Brief Communications

Novel route to *N*-alkyl- and *N*,*N*′-dialkylhydrazines by high-pressure alkylation of azines

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Reactions of alkyl halides with azines of *p*-nitrobenzaldehyde, benzaldehyde, and *p*-methoxybenzaldehyde at a high pressure (10 kbar) were studied. Hydrolysis of the reaction mixtures gives pure *N*-monoalkyl- or *N*,*N*′-dialkylhydrazines in high yields, depending on the structure of the starting azine and the solvent nature. It was found that non-symmetrical *N*,*N*′-dialkylhydrazines can be synthesized without isolating intermediate *N*-monoquaternary immonium salts. The effect of the phase transition of the solvent on the direction of the alkylation is discussed.

Key words: azines, hydrazines, high-pressure alkylation.

It is known that *N*-monoalkyl- and *N*,*N*′-dialkylhydrazines are difficult to prepare in the individual state. The published methods for the synthesis of these compounds involve alkylation of hydrazine with alkyl halides with subsequent repeated fractionation of the reaction mixtures containing mono- and polysubstitution products,[1] reduction of not easily accessible azoalkanes,[2] alkylation of *N*,*N*′-diacylhydrazines followed by hydrolysis,[3] hydrogenation of mixtures of aldehydes and hydrazine,[4] and amination of amines with hydroxylamine-*O*-sulfonic acid.[5]

Previously,[6] we showed that the high-pressure (10 kbar) alkylation of bis(benzylidene)phenylenediamines with alkyl chlorides followed by hydrolysis of the reaction mixtures affords pure *N*-monoalkyl- or *N*,*N*′-dialkylphenylenediamines; the composition of reaction products strongly depends on the nature of the starting diamine and the solvent.

In the present work, the reactions of *p*-nitrobenzaldehyde (**1a**), benzaldehyde (**1b**), and *p*-methoxybenzaldehyde azines (**1c**) with MeI (**2**), $PhCH_2Br$ (**3**), Pr^nCl (**4**), and Bu^nCl (**5**) were carried out in differently polar solvents (CH_2Cl_2, 1,4-dioxane, and MeCN) under the same conditions as in Ref. 6 (10 kbar, 50 °C, 5 h) (Scheme 1, Table 1).

Azine **1a** containing strong electron-withdrawing nitro groups in the benzene rings did not react with compounds **2**—**5** under any conditions, while azines **1b,c** were alkylated very selectively in high yields (see Table 1): in each experiment, either monoalkylhydrazines **8a**—**d** or *N*,*N*′-dialkylhydrazines **9a**—**d** were the sole reaction products, though alkyl halides **2**—**5** were used in excess (see Experimental). Azines **1b** and **1c** behaved very differently: being inert in CH_2Cl_2, the former afforded exclusively monoalkylation products **8a**—**d** in dioxane and MeCN, while the latter gave only monoalkylhydrazines **8a**—**d** in

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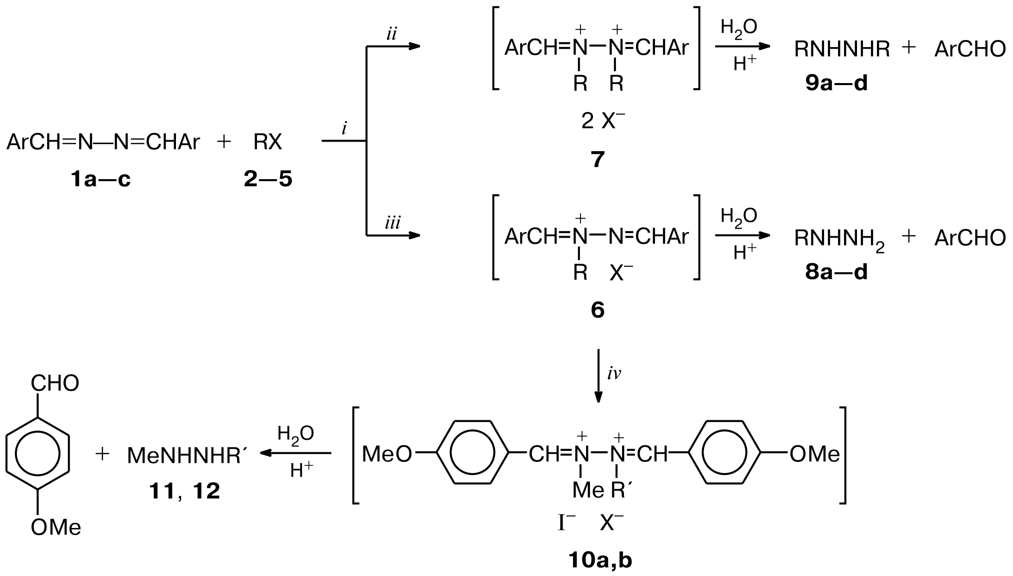
Scheme 1



Compound	R	Compound	X
2, **8a**, **9a**	Me	**2**	I
3, **8b**, **9b**	$PhCH_2$	**3**, **10a**	Br
4, **8c**, **9c**	Pr^n	**4**	Cl
5, **8d**, **9d**	Bu^n	**5**, **10b**	Cl

Reaction conditions: *i.* 10 kbar, 50 °C, 5 h. *ii.* Ar = *p*-$MeOC_6H_4$, MeCN or dioxane as a solvent. *iii.* 1) Ar = Ph, MeCN or dioxane as a solvent or 2) Ar = *p*-$MeOC_6H_4$, CH_2Cl_2 as a solvent. *iv.* **3** or **5**, dioxane, 10 kbar, 50 °C, 5 h.

Ar = *p*-$O_2NC_6H_4$ (**a**), Ph (**b**), *p*-$MeOC_6H_4$ (**c**); R′ = $PhCH_2$ (**10a**, **11**), Bu^n (**10b**, **12**)

CH_2Cl_2 and only *N*,*N*′-dialkylhydrazines **9a**—**d** in dioxane and MeCN.

Thus, the composition of alkylation products strongly depends on the nature of azines **1a**—**c** and the solvent; this effect is similar to what we observed earlier for other imines[6].

As expected, the reactivity in the series of azines **1a**—**c** increases with an increase in the donating properties of substituents in their aromatic rings (azine **1a** is absolutely inert, while azine **1c** gives bisalkylation products). The higher reactivity of azine **1c** compared to compounds **1a,b** is attributable to an efficient mesomeric charge neutralization in bisquaternized salt **7c** (Ar = *p*-$MeOC_6H_4$), which is absent from unsubstituted compound **7b** (Ar = Ph) and especially compound **7a** containing electron-withdrawing groups (Ar = *p*-$O_2NC_6H_4$). It is for this reason that the alkylation of azine **1b** gives only a monoquaternary salt (**6**, Ar = Ph), while azine **1a** is not alkylated at all.

In contrast, the nature of an alkylating agent virtually does not affect the composition and yields of alkylation products: the reaction was equally successful with both highly reactive alkyl halides **2** and **3** and, unexpectedly, poorly reactive ones **4** and **5**.

The strong effect of solvents on the direction of the alkylation is not associated with their different polar properties. The activating effects of dioxane and MeCN on the process is probably due to their crystallization at a pressure of 10 kbar. Earlier,[6] we discussed this effect in more detail.

The synthetic value of the reaction studied was also illustrated with the synthesis of non-symmetrical dialkylhydrazines **11** and **12** without isolating or purifying intermediate salt **6**. Azine **1c** was alkylated in CH_2Cl_2 to give monoquaternary salt **6** (Ar = *p*-$MeOC_6H_4$), which was converted into non-symmetrical salts **10a** or **10b** by treatment with another alkyl halide in a solvent activating dialkylation (*e.g.*, dioxane) and then hydrolyzed to non-symmetrical hydrazines **11** or **12**, respectively.

Experimental

Melting points were determined on a Boetius hot stage. GLC and MS analysis were carried out on a Finnigan MAT INCOS-50 instrument (EI, 70 eV, capillary column 30 000 × 0.25 mm with a polydimethylsiloxane grafted phase (0.25 μm)). Azines **1a**—**c** were prepared according to known procedures.[15—17]

High-pressure alkylation of azines 1a—c (general procedure). A solution of azine (**1a**—**c**) (1 mmol) and alkyl halide (**2**—**5**) (2.2 mmol) in 1 mL of CH_2Cl_2, dioxane, or MeCN was kept in a Teflon tube at 50 °C and a pressure of 10 kbar for 5 h. The reaction mixture was cooled, volatile components were removed *in vacuo*, and 20% HCl (3 mL) was added. The mixture was refluxed for 10 min and then cooled; ArCHO was extracted with

Table 1. Yields and characteristics of *N*-monoalkyl- (**8a—d**) and *N*,*N*´-dialkylhydrazines (**9a—d**, **11**, **12**)

Product	Yield[a] (%)						M.p./°C[b]		MS, m/z ($[M]^+$)
	from **1b**			from **1c**					
	CH_2Cl_2	Dioxane	MeCN	CH_2Cl_2	Dioxane	MeCN	I	II	
8a	0	89	91	81	0	0	142—144 (sulfate)	142[7]	46
8b	0	95	93	85	0	0	110—113 (monohydrochloride)	111[8]	122
8c	0	83	85	77	0	0	177—178 (oxalate)	175[9]	74
8d	0	79	85	75	0	0	165—166 (oxalate)	165[9]	88
9a	0	0	0	0	92	88	167—170 (dihydrochloride)	168[7]	60
9b	0	0	0	0	87	90	223—227 (monohydrochloride)	220—225[10]	212
9c	0	0	0	0	83	82	157—160 (dihydrochloride)	160[11]	116
9d	0	0	0	0	84	81	145—147 (dihydrochloride)	—[c]	144
11				82			142—144 (dihydrochloride)	140[13]	136
12				72			113—117 (monohydrochloride)	114—115[14]	102

[a] The yields of **8a—d** and **9a—d** were determined from the GLC data for the hydrolyzed reaction mixtures.

[b] I refers to the data of the present study; II refers to the literature data.

[c] Ref. 12: b.p. 85 °C (15 Torr).

ether (2×5 mL). The aqueous phase was evaporated to dryness *in vacuo*, the residue was dissolved in EtOH (1 mL), and AcONa (2 mmol) and a solution of picric acid (2.5 mmol) in 2 mL of EtOH were added. The precipitates of hydrazinium picrates that formed were filtered off, washed with EtOH (2 mL), dried, and eluted with $CHCl_3$ through a filter with Al_2O_3 (h = 1 cm) (picric acid was retained by the filter); the eluate was analyzed by GLC.[18] Bases **8a—d** and **9a—d** were characterized in the form of sulfates, hydrochlorides, or oxalates obtained according to known procedures.[7—12]

Synthesis of 1-benzyl-2-methylhydrazine (11) and 1-butyl-2-methylhydrazine (12). A solution of azine **1c** (1 mmol) and MeI (**2**) (2.2 mmol) in 1 mL of CH_2Cl_2 was kept in a Teflon tube at 50 °C and a pressure of 10 kbar for 5 h. The reaction mixture was cooled, volatile components were removed *in vacuo*, and compound **3** or **5** (2.2 mmol) and dioxane (1 mL) were added. The mixture was placed again in a Teflon tube and kept at p = 10 kbar as described above. On cooling, volatile components were removed *in vacuo* and 20% HCl (3 mL) was added. The mixture was refluxed for 10 min and cooled, p-$MeOC_6H_4CHO$ was extracted with ether (2×5 mL), the aqueous phase was alkalified with NaOH, and the product was extracted with ether (2×5 mL). The extracts were treated with a solution of gaseous HCl in ether to give hydrochlorides **11** and **12** in 82 and 72% yields, respectively (see Table 1).

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