[Chem. Pharm. Bull. 22(4) 965—966 (1974)] UDC 546.14.04 : 547.292' 233.04

Monobromination of Cyanoacetamides and Amidinoacetamide with Molecular Bromine

Jiro Suzuki, Kenji Suzuki and Minoru Sekiya

Shizuoka College of Pharmacy[1]

(Received October 25, 1973)

Recently in this laboratory a need arose to prepare 2-bromo-2-cyanoacetamide. As for monobromination of cyanoacetamide with molecular bromine there appear in literature the methods of bromine-treatment of its suspension in carbon tetrachloride[2] and of its acetic acid solution.[3] The latter paper[3] gave us a doubt on the product identification, since the recorded melting point, mp 176—177°, is much different from that in the former paper,[2] mp 113°, which was later confirmed as that of authentic 2-bromo-2-cyanoacetamide. The former melting point is nearly close to that of the hydrolyzed product, 2-bromomalonamide, mp 181° (decomp.), obtained in our repeated experiment. From view of our reexamination of these reported methods a necessity arose to find a practical means for preparation of 2-bromo-2-cyanoacetamide. We have found a method, bromination with bromine in acetic acid–acetic anhydride, practically convenient. Bromination of cyanoacetamide dissolved in acetic acid–acetic anhydride with one molar equivalent of bromine at 8—10° gave 83% yield of 2-bromo-2-cyanoacetamide. This method was shown to be general and capable of extension to monobromination of other cyanoacetamide derivatives. N-Methylcyanoacetamide and N,N-dimethylcyanoacetamide were as well monobrominated in good yields by this method. Description as to preparation of these two compounds has not appeared in literature. Similarly, in suspended state in acetic acid–acetic anhydride bromination of amidinoacetamide hydrochloride gave 2-amidino-2-bromoacetamide hydrobromide in 88% yield. This product well crystallized by addition of dioxane as crystals of adduct formula, $\begin{matrix}H_2N\\HN\end{matrix}\!\!>\!CCHBrCONH_2\cdot HBr\cdot O\!\!\begin{matrix}\frown\\\smile\end{matrix}\!\!O$, mp 132—133° (decomp.), unknown in literature. The method appears to be widely capable of monobromination of analogous active methylene compounds.

Experimental

2-Bromo-2-cyanoacetamide——Into a vigorously stirred solution of 50.5 g (0.6 mole) of cyanoacetamide dissolved in 460 ml of a mixture of AcOH and Ac_2O (7: 1 in volume) 95.5 g (0.6 mole) of bromine in 190 ml of AcOH was dropwise added at 8—10°, and the solution was stirred for additional 2 hr at the same temperature. The reaction solution was concentrated under reduced pressure, whereupon the resulting residue solidified on cool. Recrystallization from EtOH gave needles, mp 113—114° (lit. mp 113°[2], 117—119°[4]). Yield, 80.5 g (83%). IR ν_{max}^{KBr} cm^{-1}: 2248 (CN), 1676 (CO). *Anal.* Calcd. for $C_3H_3ON_2Br$: C, 22.11; H, 1.86; N, 17.19; Br, 49.16. Found: C, 22.56; H, 2.10; N, 17.97; Br, 49.16.

When the reaction was carried out using AcOH in place of AcOH–Ac_2O mixture as solvent, the same treatment of the reaction solution gave 55.0 g (51%) of 2-bromomalonamide, plates from EtOH, mp 179—180° (decomp.). No depression of the melting point was observed on admixture with an authentic sample, mp 181° (decomp.),[5] IR ν_{max}^{KBr} cm^{-1}: 1676 (CO). *Anal.* Calcd. for $C_3H_5O_2N_2Br$: C, 19.91; H, 2.78; N, 15.47; Br, 44.15. Found: C, 20.37; H, 3.17; N, 15.26; Br, 43.87.

1) Location: *2-2-1, Oshika, Shizuoka.*
2) G.A. Burk, U.S. Patent 3488734 (1970) [*C.A.*, **72**, 66421 (1970)].
3) A.O. Jackson and C.S. Marvel, *J. Am. Chem. Soc.*, **55**, 5000 (1933).
4) T. Hata, *Bull. Chem. Soc. Japan*, **37**, 547 (1964).
5) J.V. Backes, R.W. West and M.A. Whiteley, *J. Chem. Soc.*, **119**, 359 (1931).

NII-Electronic Library Service

2-Bromo-2-cyano-N-methylacetamide——This compound was obtained from N-methylcyanoacetamide by the same method as described above for 2-bromo-2-cyanoacetamide, but less amount of AcOH–Ac_2O was used because of easier solubility of the substrate. Yield, 81%. Prisms (from EtOH), mp 93—97°. IR ν_{max}^{KBr} cm^{-1}: 2244 (CN), 1667 (CO). *Anal.* Calcd. for $C_4H_5ON_2Br$: C, 27.14; H, 2.85; N, 15.82; Br, 45.15. Found: C, 27.34; H, 3.17; N, 15.75; Br, 45.73.

2-Bromo-2-cyano-N,N-dimethylacetamide——This compound was obtained from N,N-dimethylcyanoacetamide by the same method as described for 2-bromo-2-cyanoacetamide, but less amount of AcOH–Ac_2O was used because of easier solubility of the substrate. Yield, 85%. Prisms (from ether), mp 53—54°, bp 134—135° (3 mmHg). IR ν_{max}^{KBr} cm^{-1}: 2260 (CN), 1665 (CO). NMR τ (in 10% $CDCl_3$): 4.82 (1H, s, CH), 6.81 and 6.93 (6H, 2s, $2CH_3$). *Anal.* Calcd. for $C_5H_7ON_2Br$: C, 31.44; H, 3.69; N, 14.65; Br, 41.98. Found: C, 30.99; H, 4.01; N, 14.68; Br, 41.83.

2-Amidino-2-bromoacetamide——Into a vigorously stirred suspension of 13.8 g (0.1 mole) of amidinoacetamide hydrochloride[6] in 120 ml of AcOH–Ac_2O mixture (10: 1 in volume) 16.0 g (0.1 mole) of bromine in 32 ml of AcOH was dropwise added at 8—10°. After stirring for additional 3 hr at room temperature, the homogeneous solution was concentrated under reduced pressure. The resulting oily residue was washed with dry ether and thoroughly triturated with dioxane until solidified. Recrystallization from EtOH–dioxane (1: 2) gave leaves, mp 132—133° (decomp.). Yield, 30.8 g (88%). This material was shown to be an equimolar addition compound of 2-amidino-2-bromoacetamide, hydrogen bromide and dioxane $\left(\begin{matrix}H_2N\\HN\end{matrix}\!\!>\!CCHBrCONH_2\cdot HBr\cdot C_4H_8O_2\right)$. *Anal.* Calcd. for $C_7H_{15}O_3N_3Br_2$: C, 24.09; H, 4.33; N, 12.04. Found: C, 24.25; H, 4.66; N, 12.12.

Acknowledgement The authors are indebted to the members of Analysis Center of this college for elemental analyses.

6) E. Shaw and D.W. Woolley, *J. Biol. Chem.*, **181**, 89 (1949).

[Chem. Pharm. Bull. 22(4) 966—969 (1974)] UDC 547.94.057 : 581.192

Formation of Morphinandienone-type Compound through Methylenedioxy Cleavage by Pschorr Cyclization[1,2]

TETSUJI KAMETANI, TSUTOMU SUGAHARA, and KEIICHIRO FUKUMOTO

Pharmaceutical Institute, Tohoku University[3]

(Received October 26, 1973)

Sinomenine (I), an alkaloid isolated from *Sinomenium acutum*, was assigned to the morphinanenone structure, and Barton and his co-workers[4] suggested that the biogenesis of sinomenine (I) would be performed from (+)-reticuline (II) to give α-diketone (IV) through sinoactine (III). The α-diketone (diosphenol) was a key intermediate in the biosynthesis of sinomenine.

We have reported a simple total synthesis of morphinandienone alkaloids, (±)-amurine (V),[5] (±)-flavinantine (VI),[6] salutaridine (VII),[7] and sinoactine (III).[7] Herein we wish to report a simple synthesis of a model α-diketone type compound (VIII) through cleavage

1) This forms Part DLVI of "Studies on the Syntheses of Heterocyclic Compounds," by T. Kametani.
2) This work was reported as a communication in *Chem. Ind.*, **1969**, 833.
3) Location: *Aobayama, Sendai.*
4) D.H.R. Barton, A.J. Kirby, and G.W. Kirby, *J. Chem. Soc.* (*C*), **1968**, 929.
5) T. Kametani, K. Fukumoto, and T. Sugahara, *J. Chem. Soc.* (*C*), **1969**, 801.
6) T. Kametani, T. Sugahara, H. Yagi, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1969**, 1063.
7) T. Kametani, M. Ihara, K. Fukumoto, and H. Yagi, *J. Chem. Soc.* (*C*), **1969**, 2030.

NII-Electronic Library Service