Convenient Procedure for One-pot Conversion of Azides to *N*-Monomethylamines

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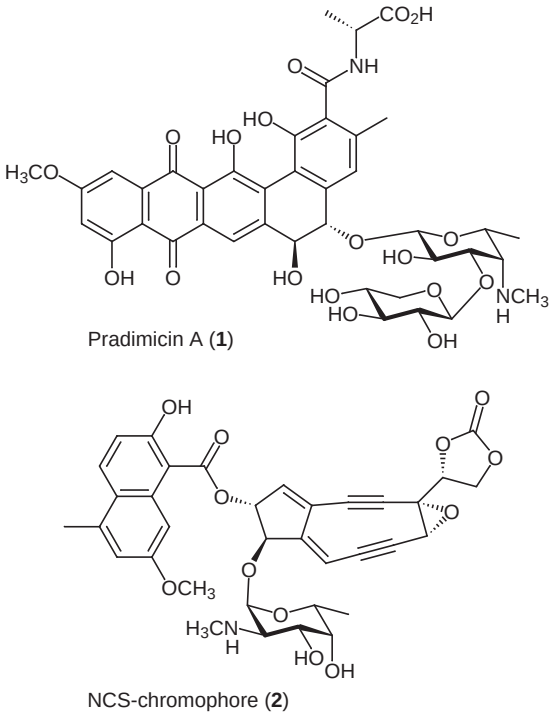
Dedicated to Prof. Ryoji Noyori for his outstanding contribution to organic chemistry.

Abstract: One-pot conversion of azides to *N*-monomethylamines is described. Two optional protocols have been developed, which share the first stage, the reaction of an azide with $(CH_3)_3P$ to generate the corresponding iminophosphorane. This Staudinger intermediate, thus generated, is either methylated with CH_3I and hydrolyzed (method A), or treated with $(HCHO)_n$ and reduced with $NaBH_4$ (method B), thereby giving the corresponding *N*-monomethylamine in high yield.

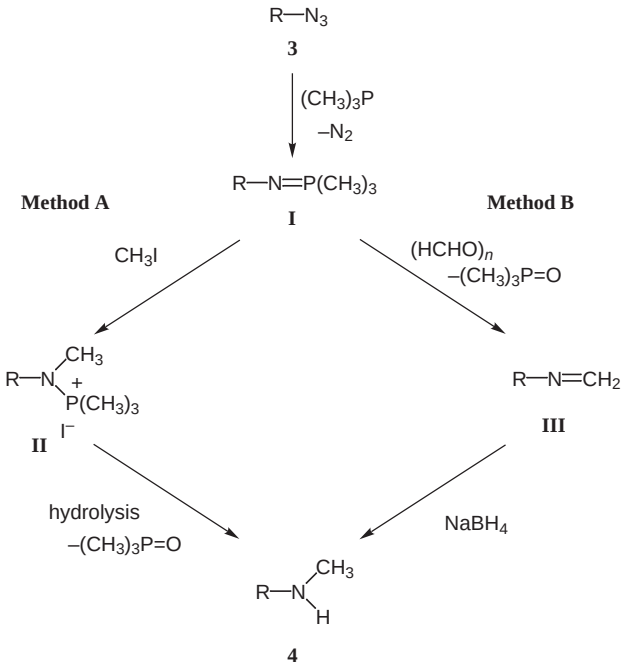
Key words: azides, *N*-monomethylamines, Staudinger reaction, iminophosphorane, aza-Wittig reaction

An *N*-monomethylamino group is often embedded as a structural motif in various biologically active natural products, such as pradimicin A (**1**)[1] and the neocarzinostatin chromophore (**2**).[2] In connection with our synthetic effort directed toward the pradimicin-benanomicin class antibiotics including **1**, we required a method for the facile construction of an *N*-monomethylamino group from the azide in a densely functionalized intermediate at the later stage of the synthetic scheme. Although many reports have appeared for the access to such a group via the corresponding *prim*-amines,[3] they are often hampered by the problems of competing bis-methylation or inapplicability to the multi-functionalized substrates. In order to avoid such complication, we became interested in the possibility of the one-pot conversion of such an azide to the corresponding *N*-monomethylamine.

We describe herein two effective methods for the one-pot synthesis of *N*-monomethylamines from the corresponding azides (Scheme 1), which seem to fulfill the above-stated criteria. The bottom line is the use of the iminophosphorane, which is easily generated from the azides by treatment with R_3P, actually $(CH_3)_3P$ (vide infra). The Staudinger intermediate,[4] thus generated, is either methylated with CH_3I and hydrolyzed (method A), or treated with paraformaldehyde and reduced with $NaBH_4$ (method B), thereby giving the corresponding *N*-monomethylamine in high yield.

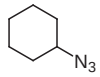
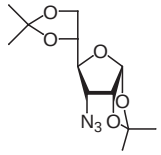
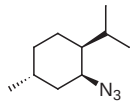
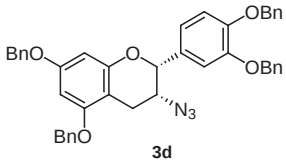
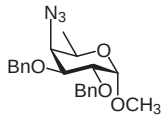
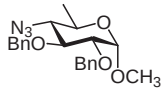


Figure



Scheme 1

Table *N*-Monomethylamination of Various Azides

run	substrate	R-N(H)CH_3 **4** (Yield/%)	
		method A[a)]	method B[b)]
1	 **3a**	76[c)]	74[e)]
2	 **3b**	68[c)]	81
3	 **3c**	73[d)]	77
4	 **3d**	86[d)]	81
5	 **3e**	86[d)]	83
6	 **3f**	80[d)]	76

a) $(CH_3)_3P$ (2.0 eq.) / toluene, CH_2Cl_2, 25 °C, 1.5 h / CH_3I (10 eq.), CH_2Cl_2, 25 °C; b) $(CH_3)_3P$ (2.0 eq.) / toluene, CH_2Cl_2, 25 °C, 1.5 h / $(HCHO)_n$ (5.0 eq.) / $NaBH_4$ (5.0 eq.), MeOH; c) hydrolysis was performed in aq.THF at 80 °C, 12 h; d) hydrolysis was performed in 2 M NaOH, 1,4-dioxane at 100 °C, 1 h; e) the corresponding *N*,*N*-dimethylamine was obtained in 18% yield.

Although both methods worked well for various substrates, it became apparent that method A is effective for the less hindered azides, while method B for the hindered ones. More importantly, method B is particularly suitable for the application to the multi-functionalized compounds in terms of the mild reaction conditions, as will be seen in the following.

Preliminary attempts showed that $(CH_3)_3P$, rather than $(C_6H_5)_3P$, is the reagent of choice because of the superior reactivity for generating the key iminophosphorane species. The reactivity difference can be roughly grasped by comparing the time required for the completion of the reaction with cyclohexyl azide (ca. 0.5 M soln. toluene), that is, $(CH_3)_3P$ (1.5 h at 25 °C), $(C_6H_5)_3P$ (12 h at 25 °C or 5 h at 80 °C). An additional advantage of $(CH_3)_3P$ over $(C_6H_5)_3P$ is the ready solubility of $(CH_3)_3P$=O in water, enabling the easy purification of the products. $(CH_3)_3P$ is currently commercially available as a stock solution (1.0 M / toluene).

Method A

Representative procedure for method A is described for the reaction of the azide **3e**: To a solution of **3e** (59.3 mg, 0.177 mmol) in CH_2Cl_2 (1.5 mL) was added a solution of $(CH_3)_3P$ in toluene (1.0 M, 0.4 mL) at room temperature. After stirring for 1.5 h, CH_3I (251 mg, 1.77 mmol) in CH_2Cl_2 (1.5 mL) was added. After stirring for 3 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was dissolved in 1,4-dioxane (2.0 mL) and aqueous NaOH (2 M, 2 mL), and heated at 100 °C for 1 h. After cooling, the products were extracted with CH_2Cl_2 (x5). The combined organic extracts were dried (K_2CO_3), and concentrated in vacuo. Purification by preparative silica-gel TLC ($CHCl_3$ / MeOH = 94 / 6) gave **4e**[5] as colorless oil (49.2 mg, 86%).

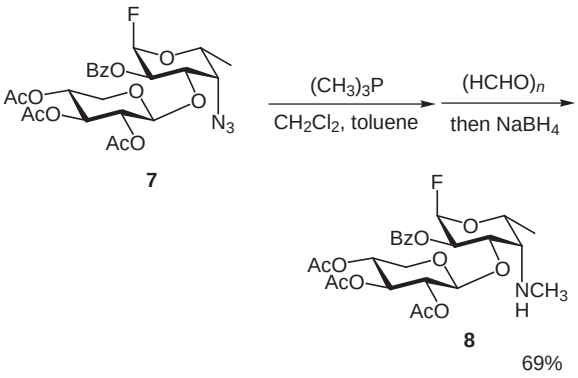
The left-side column in the Table shows the application of this protocol to various azides. In all cases listed, the initial two stages of the process, i.e. the reaction with $(CH_3)_3P$ and the methylation with CH_3I, were complete within 4 h at 25 °C, whereas the hydrolysis of the resulting phosphonium salt was far more difficult than expected, which was particularly the case for the sterically hindered substrates. Thus, in the cases of **3a** and **3b**, the hydrolysis was possible simply by heating the phosphonium salt in aqueous THF (runs 1, 2), the hydrolysis for the cases of **3c–3f** was only possible by heating under basic conditions (1 M NaOH aq., 100 °C, 1 h).

Method B

Representative procedure for method B is described also for the reaction of the azide **3e**: To a solution of **3e** (56.8 mg, 0.148 mmol) in CH_2Cl_2 (1.5 mL) was added a solution of $(CH_3)_3P$ in toluene (1.0 M, 0.3 mL) at room temperature. After stirring for 1.5 h, $(HCHO)_n$ (22.6 mg, 0.753 mmol) was added. The reaction mixture was stirred for 6 h at room temperature before treatment with MeOH (2 mL) and $NaBH_4$ (28 mg, 0.74 mmol) at 0 °C. After stirring for 0.5 h, the reaction was stopped with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (x5). The combined extracts were dried (K_2CO_3), and concentrated in vacuo. Purification by preparative silica-gel TLC ($CHCl_3$ / MeOH = 94 / 6) gave **4e**[5] as colorless oil (45.7 mg, 83%).

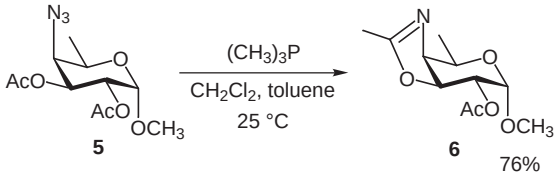
Gratifyingly, this latter protocol proved applicable to various substrates as shown in the right column of the Table. Particularly attractive was that both of the two reaction stages, i.e. the aza-Wittig reaction and the reduction, proceeded nicely without respect to, if any, the steric hindrance of the substrates (cf. method A, vide supra).

Indeed, application to a model compound **7**, corresponding to the disaccharide portion[6] of our target, cleanly gave the *N*-monomethylated compound **8** in good yield. Particularly important is that the reaction conditions proved to be mild enough to allow its application to such a base-sensitive substrate with acyl protecting groups (Scheme 2).



Scheme 2

Currently, we are studying the application of this protocol for poly-functionalized azides, which will be detailed elsewhere. However, it is interesting to note here an unexpected observation encountered along these lines (Scheme 3). The β-acyloxy azide **5** underwent an intramolecular aza-Wittig reaction[7] without regard to the co-existing paraformaldehyde, giving the oxazoline **6** in good yield. This suggests not only a limitation of the method, but at the same time a promising hint to the new synthesis of heterocycles.



Scheme 3

In summary, we have developed a method for the one-pot conversion of azides to *N*-monomethylamines. Compatibility with diverse functional groups would make the present protocol useful in organic synthesis. We are centering our attention to the total synthesis of pradimicin A by utilizing this method.

References and Notes

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