REACTION OF O-SUBSTITUTED HYDROXYLAMINES WITH ALDIMINES AND PRIMARY ALIPHATIC AMINES IN THE SYNTHESIS OF DIAZIRIDINES

N. N. Makhova, V. Yu. Petukhova, and L. I. Khmel'nitskii

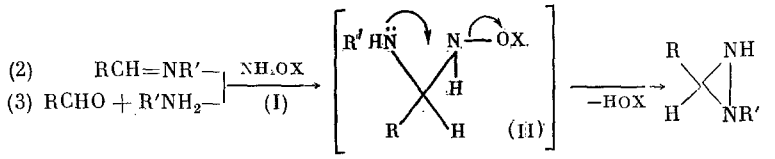
UDC 542.91:547.717:547.288.4:547.233

We have previously proposed a synthesis of diaziridines from ketones by the reaction of primary aliphatic amines with esters of ketoximes [1, 2]. This method could be extended to the synthesis of diaziridines from aldehydes [2]. Meanwhile, diaziridines of this very type are much less available. Only a few examples of their synthesis are known: the action of hydroxylamine-O-sulfonic acid (HASA) on a mixture of aldehyde and primary aliphatic amine [3] (by mixing the components); and the reaction of aldimines with aminating reagents, HASA [4] and with chloramines [5, 6].

There is a recent report [7], without indication of experimental conditions, of the synthesis of two diaziridines from aldehydes in moderate yield from the respective aldimines and a member of a new group of aminating agents, O-substituted hydroxylamines, viz., O-mesitylsulfonylhydroxylamine (Ia). The overall amination reaction can be presented as the electrophilic addition of an NH_2 group to any nucleophile, N, and the removal of an anion, $\overset{\ominus}{A}$, of the respective acid:

$$\overline{N} + NH_2A \rightarrow \overset{\oplus}{N}NH_2 + \overset{\ominus}{A} \qquad (1)$$

The part played by the aminating reagent in diaziridine synthesis is somewhat different. In the first stage it acts as a nucleophile (e.g., it adds to the imine C=N bond); only in the second stage, in the cyclization of the intermediate II, does electrophilic amination occur with removal of the anion of the acid (Scheme 2). Therefore, its behavior in diaziridine synthesis must be distinguished from that in other reactions. The present work is a study of the behavior of aminating reagents Ia-d in diaziridine synthesis by the reaction with aldehydes (Scheme 2) and by the method of mixing components:



R = R' = H, Alk; X = SO_2Mes (Ia), COMes (Ib), $C_6H_3(NO_2)_2$-2,4 (Ic), Pic (Id).

The reaction of Ia-d with aldimines was studied using N-ethylidene-n-butylamine (III) as an example. Since the reaction conditions were not given in [7], we first studied the conditions of the analogous reactions of aldimines with chloramines [5, 6]: an aprotic solvent, CH_2Cl_2; addition of amine to form the aldimine; 0-20°C. We obtained 1-butyl-3-methyldiaziridine, IV, in very low yield (5-10% by iodometric titration). The result was the same when CH_2Cl_2 was replaced by alcohol. In both solvents the aminating reagent is used up in other reactions, and is converted to the butylammonium salt of the respective acid, which separates in substantial amounts.

Butylamine can have an undesirable effect on Ia-d. Compound Ic [8] and HASA [9] decompose in the presence of strong bases with the removal of the anion of the respective acid. Primary aliphatic amines are aminated by HASA to form hydrazines [10]. We therefore carried out special tests of the action of butylamine on Ia-d at −30 to −5°C in CH_2Cl_2 and MeOH. Compounds Ia-d did not aminate butylamine; when acetaldehyde was added to the reaction mixture after the reaction was finished, the formation of the butylhydrazone V could not be established.

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 10, pp. 2331-2335, October, 1982. Original article submitted February 10, 1982.

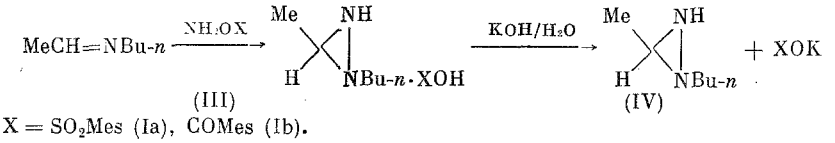
 0568-5230/82/3110-2052$07.50

It was established that Ia-d decompose to form the butylammonium salts of the respective acids; this also explains the anomalously high yields of butylammonium salt in the reaction of Ia-d with III in the presence of amine. In the case of Ic there is also a nucleophilic replacement of the hydroxyamino group by the butylamino group (Scheme 4). Such behavior of NH_2OX aminating reagents has not been previously observed. The yield of N-butyl-2,4-dinitroaniline, VI, is 13% at −30 to −20°C, and 46% at −10 to −5°C:

$$\underset{\text{(Ic)}}{H_2NOC_6H_5(NO_2)_3\text{-}2,4} + H_2NBu\text{-}n \rightarrow \underset{\text{(VI)}}{n\text{-}BuNHC_6H_3(NO_2)_2\text{-}2,4} \qquad (4)$$

The decomposing action of butylamine on aminating reagents Ia-d prompted us to study the reaction of the latter with III in the absence of amine, under the assumption that the liberated acid would form a salt with diaziridine IV being formed.

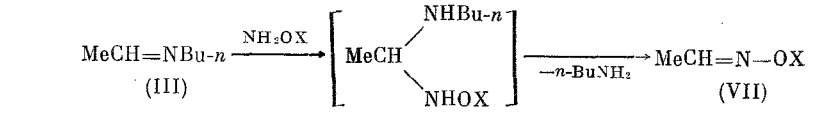
Because of the low stability of protonated diaziridines, the reaction was carried out at low temperature. The product, IV, was separated by making the reaction mixture alkaline with aqueous KOH during cooling. It turned out that under these conditions the yield of IV was indeed increased; at −10 to −5°C it was 26% for Ia, and at −60 to −40°C it was 41% for Ia, and 38.5% for Ib:



(III) (IV) (5)

X = SO_2Mes (Ia), COMes (Ib).

The behavior of the other two aminating reagents, Ic and Id, was notably different from that of Ia and Ib. At both temperatures the yield of IV was no more than 13.5% for Ic, and 3.5% for Id. Beside the diaziridine synthesis, other reactions were observed for these reagents. For Ic, besides IV, O-(2,4-dinitrophenyl)acetaldoxime, VII, was separated in yields up to 33%; its formation can be represented by the scheme:

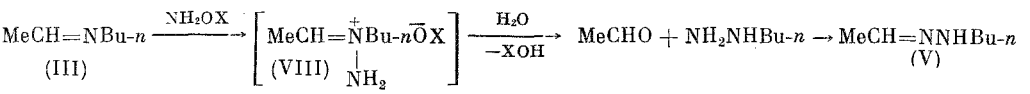


(III) (VII) (6)

X = $C_6H_3(NO_2)_2$-2,4 (Ic).

In the case of Id we obtained a mixture of IV, unreacted III, acetaldehyde butylhydrazone, V. Compounds III-V were identified by the PMR spectrum of the mixture and known samples (Table 1). As the data show, the PMR signals can be assigned to a particular structure with a high degree of probability, since the chemical shifts of the most characteristic groupings of the different compounds are substantially different from one another.

When CH_2Cl_2 is replaced by alcohol, the formation of hydrazone V becomes one of the main routes of the reaction of III with not only Id but also Ic. The most probable explanation of the formation of (V) must be, apparently, to assume the amination of III at the N atom, followed by hydrolysis of the amino derivative VIII:



(III) (VIII) (V) (7)

X = $C_6H_3(NO_2)_2$-2,4 (Ic), Pic (Id).

The portion of reagents Ia-d that was not used to form IV, V, and VII in the reaction with III was decomposed by treatment of the reaction mixture with alkali to give the salts of the respective acids (XOK). Their total amount was greater in all cases than could be formed by the reactions described above.

Thus, Ia and Ib form diaziridines in satisfactory yields, whereas for Ic and Id under the same conditions other reaction routes predominate; in particular, apparently, the amination of the aldimine at the N atom (Scheme 7). Moreover, Ic undergoes transamination with III (Scheme 6).

Diaziridine synthesis starts with a nucleophilic attack by the aminating agent at the C atom of the C=N bond (see Scheme 2); we may therefore presume that Ia and Ib are more nucleo-

TABLE 1. PMR Spectra of III-V, n-$BuNHNH_2$, and n-$BuNH_2$ in CH_2Cl_2 (δ, ppm)

Compound	Me	CH	n-Bu			NH
			NCH_2	CH_2CH_2	Me	
(III)	1,93 d	7,65 q	3,50t	1,38m	0,86t	–
(IV)	1,29 d	1,65 q	2,25t	1,35m	0,85t	2,3 br.s
(V)	1,6 d	6,32q				
	1,8d	6,73 q	3,05t	1,35 t	0,85t	4,5 br.s
		2 : 3				
n-$BuNHNH_2$	–	–	2,6t	1,4 m	0,90t	3,0 br.s
n-$BuNH_2$	–	–	2,62t	1,4 m	0,90t	3,25br.s

philic than Ic and Id. Additional evidence for this is the proposed ability of Ic and Id to aminate III at the N atom (Scheme 7) – a reaction in which their electrophilicity properties are manifested. Of these two, Ic is the more nucleophilic, since it forms diaziridine IV by reaction with III in 13.5% yield, and can attack the imine C atom of III in transamination to VII, according to Scheme 6.

The main features of the behavior of Ia-d in their reaction with aldimine III, according to Scheme 2, are retained when they are used to obtain the analogous diaziridines by the mixed component method, according to Scheme 3. Thus, when Ia-d react with butylamine and acetaldehyde in CH_2Cl_2 at –30°C, diaziridine IV is obtained only from Ia and Ib, in yields of 27 and 25%, respectively. Hydrazone V is obtained in maximum yield of 35% from Id, and the results are practically independent of whether 1 or 2 moles of amine are taken per mole of aldehyde. In all cases the yields of the salts of the respective acids are also greater than would be expected from the reactions by which IV and V are formed.

There are also some differences in the reactions by schemes 2 and 3. Thus, in the synthesis of IV from Ia, b, when the temperature was lowered to –60 to –40°C, the yield of IV did not increase, but fell, and at –30°C it was lower than in the reaction of Ia, b with III. But these differences are explainable not by the different behavior of Ia, b in reactions 2 and 3, but by the low-temperature retardation of the first reaction step, viz., the amine–aldehyde reaction; while according to reaction 2, the starting material was aldimine III, the already formed product of that reaction.

EXPERIMENTAL

PMR spectra were obtained on a Perkin–Elmer R-12 apparatus (60 MHz from HMDS). IR spectra were obtained on a UR-10 apparatus.

Reaction of Ia and Ic with III at –10 to 0°C in the Presence of Amine. To a solution of 0.7 g (7 mmole) of III, obtained according to [11], and 0.52 g 0.7 ml (7 mmole) of n-butylamine in 10 ml of solvent (CH_2Cl_2 or EtOH) was added in portions with stirring at –5 to 0°C, 7 mmole of Ia or Ic, obtained according to [12] or [13], respectively, over 10 min. The mixture was stirred at this temperature for 6 h, the solvent was distilled off in a rotary evaporator at no higher than 30°C, and 20 ml of 1:1 ether:CH_2Cl_2 was added to the residue. The precipitate was filtered off, washed with a small amount of ether, and air-dried. 1-Butyl-3-methyldiaziridine, IV, was determined in the mother liquor by iodometric titration. There was obtained for Ia: in CH_2Cl_2, 1.62 g (85%) of butylammonium mesitylenesulfonate, mp 78-80°C. IR spectrum (ν, cm^{-1}): 1090 (SO), 1490, 1600 (Ar), 2090, 2940 (NH), 2880, 2960 (CH). PMR spectrum (CD_3OD, δ, ppm): 0.87 d (3 H, Me–C–C), 1.35 m (4 H, CCH_2CH_2C), 2.15 s (3 H, 4-Me in Ar), 2.58 s (6 H, 2,6-Me_2 in Ar), 2.8 t (2 H, N–CH_2), 6.8 s (2 H, 3,5-H_2 in Ar). Found: C 56.91; H 8.13; N 4.96; S 12.20%. $C_{13}H_{23}NO_3S$. Calculated: C 57.14; H 8.42; N 5.13; S 11.70%.

In EtOH there was obtained 1.59 g (83%) of the same salt. Yield of IV in CH_2Cl_2, 5%; in EtOH, 3.5% (iodometric titration).

For Ic: in CH_2Cl_2, 1.53 g (85%), in EtOH 1.42 g (80%) of butylammonium 2,4-dinitrophenolate. Its IR and PMR spectra coincide with those obtained in [2]. Yield of IV in CH_2Cl_2 2.5%, in EtOH 10% (iodometric titration).

Reaction of Ia-d with n-Butylamine. To a solution of 4.5 g (60 mmoles) of butylamine in 59 ml of CH_2Cl_2 (or 30 ml of MeOH) was added 30 mmoles of Ia-d at –30 to –20°C in small

portions. (Compounds Ib and Id were obtained according to [14] and [12], respectively.) The mixture was stirred at this temperature for 3 h. For Ia, b, and d, the solvent was distilled off in vacuum, and the distillate was collected in a cooled receiver. The residues for Ia and Ib contained butylammonium mesitylenesulfonate or mesitylate, respectively, in ~80% yield. Mp for the former, 78-80°C (cf. above), for the latter 114-115°C (cf. [2]). The IR and PMR spectra were identical with those of known samples. For Id, instead of a salt, a tarry residue was obtained.

Solvent was distilled off from the distillate without vacuum until the volume was 3 ml, an excess of acetaldehyde was added at 0°C, and the mixture was left overnight at 20°C. The excess acetaldehyde was distilled off, and the PMR spectrum of the residue was obtained. Along with the expected acetaldehyde butylhydrazone (V), III was obtained in all cases; i.e., butylhydrazine was not formed, and acetaldehyde gave III with the remaining butylamine.

For Ic, after the reaction was finished the residue was filtered off, washed with CH_2Cl_2, and air-dried. There was obtained 6.7 g (87%) of butylammonium dinitrophenolate. The solvent was distilled from the mother liquor in vacuum, and the distillate was collected in a cooled receiver. The residue contained 0.94 g (13%) of N-butyl-2,4-dinitroaniline, VI, mp 85-87°C (cf, [2, 15]). At a synthesis temperature of −10 to −5°C, the yield of VI rose to 46%. The distillate was worked up and analyzed as described above. Only III was obtained.

Reaction of Ia-d with III in the Absence of Amine. a) 1-Butyl-3-methyldiaziridine, IV, from III and Ia, b. To a solution of 0.7 g (7 mmole) of III in 10 ml of CH_2Cl_2 at −30 to −20°C was added 1.5 g (7 mmoles) of Ia in small portions. The mixture was stirred at −10 to −5°C for 2 h, 10 ml of 10% KOH solution was added, the organic layer was separated, and the aqueous layer was extracted with three 25-ml portions of CH_2Cl_2. The organic phase was dried with K_2CO_3, the solvent was distilled off, and the residue was distilled in vacuum. There was obtained 0.21 g (26%) of IV, bp 40°C (20 mm) (cf. [3]).

Analogously, from 1.5 g (15 mmoles) of III and 3.2 g (15 mmoles) of Ia at −60 to −40°C there was obtained 0.7 g (41%) of IV; and from 1.5 g (15 mmole) of III and 2.7 g (15 mmole) of Ib (obtained according to [14]) there was obtained 0.65 g of IV (38.5%).

b) To a solution of 1.98 g (20 mmoles) of III in 40 ml of CH_2Cl_2 at −30 to −20°C was added 4 g (20 mmole) of Ic portionwise. The mixture was stirred at this temperature for 3 h, 20 ml of 10% KOH solution was added with cooling, and the precipitate was filtered off and air-dried. There was obtained 2.66 g (60%) of potassium 2,4-dinitrophenolate. The salt was dissolved in a large amount of water and acidified with concentrated HCl to pH 2-3. There was obtained 1.95 g (53%) of 2,4-dinitrophenol, mp 112-113°C (cf. [16]).

The organic layer was separated from the mother liquor. The water layer was extracted with three 25-ml portions of CH_2Cl_2, and the extract was dried with $MgSO_4$. The solvent was distilled off and the distillate was collected in a cooled receiver. The residue contained 1.49 g (33%) of 2,4-dinitrophenylacetaldoxime, VII, mp 94-95°C (cf. [2]). The IR and PMR spectra of VII were identical with those of a known sample. The solvent was distilled from the distillate in a rotary evaporator, leaving 13.5% of IV (iodometric titration). When the same reaction was carried out at −60 to −40°C, the yield of IV was 10%.

c) Analogously, from 1.0 g (10 mmoles) of III and 2.44 g (10 mmoles) of Id in 10 ml of CH_2Cl_2 at −60 to −40°C, there were obtained 1.7 g (75%) of picric acid, mp 120-121°C (cf. [16]), and 0.6 g (52.5%) of a mixture of IV, V, and unreacted III (cf. Table 1).

Reaction of Ic and Id with III in Ethanol. To a solution of 2 g (20 mmoles) of III in 10 ml of EtOH at −30 to −20°C was added 20 mmoles of Ic or Id portionwise and the mixture was stirred at that temperature for 3 h. Then 20 ml of 10% KOH solution was added and potassium 2,4-dinitrophenolate or potassium picrate was filtered off. The aqueous alcohol layer was extracted with four 50-ml portions of CH_2Cl_2, the organic layer was dried with K_2CO_3, the solvent was distilled off, and the residue was vacuum distilled. There was obtained from Ic 1.2 g of a mixture of III, IV, and V; according to PMR, IV and V were in approximately equal amounts; from Id, 0.7 g (30.7%) of V, bp 77°C (40 mm), n_D^{20} 1.4495 (cf. [17]).

Reaction of Ia-d with a Mixture of Acetaldehyde and Butylamine. To a solution of 0.7 g (16 mmoles) of acetaldehyde in 10 ml of CH_2Cl_2 at −10 to −5°C was added 2.3 g (32 mmoles) of butylamine, then at −30 to −20°C 15 mmoles of Ia-d, and the mixture was stirred at this temperature for 3 h. Then 20 ml of 10% KOH solution was added, the organic layer was separated, and the aqueous phase was extracted with three 50-ml portions of CH_2Cl_2. The organic layers

were dried with K_2CO_3, the solvent was distilled off without vacuum, and the residue was distilled. With Ic and Id, before the organic layer was separated the salt of the respective acid was filtered off. There was obtained: from Ia, 0.5 g (27.5%) of IV; from Ib, 0.44 g (25%) of IV; from Ic, 0.125 g of V; and from Id, 0.6 g (35%) of V.

CONCLUSIONS

1. We have studied the synthesis of diaziridines from aldehydes by the reaction of O-mesitylsulfonyl-, O-mesitoyl-, O-(2,4-dinitrophenyl)- and O-picrylhydroxylamines with N-ethylidene-n-butylamine, and with a butylamine–acetaldehyde mixture. For this purpose, only the first two aminating reagents are suitable.

2. Two other aminating reagents, viz., O-(2,4-dinitrophenyl)- and O-picrylhydroxylamines, can aminate aldimines at the N atom.

3. The difference in reactivity of the two pairs of aminating reagents is determined by the greater nucleophilic properties of O-mesitylsulfonyl- and O-mesitoylhydroxylamines, as compared with O-(2,4-dinitrophenyl)- and O-picrylhydroxylamines.

4. These aminating reagents do not aminate butylamine to butylhydrazine, but are decomposed by its alkalinity to yield the respective acids.

LITERATURE CITED

1. A. N. Mikhalyuk, N. N. Makhova, A. E. Bova, L. I. Khmel'nitskii, and S. S. Novikov, Izv. Akad. Nauk SSSR, Ser. Khim., 1566 (1978).
2. N. N. Makhova, V. Yu. Petukhova, and L. I. Khmel'nitskii, Izv. Akad. Nauk SSSR, Ser. Khim., 2107 (1982).
3. A. A. Dudinskaya, A. E. Bova, L. I. Khmel'nitskii, and S. S. Novikov, Izv. Akad. Nauk SSSR, Ser. Khim., 1523 (1971).
4. Csaba Szantay, J. F. Chmielewich, and T. J. Bardos, J. Med. Chem., 10, No. 1, 101 (1967).
5. E. Schmitz and D. Habisch, Chem. Ber., 95, 680 (1962).
6. E. Schmitz and K. Schinkowski, Chem. Ber., 97, 49 (1964).
7. J. Tamura, J. Minamikawa, and M. Ikeda, Synthesis, 1 (1977).
8. A. S. Radhakrishna and G. M. London, J. Org. Chem., 44, 4836 (1979).
9. E. Schmitz, R. Ohme, and G. Kozakiewicz, Z. Anorg. Allg. Chem., 339, 44 (1966).
10. G. Gever and K. Hayes, J. Org. Chem., 14, 813 (1949).
11. K. N. Campbell, A. H. Sommers, and B. K. Campbell, J. Am. Chem. Soc., 66, 82 (1944).
12. J. Tamura, J. Minamikawa, K. Sumoto, S. Fujii, and M. Ikeda, J. Org. Chem., 38, 1239 (1973).
13. A. O. Ilvespaa and A. Marxer, Helv. Chim. Acta, 46, 2009 (1963).
14. W. N. Marmer and G. Maerker, J. Org. Chem., 37, 3520 (1972).
15. Van der Kam, Rec. Trav. Chim., 45, 732 (1926).
16. Chemist's Handbook [in Russian], Vol. II, Khimiya, Moscow (1971).
17. B. V. Ioffe, V. S. Stopskii, and Z. I. Sergeeva, Zh. Org. Khim., 4, 986 (1968).