF_3} 2\ CHBr(CN)_2}$$

Next, the monobromination of various active methylene compounds by the use of dibromomalonitrile was tried, since it was found that the bromine atoms of dibromomalonitrile are much more active than those of the other dibromoamides.

When two moles of malonamide were treated with one mole of dibromomalonitrile, monobromomalonamide was obtained in a 75% yield, along with malonitrile, as is shown in the following equation:

$$\mathrm{2\ CH_2(CONH_2)_2 + CBr_2(CN)_2}$$
$$\rightarrow \mathrm{2\ CHBr(CONH_2)_2 + CH_2(CN)_2}$$

Similarly, monobromocyanoacetamide, *N*-cyclohexyl monobromocyanoacetamide, ethyl bromocyanoacetate and ethyl bromomalonate were obtained in high yields by the reaction of dibromomalonitrile with two moles of the corresponding active methylene compounds (see Table I).

On the other hand, it has been reported⁵⁾ that the bromination of malonanilide with bromine gives a mixture of several brominated products because the anilide has six replaceable hydrogen atoms in the para- and ortho-positions in each phenyl group, and two hydrogen atoms in the malonyl group.

It was established by the present experiment that the bromination of malonanilide by means of dibromomalonitrile resulted in the exclusive formation of α-monobromomalonanilide in a 85% yield.

$$\mathrm{2\ CH_2(CONHC_6H_5)_2 + CBr_2(CN)_2}$$
$$\rightarrow \mathrm{2\ CHBr(CONHC_6H_5)_2 + CH_2(CN)_2}$$

Certain mono-bromoderivatives of anilides and *N*-benzylamides were prepared by this method from the corresponding amides (see Table II).

It can be said that the method of monobromination by means of dibromomalonitrile proved remarkably effective for the synthesis of α-monobromo-derivatives of active methylene compounds containing a phenyl group.

Experimental

Reagents.—Cyanoacetamide,⁶⁾ dibromocyanoacetamide,⁷⁾ malonitrile,⁸⁾ dibromomalonitrile,⁹⁾ malonamide,¹⁰⁾ malonanilide,¹¹⁾ cyanoacetanilide,¹²⁾ *N*-benzyl cyanoacetamide,¹²⁾ acetacetanilide¹³⁾ and *N*-benzyl acetacetamide¹⁴⁾ were prepared by the literature procedures.

Ethyl malonate and ethyl cyanoacetate were obtained from a commercial source and were purified by distillation.

***N*-Ethyl Monobromocyanoacetamide and *N*-Cyclohexyl Monobromocyanoacetamide.**—A solution of *N*-ethyl cyanoacetamide (1.12 g., 0.01 mol.) and *N*-ethyl dibromocyanoacetamide (2.70 g., 0.01 mol.) in 100 ml. of 95% ethanol was refluxed for 2 hr. After the ethanol had been removed, a large amount of a white solid was separated, washed with benzene, and recrystallized from 50% ethanol. *N*-Ethyl monobromocyanoacetamide (3.21 g., 84%, m. p. 79∼81°C) was obtained.

In a similar fashion, *N*-cyclohexyl monobromocyanoacetamide (90%, m. p. 138∼141°C) was obtained.

TABLE I. BROMINATION OF ACTIVE METHYLENE COMPOUNDS BY MEANS OF DIBROMOMALONITRILE*

Monobromo-derivatives (Products)	Yield %	M. p. (°C) or b. p. (°C/mmHg)
$\mathrm{CHBr(CN)_2}$	60	63∼64, 90/16
$\mathrm{CHBr(CONH_2)_2}$	75	175∼179
$\mathrm{NCCHBrCONH_2}$	57	117∼119
$\mathrm{NCCHBrCONHC_6H_{11}}$	59	138∼141
$\mathrm{CHBr(COOC_2H_5)_2}$	52	128∼130/30
$\mathrm{CH_3COCHBrCOOC_2H_5}$	43	122/25

* Monobromo-derivatives of acetylacetone or benzoylacetone could not be obtained by this method.

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5) J. V. Backes, R. W. West and M. A. Whiteley, *J. Chem. Soc.*, **119**, 362 (1921).

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9) E. Otto and B. Löpmann, *Ber.*, **55**, 1259 (1922).

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12) K. G. Naik and Y. N. Baht, *J. Indian Chem. Soc.*, **4**, 547 (1927); *Chem. Abstr.*, **22**, 2353 (1928).

13) J. W. Williams and J. A. Krynitsky, "Organic Syntheses," Col. Vol. III, 10 (1955).

14) The procedure was modified from the method of Williams and Krynitsky in "Organic Syntheses" (cf. 13 above) for the preparation of acetanilide.

TABLE II. BROMINATION OF ACTIVE METHYLENE COMPOUNDS BY MEANS OF DIBROMOMALONITRILE

Monobromo-derivatives (Products)	Yield %	M. p. °C	N, % Calcd.	N, % Found
$CHBr(CONHC_6H_5)_2$	85	184~185	8.42	8.14
$NCCHBrCONHC_6H_5$	79	131~133	11.72	12.26
$NCCHBrCONHCH_2C_6H_5$	79	114~115	11.07	11.30
$CH_3COCHBrCONHC_6H_5$	92	143~144	5.47	5.65
$CH_3COCHBrCONHCH_2C_6H_5$	78	95~96	5.18	5.36

Monobromomalonitrile.—A solution of 0.01 mol. of malonitrile and 0.01 mol. of dibromomalonitrile in 70 ml. of 95% ethanol was refluxed for 15 min. in the presence of a catalytic amount of boron trifluoride. After the ethanol had been removed under reduced pressure, the brownish-yellow residue was distilled in vacuo to give 1.74 g. (a 60% yield) of the yellow liquid (b. p. 90°C/16 mmHg), which solidified at room temperature and melted at 63~64°C.

General Procedure of the Monobromination by Means of Dibromomalonitrile.—A solution of 0.02 mol. of an active methylene compound and 0.01 mol. of dibromomalonitrile in 70 ml. of 95% ethanol was refluxed for 15 min. in the presence of a catalytic amount of boron trifluoride. After the ethanol had been removed under reduced pressure, the precipitates were filtered and washed with ether and recrystallized from 95% ethanol. The yields and the physical constants are listed in Table I.

In a similar fashion, mono-bromoderivatives of anilides and *N*-benzyl amides were prepared. The yields and the physical constants are listed in Table II.

Summary

The monobromination of the active methylene compounds by means of the proportionation procedure between the active methylene compound and its dibromo-derivative has been investigated.

Next, the monobromination of various active methylene compounds by the use of dibromomalonitrile has been tried. The method proved remarkably effective for the synthesis of α-mono-bromoderivatives of active methylene compounds containing a phenyl group.

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