ORGANIC LETTERS

2007
Vol. 9, No. 6
1165−1167

Anionic, in Situ Generation of Formaldehyde: A Very Useful and Versatile Tool in Synthesis

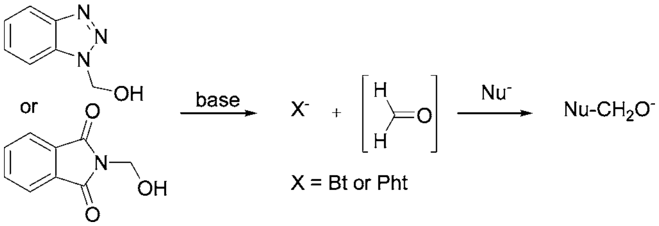
Geoffrey Deguest, Laurent Bischoff,* Corinne Fruit, and Francis Marsais

Laboratoire de Chimie Organique Fine et Hétérocyclique, CNRS UMR 6014,
IRCOF-INSA Rouen, B.P. 08, 76131 Mont-Saint-Aignan, France

laurent.bischoff@insa-rouen.fr

Received January 19, 2007

ABSTRACT



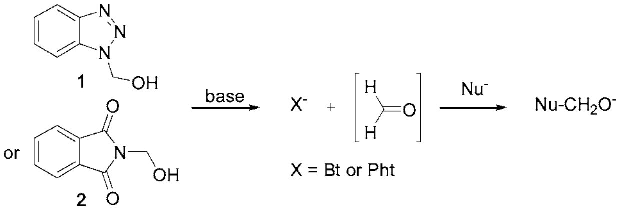
A very simple, safe and powerful method for the *in situ* generation of formaldehyde at low temperature in anhydrous conditions is described. This new tool avoids the use of gaseous formaldehyde and is suitable for basic carbon nucleophiles which cannot be generated in aqueous reaction media. Various substrates, including organolithium reagents and enolates, underwent smooth hydroxymethylation showing the versatility of this process. A Wittig reaction was also carried out in high yield.

Formaldehyde is a widespread reagent in chemistry, though its availability as a pure material is very limited. Except aqueous solutions (“formalin”), in which the aldehyde is predominantly under its hydrate structure, formaldehyde is generally generated from its poorly reactive polymeric precursors (i.e., trioxane or polyoxomethylene). Both oxidative synthesis from methanol[1] and depolymerisation[2] can be performed one pot or in a separate vessel. Thermal cracking however produces self-reactive and highly toxic gaseous formaldehyde.

We wish to report herein an extremely simple, safe and very versatile method for the in situ generation of anhydrous formaldehyde in organic solvents. This method proceeds under basic conditions, allowing subsequent hydroxymethylation of carbanionic structures such as organometallics or enolates.

Structures such as $X-CH_2OH$ are stable, provided that X has a restrained leaving group ability. Nitrogen moieties would afford a large choice of leaving groups with a possible modulation of their stabilities as anionic species. Mechanistic considerations led us to choose X among acids X−H exhibiting pKa values presumably lower than their alcohol $X-CH_2OH$ precursors. Favoring cleavage of $X-CH_2O^-$ with concomitant release of formaldehyde would be effective only if the leaving group X^- is more stable than the alcoolate (Scheme 1). For this purpose, we focused our attention toward benzotriazolylmethanol $Bt-CH_2-OH$ **1**, a commercially available reagent developed by Katritzky’s group,[3]

Scheme 1. Alkaline Generation of Formaldehyde



---

(1) For an *in situ* formaldehyde production process from methanol, see: Shreiber, E.H.; Roberts, G.W. *Chem. Ind.* **2001**, *82*, 391.

(2) Numerous examples account for the use of gaseous formaldehyde. For a recent device for continuous production by trioxane cracking, see: Kachi, H.; He, F.; Sakamoto, K. *Chem. Express* **1990**, *5*, 701.

10.1021/ol070145b CCC: $37.00

and *N*-hydroxymethyl phtalimide **2**.[4] Both have comparable pKa values around 8.3[5] and were expected to exhibit similar reactivities. We propose this mechanism rather than a nucleophilic attack at the deprotonated reagent on the basis of the electrophilic trapping of phtalimide generated in this way[4] and on the observation that only benzotriazole or phtalimide could be recovered from the crude materials. Both reagents are generally involved in reactions providing the C−O bond cleavage, (e.g., amino or amidomethylation reactions).[3] The straight cleavage of the N−C bond remains, in our knowledge, unexplored for synthetic uses of formaldehyde itself.

Initial experiments were aimed at screening the reactivity of $BtCH_2OH$ toward alkyllithium models. Starting with a 2-fold excess of n-hexyllithium or 2-pyridyllithium, treatment of $BtCH_2OH$ led to hydroxymethylation products with respectively 32% and 40% yields. Those yields were calculated from the amount of organometallic reagent, which is half-consumed during the deprotonation step. A similar yield was obtained with phenethylmagnesium chloride at room temperature, leading to phenylpropanol with a 33% yield.

In order to avoid unnecessary consumption of the nucleophilic organolithium reagent during the deprotonation step, lithium tetramethylpiperidide **3** (LiTMP) was added (Figure 1). We found that a combination of LiTMP and $BtCH_2OH$ (2 molar equiv of each) gave a better yield for this reaction.

$$\text{n-Hex-Li} \xrightarrow[\text{LiTMP } \mathbf{3}]{\text{Bt-CH}_2\text{OH } \mathbf{1}} \text{n-heptanol}$$

molar amount **1** : **3**	yield %
0.5 : 0	32
1 : 1	53
2 : 2	90

Figure 1. Optimizing molar ratio of reagent.

These encouraging results led us to explore the possibility to use a single base to generate both the nucleophilic species and formaldehyde. This method should be particularly adapted for compounds that cannot undergo deprotonation in aqueous conditions, such as precursors of unstabilised enolates or heteroaromatic anions.

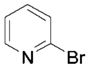
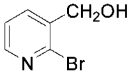
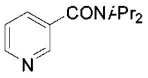
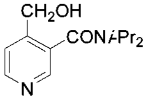
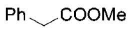
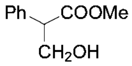
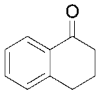
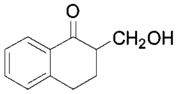
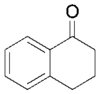
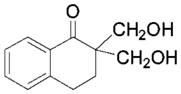
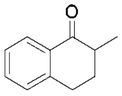
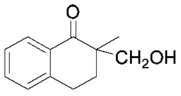
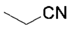
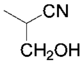
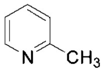
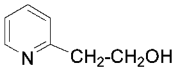
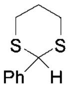
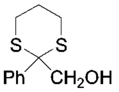
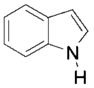
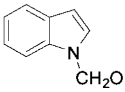
$$\text{Nu-H} \xrightarrow[\substack{\text{2) 2 BtCH}_2\text{OH} \\ \text{- 78 °C}}]{\text{1) 3 LiTMP}} \text{Nu-CH}_2\text{OH}$$

Figure 2. Simultaneous generation of nucleophile and formaldehyde.

As depicted in Figure 2, the simultaneous formation of the anionic nucleophile and $X{-}CH_2O^-$ was carried out. Two molar equivalents of $BtCH_2OH$ or *N*-hydroxymethylphtalimide and a 3-fold excess of an amide base, either LiTMP or lithium diisopropylamide (LDA), afforded very clean hydroxymethylation reactions within 1 h at −78 °C in anhydrous THF. Decreasing the amount of $BtCH_2OH$ and base resulted in lower yields. From an experimental point of view, the use of LDA allowed easy diisopropylamine removal by evaporation from the crude material. Furthermore, simple workup with water avoided the reprotonation of benzotriazole or phtalimide lithium salt, the latter being discarded in aqueous extracts.

This procedure was first successfully applied to pyridines substituted with an ortho-directing group, such as 2-bromopyridine[6] or tertiary nicotinamides[7] (Table 1, entries 1 and 2), providing a straightforward access to hydroxymethylated pyridines, which are more classically synthesized by a two step formylation-reduction sequence.[8]

Table 1. Examining the Scope of Hydroxymethylation Reactions under Conditions of Figure 2, i.e., 3 LiTMP/2 $BtCH_2OH$

entry	starting material	product	cmpd nr	isolated yield %
1			**4**	78
2			**5**	67
3			**6**	96 (81)[a]
4			**7**	63 (61)[a]
5			**8**	92[c]
6			**9**	97
7			**10**	67[b]
8	$Ph\text{-}SO_2\text{-}CH_3$	$Ph\text{-}SO_2\text{-}CH_2\text{-}CH_2OH$	**11**	53 (53)[a]
9			**12**	65[b]
10	$Ph{-}\!\!\equiv\!\!{-}H$	$Ph{-}\!\!\equiv\!\!{-}CH_2OH$	**13**	51
11			**14**	93[b]
12			**15**	50

[a] *N*-hydroxymethylphtalimide was used instead of $BtCH_2OH$; [b] deprotonation with LDA instead of LiTMP; [c] deprotonation with *t*-BuOK.

---

(3) For an exhaustive review on this reagent, see Katritzky, A. R.; Manju, K.; Singh, S. K.; Meher, N. K. *Tetrahedron* **2005**, *61*, 2555 and references cited therein.

(4) Cul, A.; Chihab-Eddine, A.; Pesquet, A.; Marchalin, S.; Daich, A. *J. Heterocycl. Chem.* **2003**, *40*, 499.

(5) Reboud-Ravaux, M. *J. Am. Chem. Soc.* **1980**, *102*, 1039.

Application of this optimized procedure to a selection of widely used enolates gave promising results (entries 3−7). Interestingly, the trapping of formaldehyde by the enolate afforded the corresponding alcoolate without any possibility of subsequent reprotonation.

Indeed, no side-reaction, such as dehydration or double hydroxymethylation was observed, except for entry 4. In this case, α-tetralone is highly enolizable and we suspected the formation of a dianionic species after the first hydroxymethylation. Interestingly, for this example the use of potassium *t*-butoxide instead of a hindered amide base afforded clean double hydroxymethylation (entry 5). Substrates yielding strongly basic anions, generated from phenylmethyl sulfone, picoline, or phenylacetylene (entries 8−10) were also studied to enhance the scope of the hydroxymethylation reaction. These conditions led to the same smooth and clean reaction, though with lower yields, presumably due to equilibrated deprotonations. It is worth noting, that the hydroxymethylation of a dithiane (entry 11), affords a simple access to a α-hydroxyketone synthon. Similarly, indole lithium salt could be used as a nitrogen nucleophile, thus allowing its *N*-hydroxymethylation.

As far as the choice of the X group was concerned, similar yields were obtained when $BtCH_2OH$ was replaced with *N*-hydroxymethylphtalimide, as illustrated by representative examples (Table 1, entries 3, 4 and 8). Both reagents exhibit comparable behavior in this reaction.

Further extension of this methodology was applied to a Wittig olefination. Under our conditions, both formaldehyde and the phosphorus ylide were generated *in situ* and the desired alkene was isolated with a good yield (Figure 3).

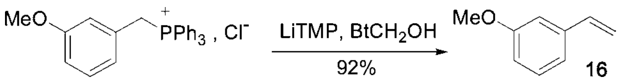


Figure 3. Wittig olefination with in situ-generated formaldehyde.

This makes our method a convenient tool for a reversed synthesis of those alkenes, since the latter are generally prepared from the aromatic aldehyde and methylene ylide.

As a conclusion, we have developed a highly efficient and extremely simple, safe, and cheap method for the straightforward introduction of an unprotected hydroxymethyl group onto carbon nucleophiles, and further uses of formaldehyde such as *N*-hydroxymethylation or Wittig olefination. This method advantageously avoids not only the use of poorly reactive formaldehyde polymers, but also the risks inherent to thermal generation of hazardous gaseous formaldehyde, or the use of toxic chloromethyl ethers which would require a subsequent deprotection step. Such procedure is of high interest for the introduction of hydroxymethyl group onto strongly basic anionic species and it is therefore a very convenient tool in synthesis.

Acknowledgment. G.D. is grateful to the MENESR for a grant. Dr. Christian Montalbetti (Evotec, U.K.) is gratefully acknowledged for fruitful discussions.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070145B

---

(6) (a) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. (b) Mongin, F.; Queguiner, G. *Tetrahedron* **2001**, *57*, 4059.

(7) (a) Epsztajn, J.; Brzezinski, J. Z.; Józwiak, A. *J. Chem. Res., Synop.* **1986**, *18*, 18. (b) Deguest, G.; Devineau, A.; Bischoff, L.; Fruit, C.; Marsais, F. *Org. Lett.* **2006**, *8*, 5889.

(8) Srinivasan, J. M.; Burks, H. E.; Smith, C. R.; Viswanathan, R.; Johnston, J. N. *Synthesis* **2005**, *2*, 330.