Mannich Reactions Using Benzyl Azide as a Latent *N*-(Phenylamino)methylating Agent

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Abstract: Treatment of benzyl azide with triflic acid or titanium tetrachloride effects 1,2-phenyl migration with concomitant liberation of molecular nitrogen. The resulting *N*-phenyl iminium ion intermediate readily combines with enolizable carbonyl substrates to form Mannich bases. © 1998 Elsevier Science Ltd. All rights reserved.

The Mannich reaction is classically a three-component condensation between an activated methylene substrate, formaldehyde, and a non-tertiary amine.[1] The reaction proceeds through the intermediate formation of an iminium salt that reacts with the enol form of the ketone component. Modern improvements on this recipe often involve alternative ways of generating this iminium salt or using a preformed version of the reagent. Herein, we describe a rearrangement approach to Mannich chemistry that is experimentally convenient and complements existing methodology. The prototypical reaction, shown in eq 1, permits the one-pot conversion of a simple ketone like cyclohexanone to the formal Mannich product **2** through the agency of benzyl azide (**1**) and acid.
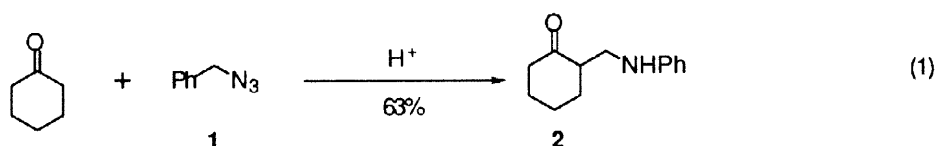

We had previously shown that ketones undergo TiCl$_4$-promoted Schmidt reactions with simple alkyl azides such as **1** (e.g., **1** + cyclohexanone → **3**, eq 2).[2] This transformation appeared to work well only with a limited set of substrates; cyclopentanones and acyclic ketones, in particular, were unreactive. In an effort to broaden the scope of this reaction, we investigated some of these unreactive substrates, finding that some of them gave Mannich-type products resulting from an apparent rearrangement of the starting azide. These new products could be optimized through the use of a strong protic acid. For example, introduction of 1.1 equiv of triflic acid to an equimolar solution of cyclohexanone and **1** in dichloromethane led not to the anticipated *N*-benzyl caprolactam (**3**), but rather to the *N*-phenyl aminomethylated cyclohexanone **2** as shown.
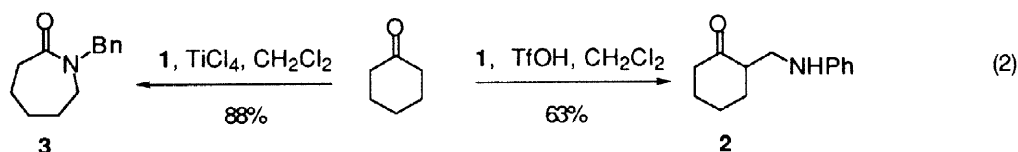
Under these conditions, the azide underwent facile conversion to the *N*-phenyl Mannich reagent **4** (X = OTf)[3] prior to reaction with the ketone. This transformation could be conveniently followed by proton NMR

(Scheme). Specifically, addition of triflic acid to a CDCl$_3$ solution of **2** triggered a rapid and complete replacement of the benzylic singlet appearing at 4.35 ppm in the parent azide with the olefinic resonances of **4**. It is likely that the reaction occurs via a [1,2]-phenyl shift of an intermediate aminodiazonium ion as shown. In related chemistry, Kuwajima has demonstrated that (trimethylsilyl)methyl azide undergoes a similar rearrangement under AlCl$_3$ promotion, affording a complexed iminium species that reacts in Mannich-like fashion with silyl enol ethers.[4] Also, Pearson and Fang have independently discovered the rearrangement shown in Scheme and examined the hetero Diels-Alder reactions of **4** with alkenes.[5]
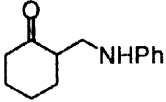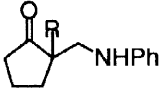
Scheme

H$_a$: δ 8.12 (dd, J = 10.4, 7.0 Hz)
H$_b$: δ 8.36 (dd, J = 17.7, 7.2 Hz)
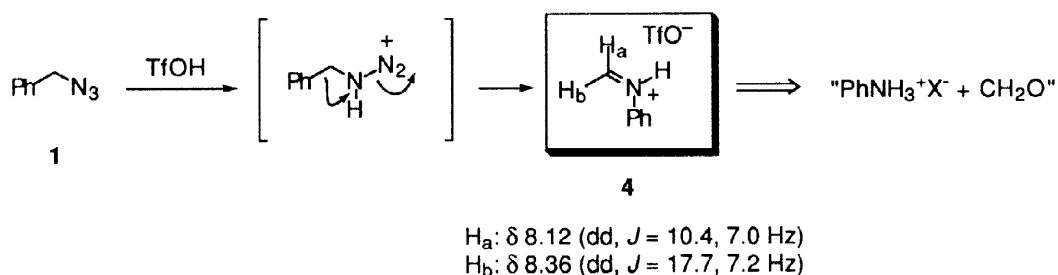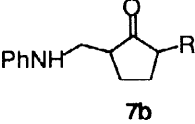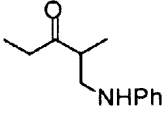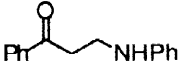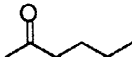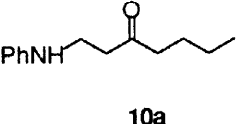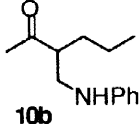
This *in situ*-formed Mannich reagent was then generated in the presence of other carbonyl substrates (most shown to be nonreactive toward azide addition) to demonstrate its versatility as a (phenylamino)methylating agent (Table).[6] The conversion of all examined carbonyl substrates to their corresponding Mannich bases matched or exceeded 50%. Unadorned cyclohexanone and cyclopentanone (entries 1 and 2, respectively) afforded their mono N-phenyl aminomethylated derivatives **2** and **5** without any detectable contamination by dialkylated material.

The nonsymmetric but doubly activated ß-keto ester in entry 3 provided the single Mannich base regioisomer **6** under standard reaction conditions. In general, doubly activated carb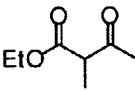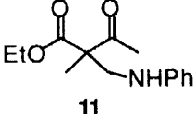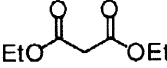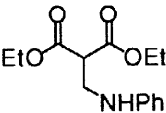onyl partners worked well in the reaction (entries 3, 8, and 9). However, 2-ethylcyclopentanone, not containing a directing group, afforded all possible regio- and diastereomeric amino ketone products **7a,b** in a ratio reflecting the thermodynamic populations of the enol isomer intermediates (entry 4).[7]

As mentioned at the outset, we also prepared a Mannich reagent related to iminium ion **4** by treating **1** with TiCl$_4$, but this method proved inferior to the triflic acid-mediated reaction as illustrated by the contrasting yields obtained for the conversions of 3-pentanone and acetophenone to their respective Mannich bases (entries 5 and 6). Additionally, it is noteworthy (at least in the case of entry 1) that triflic acid showed no signs of mediating a Schmidt reaction (cyclohexanone reacts smoothly with benzyl azide to afford N-benzylcaprolactam when treated with TiCl$_4$ (eq 2[2])). We suspect that the rearrangement of benzyl azide is simply more facile under protic conditions than in the Lewis acid medium. However, this simplistic explanation may be somewhat derailed by our observation of the formation of caprolactams, albeit in low yield, from triflic acid-mediated reactions of some other n-alkyl azides to cyclohexanone.[8]

In summary, the reaction of benzyl azide with triflic acid provides a convenient non-aldehyde-based access to N-phenyl iminium triflate **4**. This intermediate combines with a variety of carbonyl substrates to form Mannich bases. The salient features influencing the divergent reactivity between benzyl azide and ketones (Schmidt or Mannich reaction pathways) are currently under investigation and will be the subject of future reports.

Table. Acid-Mediated Reactions of Benzyl Azide with Carbonyl Substrates

entry	carbonyl substrate	product[a]	yield (%)[b]
1		**2**	63
2	R = H	**5**, R = H	50
3	R = CO$_2$Et	**6**, R = CO$_2$Et	77
4	R = Et	**7a**, R = Et + **7b**	82[c] (**7a** : **7b** = 4.6:1)
5		**8**	75 (46)[d]
6		**9**	71 (24)[d]
7		**10a** + **10b**	75[c] (**20a** : **20b** = 1:2.4)
8		**11**	77
9		**12**	59

Notes: (a) All new compounds exhibited satisfactory analytical data. (b) Yields refer to isolated, chromatographically pure compounds. (c) Combined yield of regioisomers/diastereomers. (d) Yield of reaction promoted by TiCl$_4$ is included in parentheses.

References and Notes

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(1) Recent reviews of the Mannich reaction: (a) Tramontoni, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791-1837. (b) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M. and Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 893-951. (c) Arend, M.; Westerman, B.; Risch, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1044-1070.

(2) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635-1637.

(3) Previous examples of Mannich reactions that involve the intermediacy of **4** include: (a) Grieco, P.; Bahsas, A. *Tetrahedron Lett.* **1988**, *29*, 5855-5858. (b) Katritzky, A. R.; Harris, P. A. *Tetrahedron* **1990**, *46*, 987-996. (c) Page, P. C. B.; Allin, S. M.; Collington, E. W.; Carr, R. A. E. *J. Org. Chem.* **1993**, *58*, 6902-6904.

(4) Tanino, K.; Takahashi, M.; Murayama, K.; Kuwajima, I. *J. Org. Chem.* **1992**, *57*, 7009-7010.

(5) Pearson, W. H.; Fang, W.-k. *Isr. J. Chem.* **1997**, *37*, 39-46.

(6) (a) Benzyl azide (Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* **1984**, *49*, 4237-4244) was prepared by the reaction of benzyl chloride with NaN_3 in DMF at room temperature. **CAUTION:** All organic azides should be treated as potential explosion hazards.
   (b) **General experimental procedure.** The reaction of benzyl azide with cyclohexanone is representative. Triflic acid (0.62 g, 4.2 mmol) was added dropwise to a 0 °C solution of benzyl azide (0.50 g, 3.8 mmol) and cyclohexanone (0.37 g, 3.8 mmol) in 8 mL of CH_2Cl_2. After gas evolution subsided, the solution was allowed to stir without external cooling for 20 h. The reaction was then poured over saturated $NaHCO_3$ (50 mL), extracted with CH_2Cl_2 (2×25 mL), and the combined organic layers dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography (1:4 Et_2O/hexanes) of the resulting crude product residue afforded 0.48 g (63%) of *N*-phenyl 2-methylaminocyclohexanone (**2**).[3b]

(7) House, H. O.; Trost, B. M. *J. Org. Chem.* **1964**, *29*, 1339-1341.

(8) Gracias, V.; Frank, K. E.; Milligan, G. L.; Aubé, J. *Tetrahedron* **1997**, *53*, 16241-16252.