Pergamon

Tetrahedron Letters, Vol. 36, No. 2, pp. 281-282, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02219-4

One-Pot Synthesis of Primary E-Allylic Amines

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Abstract: *The Preparation of Primary E-Allylic Amines is performed in a one-pot procedure by subsequent treatment of lithiomethylphosphonate with nitriles, followed by addition of aldehydes and sodium borohydride.*

Primary allylic amines are an important class of compounds not only for their utility as intermediates in organic synthesis but also because of their physiological properties[1] and their presence in several natural products.[2] Despite the growing interest in these types of compounds, only a relatively small number of procedures are available for their synthesis.[2,3] However, in many cases, relatively low chemical yields and the necessity for previous protection of the amine function are some of the apparent limitations on these procedures.[2,3]

Previously, we had reported a facile method for the α,β-unsaturated ketone in which α,β-unsaturated imine **3** had been a key intermediate.[4] In connection with this result, we studied a direct and convenient method for the conversion of α,β-unsaturated imine **3** into the corresponding allylic amine **4**. The process is highly stereoselective, affording exclusively the stereoisomer E. In the case of α,β-unsaturated imine which come from aliphatic aldehyde, saturated amine product was obtained as a side product (Entry **f**,**g**). Here, as the reaction temperature increase, saturated amine formed in higher ratio (Entry **g**). In the treatment of $LiAlH_4$ in THF, no allylic amines were obtained. It seems that deprotonation of imine by $LiAlH_4$ prevented the reduction of **3**.

General experimental procedure: To a stirred solution of diethyl methylphosphonate(1 mmol) in dry THF(3 ml), is added BuLi(1 mmol, 1.6 M in hexane) at -78°C under N_2 atmosphere. Nitrile(1 mmol) is added and the mixture is warmed to -5°C for 1h. Aldehyde is added and the mixture is warmed to r.t for 30 min.

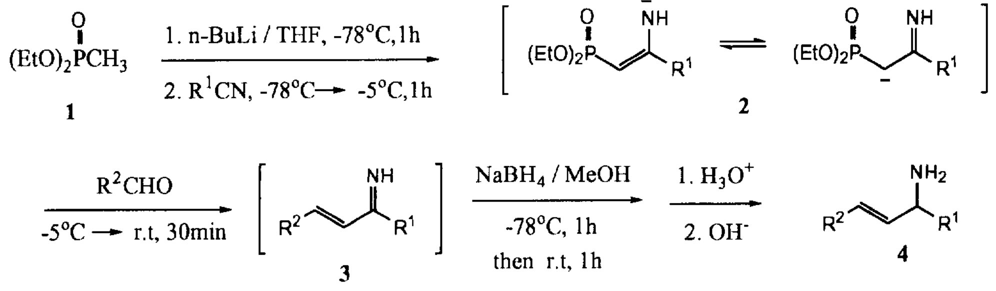
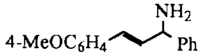
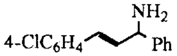
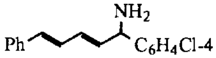
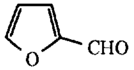
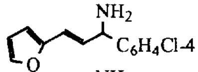
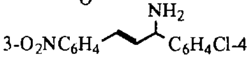
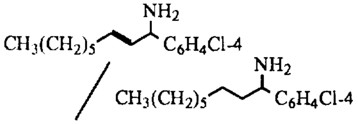
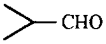
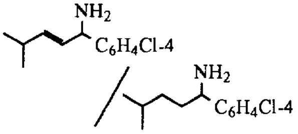
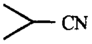
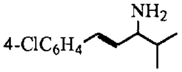


Table. Obtained Primary E-Allylic Amines

Entry	Nitrile	Aldehyde	Product[a]	Yield(%)[b]
a	PhCN	4-$MeOC_6H_4CHO$		85
b	PhCN	4-ClC_6H_4CHO		83
c	4-ClC_6H_4CN	t-PhCH=CHCHO		85
d	4-ClC_6H_4CN			83
e	4-ClC_6H_4CN	3-$O_2NC_6H_4CHO$		80
f	4-ClC_6H_4CN	$CH_3(CH_2)_5CHO$		70 (6 / 4)
g	4-ClC_6H_4CN			69 (8 / 2) (5 / 5)[c]
h		4-ClC_6H_4CHO		58

[a] All the compounds were fully characterized. Allylic amine has the E configuration as J_{HH} across the double bond is 15.2 - 16.2 Hz. [b] Isolated yield. [c] Reduction to the allylic amine was carried out at 10 °C.

To the resulting solution, which is cooled to -78°C, $NaBH_4$(2 mmol) and MeOH(5 ml) is added. After maintain at -78°C for 1h, the mixture is warmed to r.t and 3% HCl (3 ml) is added and stirring continued for 1h. The mixture is made alkaline(ph 12) with NaOH pellets and extracted with EtOAc(3 x 20 ml). The combined organic extracts are dried($MgSO_4$) and evaporated to give primary allylic amine, which is purified by short-path column chromatograpy on silica gel(EtOAc).

ACKNOWLEDGEMENT: We thank the Korea Research Foundation for financial support.

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(*Received in Japan* 29 *July* 1994; *revised* 24 *October* 1994; *accepted* 4 *November* 1994)