Tetrahedron Letters 49 (2008) 7209–7212

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A distinct approach for the rapid synthesis of homoallylic amines starting directly from nitro compounds in water ☆

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ARTICLE INFO

Article history:
Received 29 August 2008
Revised 27 September 2008
Accepted 3 October 2008
Available online 7 October 2008

Keywords:
Homoallylic amine
Nitroarene
In/HCl
Three-component reaction
Allylation

ABSTRACT

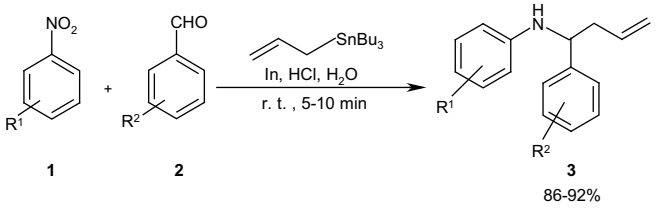
Three-component reactions of nitroarenes, benzaldehydes, and allyltributylstannane using indium in dilute aqueous HCl at room temperature afford the corresponding homoallylic amines in high yields within 5–10 min. The conversion in one-pot synthesis involves the following steps: (i) reduction of nitro compounds to amines, (ii) formation of imines from amines and aldehydes, and (iii) allylation of imines.

Homoallylic amines are important building blocks for the preparation of various biologically active molecules.[1] A straightforward synthesis of homoallylic amines involves the nucleophilic addition of allyltin reagents to imines, which are generated in situ from aldehydes and amines in the presence of a catalyst.[2] However, the long reaction times, unsatisfactory yields, and tedious workups are drawbacks in several of the methods employed earlier using various catalysts. To find a suitable catalyst which is active in the presence of amines and water (produced during the formation of imines) is problematical.

In connection with our work[3] on the development of useful synthetic methodologies, we have discovered that homoallylic amines can be synthesized efficiently via the three-component reaction of nitroarenes, benzaldehydes, and allyltributylstannane using indium in dilute aqueous HCl at room temperature (Scheme 1).

Initially, the reaction of nitrobenzene, benzaldehyde, and allyltributylstannane was carried out using different metals such as Zn, Sn, In, and Fe in aqueous HCl. Considering the reaction times and yields at room temperature, In was found to be most effective (Table 1, entry c).

Subsequently, a series of homoallylic amines were conveniently prepared[4] using this metal (Table 2). The products were formed in high yields (86–92%). The impressive point of note is that the conversion occurred very rapidly within 5–10 min. Previously, in some reported methods, the preparation of homoallylic amines required



Scheme 1.

Table 1
Synthesis of homoallylic amine **3a** using different metals[a]

Entry	Metal	Time	Yield (%)
a	Sn	8 h	60
b	Zn	5 h	68
c	In	5–10 min	92
d	Fe	12 h	20
		2 h[b]	55

[a] Conditions: nitrobenzene (1 mmol), benzaldehyde (1 mmol), allyltributylstannane (1.1 mmol), metal (2 mmol), 1 N HCl, rt.
[b] The reaction was conducted at 80 °C.

☆ Part 172 in the series, 'Studies on novel synthetic methodologies'.

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doi:10.1016/j.tetlet.2008.10.010

Table 2
Synthesis of homoallylic amines using indium in dilute aqueous HCl at room temperature[a]

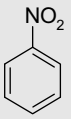
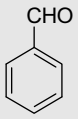
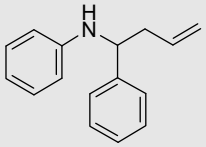
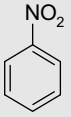
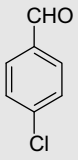
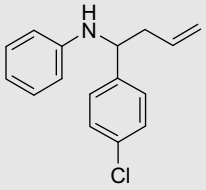
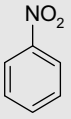
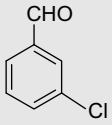
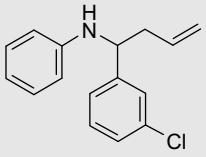
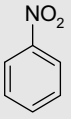
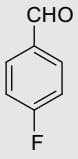
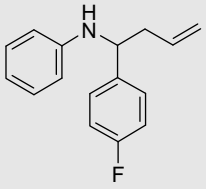
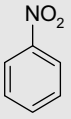
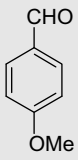
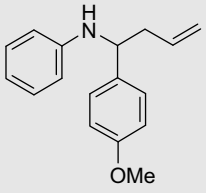
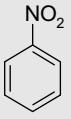
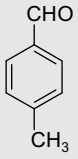
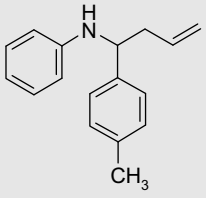
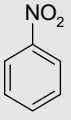
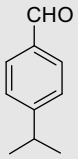
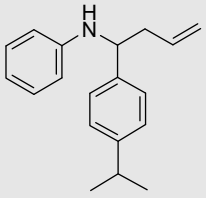
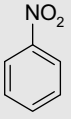
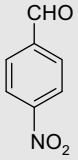
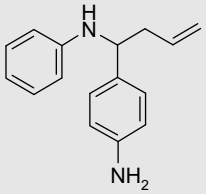
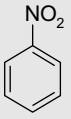
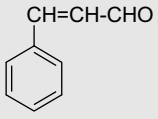
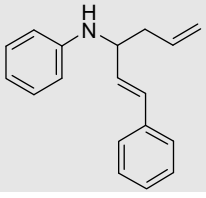
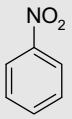
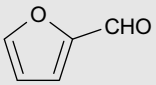
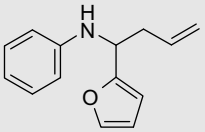
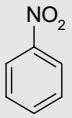
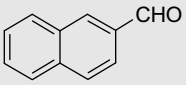
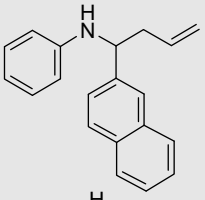
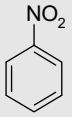
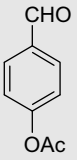
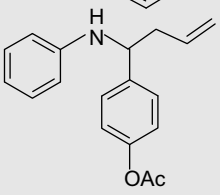
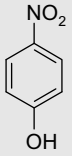
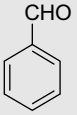
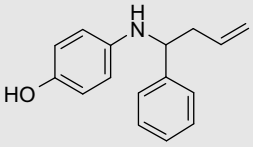
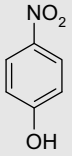
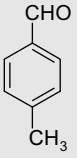
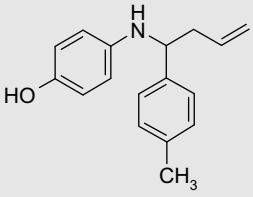
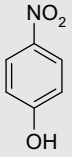
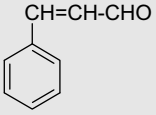
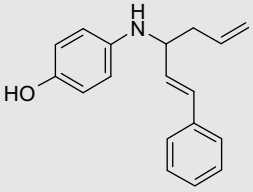
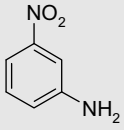
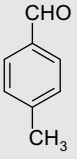
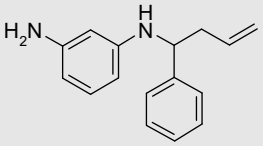
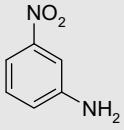
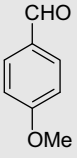
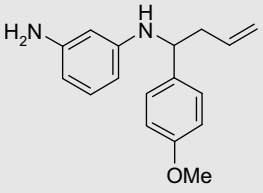
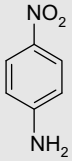
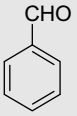
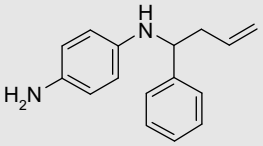
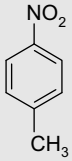
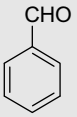
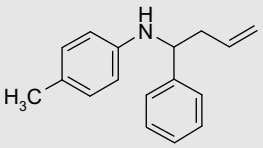
Entry	Nitroarene **1**	Aldehyde **2**	Product **3**	Time (min)	Isolated yield (%)
a				4	88
b				5	91
c				6	88
d				5	91
e				7	86
f				6	89
g				7	87
h				5	92
i				6	88

Table 2 (*continued*)

Entry	Nitroarene **1**	Aldehyde **2**	Product **3**	Time (min)	Isolated yield (%)
j				7	89
k				8	87
l				5	92
m				7	88
n				8	87
o				10	86
p				6	88
q				8	87
r				5	90
s				5	89

[a] The structures of the products were determined from their spectral (IR, ^{1}H and ^{13}C NMR and MS) and analytical data.

several hours.[2] Various derivatives of nitrobenzene were used to prepare homoallylic amines. Both aromatic and heteroaromatic aldehydes underwent the conversion smoothly. The presence of electron-donating or electron-withdrawing groups on the nitro compounds or aldehydes did not affect the reactions. The corresponding alcohols, as reduction products of the aldehydes, were not obtained. Acid sensitive aldehydes such as cinnamaldehyde (Table 2, entry i) and furfuraldehyde (entry j) and the sterically hindered aldehyde 2-naphthaldehyde (entry k) afforded the corresponding homoallylic amines in impressive yields. The present method is highly selective for aldehydes as ketones did not undergo the conversion. Halogen substituents and a conjugated double bond were unaffected by the reaction. The allyl group also remained intact. The reactions with nitroamines (entries p, q, and r) afforded only monohomoallylic amines. The structures of the products were determined from their spectral (IR, ^{1}H and ^{13}C NMR and MS) and analytical data.[4]

The present conversion consists of three steps in one-pot. Initially, the nitrobenzenes are reduced to anilines by In/HCl at room temperature. These anilines then react immediately with benzaldehydes to form the corresponding imines. Finally, the imines undergo allylation with allyltributylstannane to produce the homoallylic amines.

Recently, indium has emerged as a metal of high potential in organic synthesis.[5] It is unaffected by air or oxygen at room temperature. It generally does not affect oxygen and nitrogen-containing functional groups. Here, it has been utilized successfully for the synthesis of homoallylic amines starting from nitrobenzenes. The conversion has been carried out efficiently in water, and no additional organic solvents were required.[6]

In conclusion, we have developed an efficient one-pot synthesis of homoallylic amines via three-component reaction of nitroarenes, benzaldehydes, and allyltributylstannane using indium in dilute aqueous HCl at room temperature. The direct application of nitroarenes, rapid conversion (only 5–10 min), excellent yields (86–92%) are notable features of the present novel method. The exploration of the scope of the present conversion with nitroalkanes and alkyl aldehydes is in progress.

Acknowledgments

The authors thank CSIR and UGC, New Delhi for the financial assistance.

References and notes

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4. *General experimental procedure*: To a mixture of a nitrobenzene (1 mmol), 1 N aqueous HCl (1 mL) and indium (325 mesh, 2 mmol, 0.228 g) in water (5 mL) were added benzaldehyde (1 mmol) and allyltributylstannane (1.1 mmol). The resulting mixture was stirred at room temperature, and the reaction was monitored by TLC. After completion, the mixture was washed with saturated $NaHCO_3$ solution (3×5 mL) and water (3×5 mL) and subsequently extracted with EtOAc (3×5 mL). The extract was concentrated under reduced pressure, and the residue was subjected to column chromatography (silica gel, hexane) to obtain pure homoallylic amine.
The spectral and analytical data of novel products are given below.
Compound **3d**: IR (KBr): 3414, 1623, 1527, 1345, 1273 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.34–7.23 (4H, m), 7.01 (2H, t, J = 8.0 Hz), 6.61 (1H, t, J = 8.0 Hz), 6.38 (2H, d, J = 8.0 Hz), 5.72 (1H, m), 5.22–5.13 (2H, m), 4.32 (1H, br t, J = 7.0 Hz), 4.03 (1H, br s), 2.58 (1H, m), 2.45 (1H, m); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 136.5, 134.8, 129.7, 129.5, 126.1, 118.1, 117.3, 113.6, 56.5, 43.3; ESIMS: *m/z* 242 $[M+H]^+$ Anal. Calcd for $C_{16}H_{16}FN$: C, 79.67; H, 6.64; N, 5.81. Found: C, 79.84; H, 6.44; N, 5.68%
Compound **3h**: IR (KBr): 3400, 1641, 1514, 1434, 1203 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.21 (2H, d, J = 8.0 Hz), 7.08 (2H, d, J = 8.0 Hz), 7.02 (2H, t, J = 8.0 Hz), 6.58 (1H, t, J = 8.0 Hz), 6.41 (2H, d, J = 8.0 Hz), 5.76 (1H, m), 5.20–5.04 (2H, m), 4.34 (1H, br t, J = 6.0 Hz), 4.02 (1H, br s), 2.58 (1H, m), 2.46 (1H, m); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 136.6, 134.9, 129.8, 129.3, 126.5, 118.3, 117.4, 116.7, 113.9, 56.6, 43.2; ESIMS: *m/z* 239 $[M+H]^+$ Anal. Calcd for $C_{16}H_{18}N_2$: C: 80.67; H, 7.56; N, 11.77. Found: C, 80.32; H, 7.63; N, 11.84.
Compound **3l**: IR (KBr): 3408, 1766, 1603, 1504, 1205 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.32–7.18 (2H, m), 7.09–6.91 (4H, m), 6.61 (1H, t, J = 8.0 Hz), 6.40 (2H, d, J = 8.0 Hz), 5.72 (1H, m), 5.21–5.12 (2H, m), 4.33 (1H, m), 4.05 (1H, d, J = 6.0 Hz); 2.61 (1H, m), 2.24 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.6, 140.2, 137.1, 135.0, 132.9, 130.2, 129.4, 128.7, 128.0, 127.4, 126.3, 117.5, 56.8, 37.5, 23.1; ESIMS: *m/z* 282 $[M+H]^+$ Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98. Found: C, 76.43; H, 6.62; N, 4.82.
Compound **3o**: IR (KBr): 3451, 1631, 1459, 1251 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.36–7.02 (7H, m), 6.69–6.51 (3H, m), 6.15 (1H, dd, J = 14.0, 6.0 Hz), 5.81 (2H, m), 4.02 (1H, m), 3.71 (1H, br s), 2.52–2.34 (2H, m); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 147.6, 137.2, 134.8, 131.5, 130.7, 129.2, 128.9, 127.3, 126.7, 118.5, 117.9, 113.4, 54.9, 40.6; ESIMS: *m/z* 266 $[M+H]^+$ Anal. Calcd for $C_{18}H_{19}NO$: C, 81.51; H, 7.17; N, 5.28. Found: C, 81.93; H, 7.21; N, 5.32.
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