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A safe and convenient method for the preparation of triflyl azide, and its use in diazo transfer reactions to primary amines

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Abstract—A safe and convenient method for the copper(II)-catalyzed diazo transfer from triflyl azide to primary amines is reported. By replacing CH_2Cl_2 by toluene the formation of hazardous side products, for example, azido-chloromethane and diazidomethane can be avoided.

1. Introduction

Azides are versatile functional groups that undergo a variety of reactions, such as 1,3-dipolar cycloadditions and rearrangement processes, or act as precursors for nitrene chemistry.[1] In addition, azides are widely used as convenient protecting groups for primary amines. Traditionally, the introduction of azides has been achieved by substituting appropriate leaving groups with inorganic azide. However, in the last 15 years, diazo transfer from triflyl azide (TfN_3) to primary amines has found wide use. Although this approach has already been published by Cavender and Shiner[2] in 1972, it was rarely applied until the early 1990s.[3]

In 1996, Wong and co-workers introduced[4] a mild transition metal-catalyzed modification of the original diazo transfer procedure, and in 2002, he elucidated[5] its copper(II)-catalyzed mechanism. A successful application in aminoglycoside synthesis was published by the same group.[6]

However, a general drawback of diazo transfer is the formation of hazardous intermediates, for example, TfN_3, which can only be handled in solution.[2] Furthermore, in all published procedures for the preparation of triflyl azide and its application in the diazo transfer to primary amines, triflic anhydride and sodium azide are used in a biphasic system of CH_2Cl_2/H_2O. Under these reaction conditions, nucleophilic substitutions on CH_2Cl_2 leading to azido-chloromethane and/or diazidomethane tend to occur. Thus, the formation of perilous diazidomethane has been reported by Hassner et al.[7,8] upon shaking an azide anion source in CH_2Cl_2. When this reaction mixture was pipetted or used for IR spectroscopy (films between NaCl plates) explosions occurred.[8] As a consequence of the formation of diazidomethane several additional explosions were reported, leading to the destruction of facilities and severely injured staff. Therefore, several laboratories reported that they banned the use of halogenated solvents in combination with sodium azide.[9–11]

2. Results and discussion

In order to avoid the formation of azido-chloromethane and diazidomethane, as well as high concentrations thereof, we tested various replacements for CH_2Cl_2. Toluene was identified as a solvent replacement for the preparation of TfN_3 to avoid the formation of hazardous diazidomethane and potentially hazardous azido-chloromethane byproducts in the typical solvent used, and furthermore, for the application of TfN_3 in the diazo transfer reaction. Toluene is inert towards sodium azide under the employed conditions and, because of its boiling point, high concentrations of TfN_3 can easily be avoided (Fig. 1).

Wong reported that carefully adjusted homogeneous reaction conditions are a prerequisite for a successful diazotransfer.[4,5] Therefore, three different solvent ratios leading to monophasic mixtures (see ternary phase

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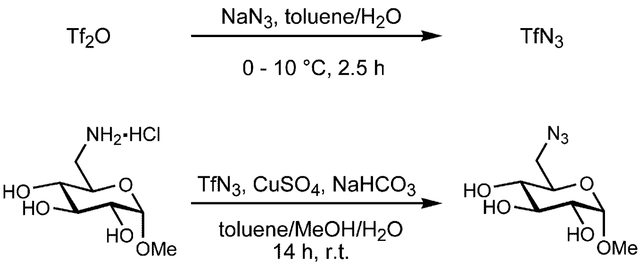


Figure 1. Preparation of TfN_3 and diazo transfer to a primary amine using toluene as co-solvent.

Table 1. Diazo transfer reaction **1** → **2** using different solvent ratios

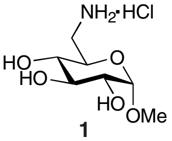
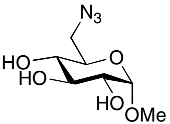
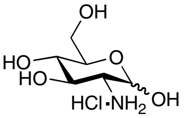
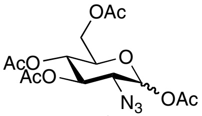
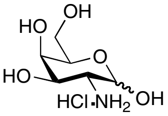
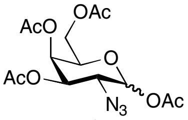
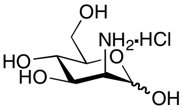
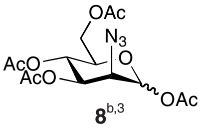
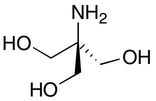
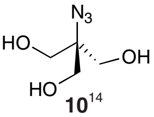
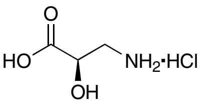
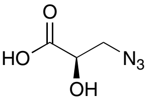
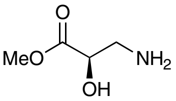
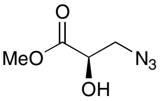
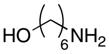
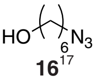
Entry	Solvent ratios (H_2O/PhMe/MeOH)	Yield[a] (%)
1	1/1.7/6.7, homogeneous	Quant.
2	1.3/1/5.4, homogeneous	74
3	1/4.3/10, homogeneous	Quant.
4	1/1/1, heterogeneous	96

[a] Isolated yields.

diagram[13]) for H_2O/PhMe/MeOH were tested (Table 1, entries 1–3), using methyl 6-amino-6-deoxy-α-D-glucopyranoside (**1**) as starting material. Under all three conditions, the desired azide **2** was obtained in good to excellent yield. Furthermore, the diazo transfer also turned out to be successful under heterogeneous conditions (Table 1, entry 4).

To test the scope of this modified version of the diazo transfer reaction, a number of primary amines were

Table 2. Results of the diazo transfer under homogeneous conditions using H_2O/PhMe/MeOH 1/1.7/6.7 (see also Refs. 12 and 14–17)

Entry	Amine	Azide	Time (h)	Yield[a] (%)
1	 **1**	 **2**[12]	14	Quant.
2	 **3**	 **4**[b,3]	21	72
3	 **5**	 **6**[b,3]	36	50
4	 **7**	 **8**[b,3]	36	19
5	 **9**	 **10**[14]	14	Quant.
6	 **11**	 **12**[15]	14	83
7	 **13**	 **14**[16]	14	93
8	 **15**	 **16**[17]	14	52

[a] Isolated yields.

[b] For purification the crude products were acetylated.

investigated. The reactions were carried out in a monophasic solvent mixture of H_2O/PhMe/MeOH 1/1.7/6.7. The triflyl azide solution in toluene was added to a mixture of the amine, sodium hydrogencarbonate and copper(II) sulfate in water, followed by methanol to obtain a homogeneous turquoise solution. The TLC indicated the reactions to be complete within 14 h, except for the amines **3**, **5** and **7**. Even after 21 and 36 h, respectively, they yielded the corresponding azides **4**, **6** and **8** only in moderate yields (Table 2, entries 2–4). The decrease in yield for **4**, **6** and **8** is probably due to the increasing steric hindrance, which is in agreement with results reported by Vasella et al.[3]

In conclusion, we have shown that (1) toluene can be used instead of dichloromethane for the generation of triflyl azide and (2) the TfN_3/toluene solution can directly be applied to the diazo transfer to primary amines. This method is therefore significantly safer than the previously reported procedure, because highly hazardous diazidomethane can no longer be formed. Furthermore, the reaction proceeds smoothly under homogeneous, but also heterogeneous conditions (Table 1). This is a significant improvement, considering the necessity of the reported delicate adjustment of the solvent ratio using CH_2Cl_2.[5] Because the safety risk originating from the formation of azido-chloromethane and diazidomethane can be avoided, even an industrial application of this novel diazo transfer methodology is possible.

3. Experimental

3.1. Preparation of the triflyl azide stock solution

After sodium azide (545 mg, 8.38 mmol) was dissolved in water (1.37 mL), toluene (1.37 mL) was added. The mixture was cooled to 0 °C under vigorous stirring. After the dropwise addition of triflic anhydride (896 μL, 4.19 mmol) and further vigorous stirring for 30 min at 0 °C, the temperature was raised to 10 °C and the biphasic mixture was stirred for 2 h. A saturated aqueous solution of sodium hydrogencarbonate was added dropwise until gas evolution had ceased. The two phases were separated and the aqueous layer was extracted with toluene (2 × 1.37 mL). The combined organic layers were used in the subsequent diazo transfer reactions.

3.2. Typical procedure for the diazo transfer reaction

The amine (0.23 mmol), sodium hydrogencarbonate (78 mg, 0.93 mmol) and copper(II) sulfate pentahydrate (2.2 mg, 0.01 mmol) were dissolved in water (0.3 mL). Triflic azide stock solution (0.51 mL) was added, followed by the addition of methanol (1.98 mL) to yield a homogeneous system. Subsequently, the blue mixture was stirred vigorously at room temperature. Complete consumption of the amine was monitored by TLC and is also indicated by a colour change of the reaction mixture from blue to green. Solvents were removed in vacuo with a rotary evaporator keeping the temperature strictly below 25 °C. The residue was purified by chromatography on silica gel (eluant: dichloromethane–methanol). Fully unprotected sugars were transformed into their acetates with Ac_2O/pyridine prior to chromatography.

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14. Trishydroxymethyl-methyl azide (**10**). ^{1}H NMR (DMSO-d_6, 500.1 MHz): δ 3.48 (d, $^3J = 5.5$ Hz, 6H, 3CH_2OH), 4.85 (t, $^3J = 5.5$ Hz, 3H, 3CH$_2$OH); ^{13}C NMR (DMSO-d_6, 125.8 MHz): δ 61.4 (CH$_2$), 68.9 (C). IR (film, cm^{-1}): 759 (s), 822 (s), 2104 (s, N$_3$), 2250 (s), 3431 (br s, O-H); ESI-MS, pos. ionization: 147.98 $[M+H]^+$; neg. ionization: 145.89 $[M-H]^-$, 191.91 $[M+HCO_2]^-$.
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