Synthetic Methods

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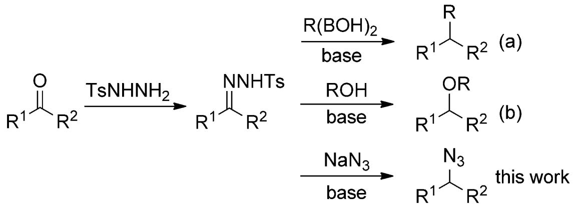
Reductive Azidation of Carbonyl Compounds via Tosylhydrazone Intermediates Using Sodium Azide[**]

José Barluenga, María Tomás-Gamasa, and Carlos Valdés**

The azide functionality has drawn considerable interest since the late 19th century as a result of its versatile reactivity. Organic azides have found wide application in organic synthesis as precursors of fundamental nitrogen functionalities[1,2] as well as of nitrogen-containing heterocycles. Moreover, the development of the Cu-catalyzed azide–alkyne cycloaddition,[3,4] the most representative example of click chemistry,[5] has established new perspectives for the use of azides in drug discovery[6] and also in materials science, supramolecular chemistry, polymer chemistry, and biotechnology.[7] Thus, azides have recently acquired a privileged position at the interface between chemistry, biology, medicine, and materials science.

The common incorporation of the azide group into organic frameworks relies on the classic nucleophilic substitution reaction of appropriate electrophilic substrates with azide anions.[8] Other methods for the synthesis of alkyl azides involve diazo transfer reactions to alkyl amines,[9] reactions of carbon nucleophiles with electrophilic azides,[10] and hydroazidations of alkenes.[11] Importantly, while the reductive amination of carbonyl compounds is recognized as one of the most general protocols to synthesize amines, access to alkyl azides from carbonyl compounds remains almost unknown. In this context, Banert et al. have recently demonstrated the generation of α-azidoalcohols by hydroazidation of aldehydes with hydrazoic acid.[12]

On the other hand, tosylhydrazones are versatile tools for the modification of carbonyl compounds.[13] On the basis of our previous work on metal-free C–C and C–O bond-forming reductive coupling of tosylhydrazones (Scheme 1, a and b, respectively),[14] we now report a new synthesis of alkyl azides that is based on a new metal-free C–N bond-forming reductive coupling reaction (Scheme 1).[15,16] Specifically, primary and secondary azides are prepared from carbonyl compounds by reductive azidation of the readily available tosylhydrazones as carbonyl surrogates with azide anions.



Scheme 1. Metal-free reductive couplings between carbonyl compounds and boronic acids (a), alcohols (b), and azides via tosylhydrazone intermediates.

To establish the appropriate reaction conditions, some experiments were undertaken with the hydrazone derived from 4-methylacetophenone **1a** and sodium azide. The results are briefly summarized as follows: 1) heating of tosylhydrazone and azide anions in the presence of base led to a complex mixture constituted primarily of hydrazone degradation products; 2) the formation of the expected benzyl azide **2a** requires the presence of tetrabutylammonium bromide (TBAB) as the phase transfer catalyst; 3) other parameters, for example, base (potassium carbonate), temperature (110°C), solvent (1,4-dioxane), stoichiometric ratio (**1a**/NaN$_3$/base/TBAB = 1:3:1:3), were optimized (Table 1, entry 1); thus, the treatment of *N*-tosylhydrazone **1a** (1 equiv, 0.1 M) with sodium azide under the above reaction conditions afforded the azide **2a** in a reasonable 60% yield after purification.

With this protocol in hand, the scope of the reaction was investigated, thus a series of representative hydrazones **1** was subjected to the optimized reaction conditions. It must be noted that the volume of solvent as well as temperature and reaction times had to be optimized for each particular substrate (Table 1). The reaction works well for both aldehydes (Table 1, entries 7–12) and ketones (entries 1–6, 13, and 14) furnishing primary and secondary alkyl azides, respectively. Aromatic carbonyls with electron-withdrawing (Table 1, entries 4–7) and -donating groups (entries 1–3, 8, and 9) as well as with halogen substituents (entries 4 and 6) are perfectly compatible with the reaction conditions. Moreover, heteroarylcarbonyl compounds, both π-excessive and π-deficient heterocycles, afforded moderate yields of the corresponding azides (Table 1, entries 10 and 11, respectively). Interestingly, the azide functionality can be efficiently installed in the α position of an ester, as is exemplified in entry 13 in Table 1.

We then moved to the development of the one-pot version of this transformation. With our previous background in this field it was straightforward to establish a new protocol by using carbonyl compounds as the starting materials (Scheme 2). By heating these substrates in the presence of tosylhydrazide at 80°C for 90 min and subsequently adding

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[*] Prof. J. Barluenga, Dr. M. Tomás-Gamasa, Dr. C. Valdés
Instituto Universitario de Química Organometálica "Enrique Moles". Universidad de Oviedo
c/Julián Clavería 8. Oviedo. 33006 (Spain)
E-mail: barluenga@uniovi.es
acvg@uniovi.es

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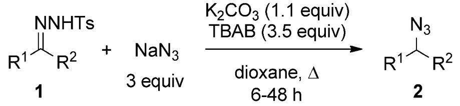
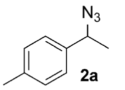
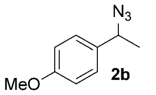
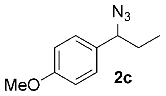
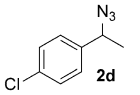
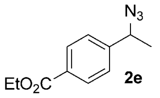
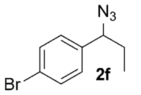
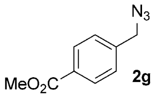
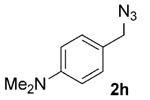
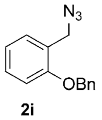
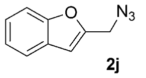
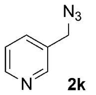
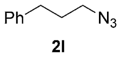
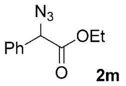
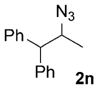
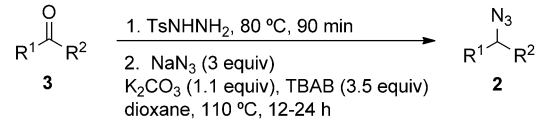
Table 1: Reductive azidation of tosylhydrazones **1** with sodium azide.[a]



Entry	Volume[d] [mL]	*t* [h]	Compound **2**	Yield [%][b]
1	1.1	12	 **2a**	60
2	1.1	24	 **2b**	57
3	1.1	24	 **2c**	78
4	1.1	24	 **2d**	45
5	1.1	12	 **2e**	36
6	1.0	9	 **2f**	44
7	1.1	12	 **2g**	66
8	1.7	12	 **2h**	48
9	2.8	12	 **2i**	55
10	1.1	12	 **2j**	56
11	1.1	12	 **2k**	45
12	1.1	20	 **2l**	82
13	2.8	48	 **2m**	43
14[c]	1.5	1	 **2n**	44

[a] Reaction conditions: *N*-tosylhydrazone **1** (0.3 mmol, 1.0 equiv); NaN_3 (0.9 mmol, 3.0 equiv); K_2CO_3 (1.05 mmol, 1.1 equiv); 1.0–2.8 mL of dioxane, 110 °C; TBAB (3.5 equiv); 6–24 h. [b] Yields were calculated by using ^1H NMR spectroscopy with the use of an internal standard. [c] Microwave-assisted reaction. [d] Volume of dioxane, which determines the concentrations of the used reagents.

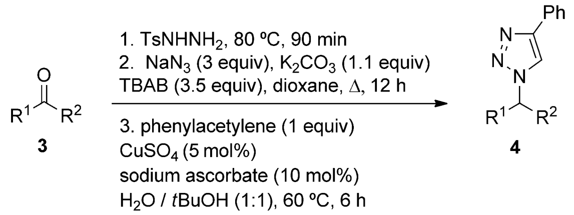
the rest of the reagents, the azides were again obtained in yields that were only slightly lower than those reached by following the two-step procedure.[17]



R^1 = PMP, R^2 = Me	**2b:** 50%
R^1 = PMP, R^2 = Et	**2c**: 65%
R^1 = Tol, R^2 = Me	**2a**: 38%
R^1 = 2-(benzyloxy)phenyl, R^2 = H	**2i**: 65%

Scheme 2. One-pot synthesis of azides from carbonyl compounds. PMP = *p*-methoxyphenyl, Tol = *p*-tolyl.

Once this protocol was established, we considered the possibility of using these substrates in the classical click ligation with a terminal acetylene. Delightfully, we found a procedure in which it was not necessary to isolate the in situ formed azide prior to the cyclization step with the alkyne (Scheme 3). Indeed, after the azide had directly been synthesized from the carbonyl, the solvent was removed under reduced pressure, and subsequently the reagents that were needed to achieve the Cu-catalyzed [3+2] cycloaddition[5] were added; this sequence led directly to the triazole.[18] This is indeed an unprecedented transformation in which the triazole is synthesized directly from a carbonyl compound.



4a, R^1 = PMP, R^2 = Me; 53%
4b, R^1 = PMP, R^2 = Et; 50%
4c, R^1 = 2-(benzyloxy)phenyl-, R^2 = H; 65%
4d, R^1 = Tol, R^2 = Me; 45%

Scheme 3. One-pot, three-step synthesis of triazoles from carbonyl compounds.

In conclusion, a novel reaction of tosylhydrazones, a surrogate of the fundamental carbonyl compounds, is reported. This reductive azidation complements the reactivity of carbonyl derivatives toward nitrogen nucleophiles, thus enhancing the array of nitrogen derivatives available from carbonyl compounds. The reaction is a direct method to obtain primary and secondary alkyl azides, the latter being hardly accessible by nucleophilic displacement. The simplicity of the reaction is noteworthy as it requires neither the participation of a metal catalyst nor the use of dry components (solvent and reagents). Moreover, the transformation can be carried out in a one-pot fashion, resulting in the direct transformation of carbonyl compounds into azides. Additionally, the one-pot combination of this reaction with the Cu-catalyzed [3+2] ligation with a terminal alkyne provides triazoles directly from carbonyl compounds.

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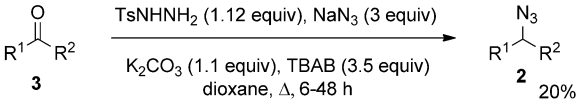
[17] Moreover, the reaction can be also carried out in a multicomponent-fashion by heating all the reagents together from the early beginning.



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