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Indium-mediated propargylation of imines and imine oxides in aqueous media: propargylation of >C=N- centres

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Abstract—The indium-catalysed coupling of propargyl bromide with a variety of imines and imine oxides afforded the corresponding propargylated products in high yields under mild conditions.

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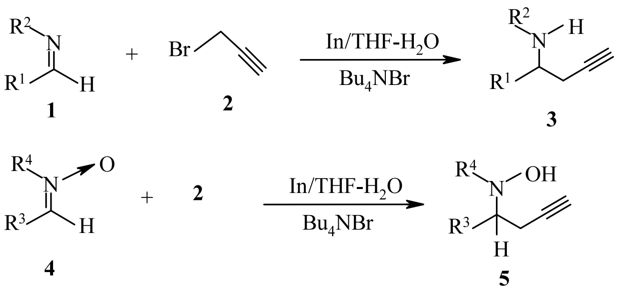
There has been growing interest in the use of reactions of metallic elements[1] in aqueous media, as they offer significant advantages over conventional reactions in dry organic solvents. The development of such reactions also offers the possibility of obtaining environmentally benign reaction conditions.[2] The study and application of Barbier–Grignard type reactions[3] in water is still in its infancy. Since their history is only a decade old, the full synthetic potential of such reactions is still waiting to be explored.[4] The application of the Grignard reaction in carbon–carbon bond-forming reactions for large-scale industrial application is limited[5] by the expense of the metal, the anhydrous ether solvents required and complications of waste solvent disposal. The use of water as solvent could reduce or eliminate environmental damage by organic wastes.[6] Barbier-type reactions have been used to allylate carbonyl compounds promoted by various metals.[3] Also, propargyl halides add to aldehydes in the presence of tin,[7] indium,[8] zinc,[9] and lead.[10] Even unconventional substrates such as nitrobenzene[11] and diphenyldiselenide[12] undergo Barbier-type alkylations in aqueous media. However, the addition of organometallic reagents to the C=N double bonds of imines or imine oxides has been severely restricted both by the poor electrophilicity of the azomethine carbon and by the tendency of enolisable imines and imine derivatives to undergo deprotonation rather than addition.[13] Nitrones possess both a highly polarised C=N double bond, which is responsible for their good electrophilic reactivity, and a reactive oxygen atom, making them capable of reacting with organometallic compounds to generate a host of products. In continuation of our studies on metal mediated Barbier-type allylations,[14] we report herein an efficient indium mediated propargylation of various imines **1** and imine oxides **4** derived from aromatic aldehydes in aqueous media. The reactions proceed in high yields at room temperature without the formation of any side products. In contrast to a very recent report,[15] the indium mediated alkynylation of aldehydes under thermal conditions gave a benzylic alcohol as a by-product along with the homoalkynyl alcohols (Scheme 1).



Scheme 1.

In a typical procedure, indium metal powder (1.14 g, 10 mmol) was added at 0°C to a solution of propargyl bromide (1.18 g, 10 mmol) in 10 ml of THF–H_2O (2:1) in a 100 ml flask and the mixture stirred. To this mixture was added Bu_4NBr (0.33 g, 1 mmol) and then the mixture was stirred for 20 min to give a clear solution. Imine **1a** (2.25 g, 10 mmol) was added in portions and the resulting mixture was stirred at room temperature for 7 h. After completion (as monitored by

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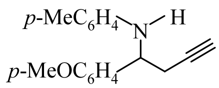
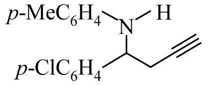
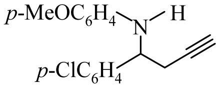
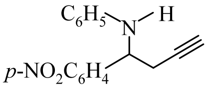
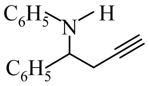
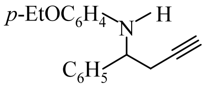
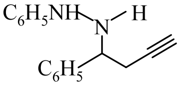
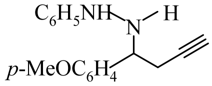
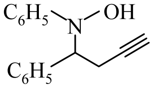
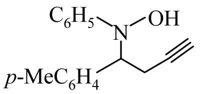
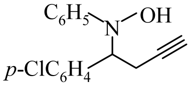
TLC), the reaction mixture was quenched by the addition of dilute HCl (2 ml) and the resulting mixture was poured into ice water, extracted with CH_2Cl_2 (3×20 ml), the extract washed with bicarbonate solution, brine and the combined organic layers dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude product which was subjected to column chromatography using petroleum ether/$CHCl_3$ (2:3) as eluent to afford **3a** (80%). When propargyl bromide was replaced by propargyl chloride in the above reaction, the coupling proceeded efficiently and the corresponding alkynylated product **3a** was obtained in 75% yield after 9 h. Similarly, the alkynylindium reagent added to the carbon–nitrogen double bond of aldonitrone **4a** and hydrazone **1g** in a Bu_4NBr–THF–H_2O system. The reaction proceeded conveniently and no trace of *N*-alkynylated product could be detected. However, a ketimine (derived from acetophenone and aniline) did not undergo alkynylation with propargyl bromide even after 16 h of stirring at room temperature. Increasing the reaction time further gave no significant improvement and resulted in decomposition of the starting

Table 1. Indium-mediated alkynlation of imines **1** and imine oxides **4**

Entry	Imines **1**/ Nitrones **4**		Products 3,5	Reaction time, h	Yield[a] %
1	**1a**	$R^1 = p\text{-MeOC}_6H_4$ $R^2 = p\text{-MeC}_6H_4$	 **3a**	7	80
2	**1b**	$R^1 = p\text{-ClC}_6H_4$ $R^2 = p\text{-MeC}_6H_4$	 **3b**	8	75
3	**1c**	$R^1 = p\text{-ClC}_6H_4$ $R^2 = p\text{-MeOC}_6H_4$	 **3c**	7	75
4	**1d**	$R^1 = p\text{-NO}_2\text{-C}_6H_4$ $R^2 = C_6H_5$	 **3d**	8	70
5	**1e**	$R^1 = C_6H_5$ $R^2 = C_6H_5$	 **3e**	8	80
6	**1f**	$R^1 = C_6H_5$ $R^2 = p\text{-EtOC}_6H_4$	 **3f**	9	70
7	**1g**	$R^1 = C_6H_5$ $R^2 = NHC_6H_5$	 **3g**	10	50
8	**1h**	$R^1 = p\text{-MeOC}_6H_4$ $R^2 = NHC_6H_5$	 **3h**	11	43
9	**4a**	$R^3 = C_6H_5$ $R^4 = C_6H_5$	 **5a**	9	55
10	**4b**	$R^3 = p\text{-MeC}_6H_4$ $R^4 = C_6H_5$	 **5b**	9	60
11	**4c**	$R^3 = p\text{-ClC}_6H_4$ $R^4 = C_6H_5$	 **5c**	10	62

[a] Yield refers to pure isolated products, fully characterised by ^1H NMR and IR spectroscopy and by comparison with authentic samples.

materials. It is relevant to note that during allylations in aqueous media many imines are hydrolysed to the corresponding carbonyl compounds before allylation occurs, thus giving the homoallylic alcohols.[2] Also, it is notable that indium promotes[15] the homocoupling of imines in aqueous media to give the corresponding 1,2-diamines. However, with indium activated by Bu_4NBr[10] under our reaction conditions, we observed neither the formation of hydrolysed products nor 1,2-diamines.

The use of Bu_4NBr was found to be important, as the alkynylation did not proceed at all with indium alone. It is obvious that activation of the metal is needed for this reaction to proceed. Approximately 0.1 equiv. of Bu_4NBr was found to be sufficient for these reactions and the use of a large excess did not lead either to higher yields or faster reaction rates. It is also interesting to note that the nature of the solvent controlled the formation of homoalkynylated products. The reaction failed to produce any desired compound when THF alone was used as the solvent. Also, no isolable product was formed when the reaction was run in water or DMF alone. After screening the reaction conditions, the optimum solvent for this propargylation reaction was seen to be a 2:1 mixture of THF–H_2O.

The results in Table 1 reveal the generality of this methodology in terms of structural variations of the imine, nitrone or hydrazone moiety; in each case homoalkynylic products were isolated in good yields. Furthermore, electron-donating or withdrawing groups on the aromatic ring did not seem to affect the reaction significantly, either in the yield of the product or the rate of the reaction. Moreover, a nitro function was not reduced under the reaction conditions. Thus, 4-nitrobenzaldehyde imine **1d** was successfully propargylated. Usually, a nitro group is sensitive to reduction by metals and is not tolerated under Barbier conditions.[16] In this context, the use of an additive as an activating agent is superior to the use of Al, Fe or $NaBH_4$ reported previously.[17] Although the detailed mechanism of the reaction is not clear, it is likely that Bu_4NBr effects the generation of an active organoindium reagent.[10] All the compounds obtained were characterised by IR and ^1H NMR spectroscopy, and finally, by comparison with authentic samples.

In conclusion, this simple and easily reproducible technique using indium under aqueous conditions affords various homoalkynyl amines and homoalkynyl hydroxylamines of potentially high synthetic utility in high yields and without the formation of any undesirable side products.

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