Pergamon

Tetrahedron Letters 40 (1999) 3937–3938

TETRAHEDRON
LETTERS

A Novel, Simple, Chemoselective and Practical Protocol for the Reduction of Azides Using In / NH_4Cl

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Received 11 January 1999; revised 18 March 1999; accepted 22 March 1999

Abstract : A simple, mild and efficient method for the reduction of azides to amines using In / NH_4Cl is described.

Keywords : Azides, amines, indium, palladium

The reduction of azides to amines is an important transformation in synthetic organic chemistry, used to construct a variety of biologically active molecules, especially in heterocyclic and medicinal chemistry [1]. Although quite a number of methods have been reported [2-9] for this reductive process, $LiAlH_4$ and Pd/C-H_2 are the most commonly used reagent systems. However, in spite of their potential utility most of the reported methods suffer from significant drawbacks which include incompatibility with other functionalities and protecting groups, use of expensive and hazardous reagents, drastic reaction conditions, long reaction times and cumbersome product isolation procedures. In view of this, there is a need to develop milder and chemoselective methodology for the multistep synthesis of complex molecules. In connection with our ongoing programme for the synthesis of natural product analogues of biological interest, we required this conversion, under mild reaction conditions, since the use of excess $LiAlH_4$ in the reduction of azide (entry-1) caused extensive decomposition. In this (*letter*), we report a novel, efficient, simple and practical method for the conversion of azides to amines using indium metal under mild reaction conditions.

$$R{-}N_3 \xrightarrow[\text{EtOH, reflux}]{\text{In, }NH_4Cl} R{-}NH_2$$

Scheme-1

Azides were treated with indium metal and ammonium chloride in ethanol under reflux to give the corresponding amines in quantitative yields (Scheme-1). The results obtained with a variety of azides demonstrate the generality of the reaction and are summarized in Table-1. Under the present reaction conditions a variety of functionalities and protecting groups are uneffected eg., olefins (entry-13,14), carboxylic acids (entry-7), esters (entry-8), acetonide

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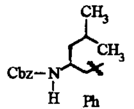
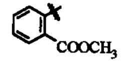
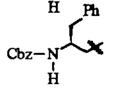
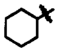
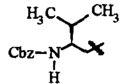
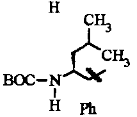
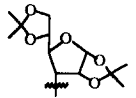
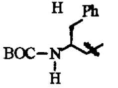
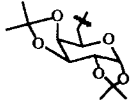
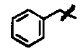
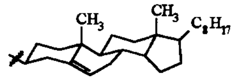
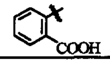
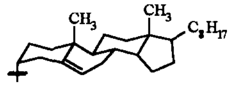
IICT Communication No. 4218

PII: S0040-4039(99)00614-0

Table : Reduction of azides to amines using In / NH_4Cl

Entry	R	Reaction Time (h)	Yield^a (%)	Entry	R	Reaction Time (h)	Yield^a (%)
1		2	96	8		1	92
2		2	91	9		3	86
3		2	94	10		3	89
4		2	97	11		2	91
5		2	92	12		2	89
6		1	98	13		2	94
7		1	96	14		2	88

a Isolated yield

(entry-11,12), *tert*-butoxycarbonyl (entry-4,5) and benzyloxycarbonyl (entry1-3), and the methodology is applicable to aliphatic and aromatic azides. All the amines obtained were fully characterized by ^1H NMR, IR, Mass spectral data and were found to be in good agreement with authentic samples.

In summary, we have demonstrated a novel, mild, general and efficient methodology for the reduction of azides to amines using In / NH_4Cl with practical applicability for the first time. This novel methodology is applicable to a wide range of substrates.

Acknowledgement : Authors G.V.S.R. and G.V.R. thanks CSIR (India) for fellowship.

Typical procedure : To a solution of the azide (2 mmol) in ethanol (6 ml) was added indium powder (2 mmol) and NH_4Cl (2 mmol). The resulting reaction mixture was heated at reflux with constant stirring (1-3 h). After completion of the reaction (monitored by TLC), the reaction mixture was brought to room temperature, diluted with ethylacetate (10 ml), stirred for 10 min and passed through a short pad of celite to give a clear solution. Removal of solvent under reduced pressure gave the amines in pure form.

Representative data for compound 11 : Pale yellow syrup, ^1H NMR (200 MHz, $CDCl_3$) : δ 1.30 (s, 3H), 1.38 (s, 3H), 1.40 (s, 3H), 1.50 (s, 3H), 2.50-3.78 (m, 3H), 4.20 (d, 1H, J = 4.2 Hz), 4.30 (m, 1H), 4.55 (d, 1H, J = 4.6 Hz), 6.0 (d, 1H, J = 4.6 Hz).

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