A Simple Alkylative Approach to Monoalkylhydrazines

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Phase-transfer-catalyzed *N*-alkylation of acetone *N*-(diethoxyphosphoryl)hydrazone, followed by deprotection with *p*-toluenesulfonic acid monohydrate in ethanol, represents a novel and convenient synthesis of monoalkylhydrazines.

Considerable interest in the preparation of various hydrazine derivatives arises from their potential application (*via* the familiar hydrazone route) for the synthesis of various heterocyclic compounds containing N-N bonds.[1] Among the spectrum of various reactions leading to monoalkylhydrazines, two major procedures – alkylation of hydrazine itself or electrophilic amination of primary amines – are recommended in the literature. Both procedures suffer, however, from several inconveniences. Low yields of products (ca. 30%) usually result[2,3] from direct alkylation of hydrazine, which is used in relatively low excess (4:1) with respect to the alkylating agent, because of the difficulty in controlling both the number of alkyl groups introduced and also the regiospecificity of the alkylation. Higher yields (up to 70%) can be obtained by using tenfold excess of hydrazine,[4] but the work-up procedure, in this case, becomes tedious and time-consuming. Electrophilic amination of primary amines with hydroxylamine-O-sulfonic acid[5] or chloramine[6,7] in the presence of alkali also demands a relatively large excess of an amine (5–6 moles per mole of the aminating agent), and in spite of its generality, it is relatively expensive and therefore unattractive, especially for large-scale preparations. Several specific procedures leading to monoalkylhydrazines and based on selective alkylation of some hydrazine derivatives have been also reported. *N*-Alkylation of acetone *N*-acetylhydrazone followed by subsequent acid hydrolysis was recommended for the preparation of benzylhydrazine hydrochloride[8] and later used[9] for introducing *p*-bromobenzyl residue into the hydrazine molecule. Some years ago phase-transfer catalysis was first successfully applied for selective *N*-alkylation of diphenylphosphinohydrazide[10] and *N'*-acetyl-*N*-alkyldiphenylphosphinohydrazides[11] offering a new approach to the synthesis of monoalkylhydrazines and 1,2-dialkylhydrazines, respectively. Both procedures, although reliable and relatively convenient in small scale, are, however, laborious and rather expensive due to the high cost of diphenylphosphinohydrazide.

Looking for a more economic synthesis of monoalkylhydrazines we have recently found that acetone *N*-(diethoxyphosphoryl)hydrazone (**1**) can be easily prepared in high yield.[12] This compound, which is the hydrazine derivative suitably protected for monoalkylation, could be considered as potential starting material for the preparation of monoalkylhydrazines. According to our expectations hydrazone **1** reacts smoothly with sodium hydride in benzene to form the well stabilized anion, easily soluble in this solvent. Surprisingly, this anion cannot be effectively and quantitatively alkylated even with a large excess of an alkyl bromide and a prolonged reaction time (up to 8 h in boiling benzene). Considerable amounts (up to 50%) of unreacted **1**, detected (^{31}P-NMR) in the alkylation product after work-up, render this reaction practically useless from the preparative point of view.

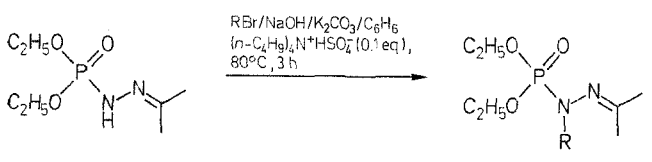
No such difficulties are, however, encountered when alkylation of **1** is performed under solid-liquid phase-transfer conditions

Table. Preparation of Monoalkylhydrazine *p*-Toluenesulfonates **3**

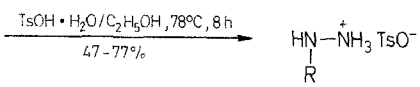
Product	Yield[a] (%)	m.p.[b] (°C)	Molecular Formula[c]	IR (KBr)[d] (cm^{-1})	^{1}H-NMR (D_2O/TMS_{ext})[e] (ppm)
3a	64	122–124	$C_9H_{16}N_2O_3S$ (232.2)	3450 (NH), 1640 (NH_3^+), 1225, 1200, 1140, 1040, 825	1.27 (t, 3H, J = 7.0 Hz); 2.41 (s, 3H); 3.24 (q, 2H, J = 7.0 Hz); 7.26–7.87 (m, 4H)
3b	77	116–118	$C_{11}H_{20}N_2O_3S$ (260.3)	3460 (NH), 1610 (NH_3^+), 1210, 1185, 1125, 1035, 810	0.96 (t, 3H, J = 6.5 Hz); 1.12–1.85 (m, 4H); 2.44 (s, 3H); 3.20 (t, 2H, J = 7.5 Hz); 7.27–7.90 (m, 4H)
3c	69	126–130	$C_{11}H_{20}N_2O_3S$ (260.3)	3470 (NH), 1630 (NH_3^+), 1220, 1195, 1130, 1035, 815	0.94 (d, 6H, J = 6.2 Hz); 1.99 (9 lines, 1H, J = 6.2 Hz); 2.32 (s, 3H); 2.96 (d, 2H, J = 6.2 Hz); 7.15–7.82 (m, 4H)
3d	56	111–115	$C_{13}H_{24}N_2O_3S$ (288.35)	3400 (NH), 1635 (NH_3^+), 1230, 1190, 1130, 1040, 815	0.89 (t, 3H, J = 6.0 Hz); 1.15–1.88 (m, 8H); 2.41 (s, 3H); 3.15 (t, 3H, J = 7.5 Hz); 7.27–7.85 (m, 4H)
3e	72	143–144	$C_{14}H_{18}N_2O_3S$ (294.3)	3360 (NH), 1610 (NH_3^+), 1225, 1190, 1130, 1040, 815, 750	2.34 (s, 3H); 4.26 (s, 2H); 7.50 (s, 5H); 7.22–7.84 (m, 4H)
3f	73	124–125	$C_{16}H_{22}N_2O_3S$ (322.4)	3320 (NH), 1630 (NH_3^+), 1220, 1180, 1125, 1035, 815, 750	2.01 (qt, 2H, J = 7.0 Hz); 2.42 (s, 3H); 2.76 (t, 2H, J = 7.0 Hz); 3.19 (t, 2H, J = 7.0 Hz); 7.36 (s, 5H); 7.25–7.80 (m, 4H)
3g	47	97–98	$C_{10}H_{16}N_2O_3S$ (244.25)	3470 (NH), 1640 (NH_3^+), 1220, 1195, 1140, 1040, 820	2.34 (s, 3H); 3.74 (d, 2H, J = 6.0 Hz); 5.30–6.13 (m, 3H); 7.15–7.85 (m, 4H)

[a] Yield of crude products.
[b] After recrystallization from ethanol/ether.
[c] Satisfactory microanalyses obtained: C ±0.20, H ±0.30, N ±0.30.
[d] Recorded on a Specord 71 IR (C. Zeiss) spectrophotometer.
[e] Measured at 80 MHz with a Tesla BS 487C spectrometer.

(PTC).[10] A similar technique was found useful for *N*-alkylation of tosylhydrazones,[13] but subsequent deprotection, which would evidently demand rather forcing conditions, was not developed. The reaction of **1** with primary alkyl bromide in a two-phase system consisting of solid, powdered sodium hydroxide and potassium carbonate suspended in benzene in the presence of 0.1 molar equivalents of tetra-*n*-butylammonium hydrogen sulfate as catalyst proceeds rapidly at reflux temperature and is complete after 3 h, affording the corresponding acetone *N*-alkyl-*N*-(diethoxyphosphoryl)hydrazone (**2**) in high yield. Crude **2** does not reveal the presence of any undesirable impurities (^{1}H-NMR, ^{31}P-NMR) and needs no purification before deprotection. *N*-Alkylation of **1** is restricted to primary halides and does not take place at all with secondary substrates.



1 2a-g



Ts = 4-$CH_3C_6H_4SO_2$ 3a-g

2/3	R	2/3	R
a	C_2H_5	**e**	$C_6H_5CH_2$
b	*n*-C_4H_9	**f**	$C_6H_5(CH_2)_3$
c	*i*-C_4H_9	**g**	$H_2C{=}CHCH_2$
d	*n*-C_6H_{13}		

The presence of acidic hydrogen atoms in the alkylating agent (e.g., propargyl bromide) is also detrimental. Simultaneous removal of both the diethoxyphosphoryl group and the hydrazone residue can be easily accomplished by refluxing crude **2** with one equivalent each of *p*-toluenesulfonic acid monohydrate and water in ethanol for 8 h. Evaporation of the solvent followed by precipitation of the product with ether affords monoalkylhydrazine *p*-toluenesulfonates **3** as crystalline solids. Analytically pure samples of **3** are obtained by dissolving the crude *p*-toluenesulfonates in warm ethanol and reprecipitation with ether. Yields, melting points, and spectroscopic data of monoalkylhydrazine *p-toluenesulfonates* **3** are compiled in the Table.

The reported approach to monoalkylhydrazines is superior to the previously described alkylating procedures in that: (a) it seems to be of general character at least for primary halides; (b) the starting material is inexpensive and easily available; (c) the intermediate **2** does not need purification; (d) the simple and clean deprotection step leads to pure monoalkylhydrazine *p*-toluenesulfonates **3**, which are stable, non-hygroscopic, and easily isolable.

Acetone *N*-(diethoxyphosphoryl)hydrazone (1):
Compound **1** is prepared in 80% yield according to the previously described procedure.[12] Purification by distillation *in vacuo* (b.p. 132–134°C/0.4 torr; bath temp. 160–170°C) is more convenient than recrystallization from hexane/benzene (2:1).

Monoalkylhydrazine *p*-toluenesulfonates (3); General Procedure:
Alkyl bromide (0.03 mol) in benzene (10 ml) is added dropwise with stirring to the refluxing solution of acetone *N*-(diethoxyphosphoryl)hydrazone (**1**; 5.2 g, 0.025 mol) in benzene (70 ml) containing solid, finely powdered sodium hydroxide (4.0 g, 0.1 mol), potassium carbonate (5.5 g, 0.04 mol), and tetra-*n*-butylammonium hydrogen sulfate (0.85 g, 0.0025 mol). Stirring is then continued for 3 h at 80°C. The resultant mixture is cooled to room temperature and filtered. The precipitate is washed with benzene (2 × 10 ml) and the washings are combined with the filtrate. The benzene solution is washed with water until neutral (*caution*: do not wash with water for R ⩽ C_4), dried with magnesium sulfate, and evaporated under reduced pressure. The oily residue is mixed with ethanol (15 ml), *p*-toluenesulfonic acid monohydrate (4.75 g, 0.025 mol), and water (0.45 ml, 0.025 mol). The resultant mixture is refluxed gently for 8 h, and then evaporated under reduced

pressure. Ether (40 ml) is added to the residue and the crystalline precipitate of monoalkylhydrazine *p*-toluenesulfonate **3** is filtered off, washed with ether, and recrystallized, if necessary, by dissolving in warm ethanol and reprecipitation with an excess of ether.

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