Convenient Procedure for the Indium-Mediated Hydroxymethylation of Active Bromo Compounds: Transformation of Ketones into α-Hydroxymethyl Nitroalkanes

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In memory of Professor Jose M. Concellón

Abstract: A very simple, safe and powerful method for the hydroxymethylation of 2-bromoesters and lactones under anhydrous conditions that avoids the use of gaseous formaldehyde is described. Moreover, under these conditions, bromonitroalkanes were converted into the corresponding α-monohydroxymethylated nitroalkanes, which are precursors of the corresponding α-amino acids. Considering the easy transformation of ketones into bromonitroalkanes, this represents a method for the formal synthesis of α-amino acids from ketones.

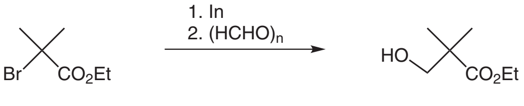
Key words: hydroxymethylation, indium, esters, nitroalkanes, amino acids

Formaldehyde is one of the most important C1 electrophiles in organic synthesis and is widely used in chemistry despite its limited availability as a pure material. Formaldehyde is available in aqueous solutions (‘formalin’), in which the aldehyde is predominantly in its hydrate structure. Evidently, this solution cannot be used for substrates and reactions that are moisture sensitive. In these cases formaldehyde is usually generated from its polymeric precursors (i.e., trioxane or polyoxomethylene). Thermal cracking, however, produces self-reactive and highly toxic gaseous formaldehyde.[1] Consequently, even though hydroxymethylation of enolates with formaldehyde provides an efficient method to introduce a C1 functional group at the α-position of carbonyl groups, the hydroxymethylation of enolates under Reformatsky conditions is not common in the literature.[2] In general, polymeric precursors of formaldehyde, such as paraformaldehyde, are poorly reactive but there are a few examples in the literature in which paraformaldehyde is reactive enough to be used directly in the reaction,[3] including a couple of metal-mediated procedures.[4]

We wish to report here an extremely simple, safe and versatile method for the hydroxymethylation of enolates and nitronates based on an indium-mediated reaction with solid paraformaldehyde. This reaction proceeds under very mild and nonbasic conditions.

The initial studies were performed with commercially available ethyl bromoisobutyrate (**1**: Scheme 1).

The reaction was tested under different conditions in terms of temperature, solvents and concentration and the results are summarized in Table 1.



1 **2**

Scheme 1 Indium-mediated reaction of ethyl bromoisobutyrate and paraformaldehyde

Table 1 Hydroxymethylation of Ethyl Bromoisobutyrate

Entry	Conditions	Solvent	In (equiv)	**1** (equiv)	Yield
1	r.t.	toluene	1.5	1.2	–
2	r.t.	DMF	1.5	1.2	–
3	r.t.	THF	1.5	1.2	–
4	reflux	toluene	1.5	1.2	42%
5	80 °C	DMF	1.5	1.2	58%
6	reflux	THF	1.5	1.2	55%
7	sonication	toluene	1.5	1.2	62%
8	sonication	DMF	1.5	1.2	75%
9	sonication	THF	1.5	1.2	80%
10	sonication	THF	2.5	2.4	78%
11	sonication	THF	1.5	1.2	80%

The reaction failed to give the desired hydroxymethylated esters at room temperature under any of the conditions tested. On heating the reaction mixture, however, the hydroxymethylated esters were successfully obtained using DMF, THF or toluene as solvents. Ultrasonic irradiation has previously proven useful in indium-mediated protocols.[5] As a result, the reaction was also carried out with the vessel immersed in an ultrasonic cleaning bath, a process that gave the hydroxymethylated esters in better yields.

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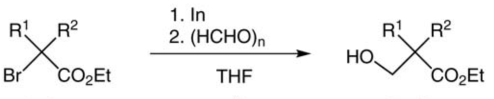
Increases in the concentration of bromoester or indium did not alter the yields.

In summary, the best conditions to carry out the reaction described here, both in terms of yield and simplicity of the procedure, are given in entry 9 (Table 1). Once the reaction conditions had been optimized, the method was applied to a series of commercial bromoesters. Thus, 1.5 equivalents of **3–6**, one equivalent of indium powder and one equivalent of solid paraformaldehyde were reacted in THF under sonication (Scheme 2).[6]



Scheme 2 Indium-mediated reaction of bromoesters and paraformaldehyde

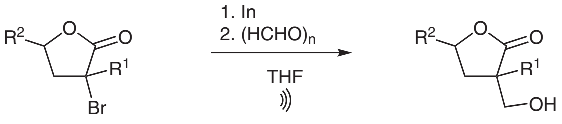
Under these conditions the corresponding hydroxymethylated esters **7–10**[7] were obtained after aqueous workup in excellent yields and without further purification (Table 2).

Table 2 Hydroxymethylation of α-Bromoesters under the Optimized Conditions

Ester	R^1	R^2	Product	Yield
3	Me	H	**7**	69%
4	Et	H	**8**	61%
5	*n*-Pr	H	**9**	75%
6	Ph	H	**10**	72%

The scope of this new methodology was further investigated by using cyclic enolates as starting materials.

2-Bromolactones **11–13** were submitted to the same reaction conditions as above (Scheme 3) and this gave the corresponding 2-hydroxymethyllactones **14–16** in good yields (Table 3).

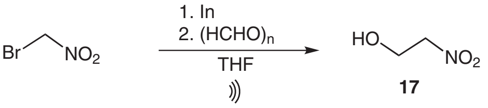


Scheme 3 Indium-mediated reaction of bromolactones and paraformaldehyde

Table 3 Hydroxymethylation of α-Bromolactones

Lactone	R^1	R^2	Product	Yield
11	Me	Me	**14**	78%
12	Me	H	**15**	69%
13	H	Me	**16**	70%

Taking into account these satisfactory results, we decided to investigate the application of this procedure to the hydroxymethylation of bromonitroalkanes. We recently reported a novel indium-mediated reaction of bromonitroalkanes and aldehydes, a process that constitutes an interesting alternative to the Henry reaction and allows the corresponding 2-nitroalkanols to be obtained in high yields and under mild conditions.[8] In order to investigate the indium-mediated hydroxymethylation of bromonitro compounds, bromonitromethane (1.5 equiv) was reacted with indium powder (1 equiv) and paraformaldehyde (1 equiv) in THF under sonication. This reaction gave 2-nitroethanol (**17**) in good yield after aqueous workup (Scheme 4).

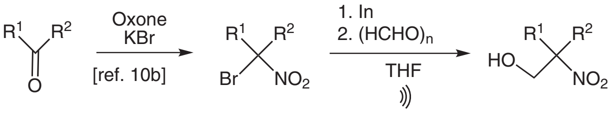


Scheme 4 Indium-mediated reaction of bromonitromethane and paraformaldehyde

This indium-mediated hydroxymethylation of bromonitroalkanes has many advantages in comparison to the hydroxymethylation of nitronates based on the Henry reaction with formaldehyde, including the possibility of avoiding basic conditions and the higher yields obtained. However, the most important drawback of the classical Henry reaction of nitronates and formaldehyde, which is overcome in the new procedure reported here, is the lack of regioselectivity. Thus, when primary nitronates are treated with formaldehyde under classical Henry conditions, the α,α-dihydroxymethylated derivative is always the major product isolated from the reaction mixture.[9] However, the indium-mediated reaction of bromonitroalkanes with α-hydrogens, in this case bromonitromethane with paraformaldehyde, afforded the monohydroxymethylated derivative **17** as the only product.

Considering the satisfactory results obtained in the indium-mediated hydroxymethylation of bromonitromethane using solid paraformaldehyde as a source of formaldehyde electrophile, as well as the previously described procedure to obtain bromonitroalkanes from ketones via the corresponding oximes,[10] we decided to investigate the conversion of several ketones **18–22** into bromonitroalkanes **23–27** and the hydroxymethylation of the latter compounds under the same conditions used for bromonitromethane (Scheme 5).

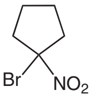
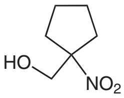
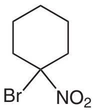
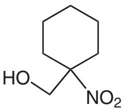
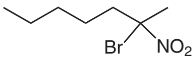
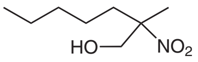
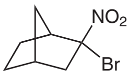
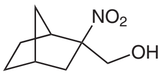
Under these conditions, α-hydroxymethyl nitro compounds **28–32**[11] were obtained in good yields after aque-



Scheme 5 Conversion of ketones into α-hydroxymethyl nitroalkanes

ous workup (Table 4). This procedure constitutes an interesting new route for the transformation of ketones into α-hydroxymethyl nitro compounds, which in turn are precursors of the corresponding α-amino acids.

Table 4 Hydroxymethylation of Bromonitroalkanes Derived form Ketones

Bromonitroalkane	Product	Yield
 **23**	 **28**	71%
 **24**	 **29**	75%
 **25**	 **30**	75%
 **26**	 **31**	73%
 **27**	 **32**	76%

In summary, a simple, safe and efficient procedure for the hydroxymethylation of 2-bromoesters and lactones has been developed. The process occurs under anhydrous conditions and is based on an indium-mediated Reformatsky reaction with solid paraformaldehyde. The application of the procedure to bromonitroalkanes was also successful, and this constitutes a new access to α-hydroxymethyl nitro compounds, which are precursors of the corresponding α-amino acids. Together with the previously reported procedure for the transformation of ketones into bromonitroalkanes, we now have a method for the formal synthesis of α-amino acids from ketones.

Work is currently under way in our laboratory aimed at developing an enantiospecific version of this reaction.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(6) **General Procedure**: To a suspension of indium powder (0.5 mmol) in THF (1 mL), the 2-bromocompound (0.75 equiv) was added and the mixture was sonicated for 20 min. Paraformaldehyde (0.5 mmol) was then added and sonication was continued for a further 4 h. The reaction mixture was quenched with sat. aq $NaHCO_3$ (10 mL) and extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo to obtain pure hydroxymethylated compounds.

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