

A SIMPLE AND EFFICIENT METHOD FOR THE THREE COMPONENT SYNTHESIS OF HOMOALLYLIC AMINES CATALYZED BY ZINC ACETATE.

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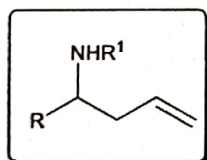
ABSTRACT

A simple and efficient method for the synthesis of homoallylic amines(a-m) has been developed by using Zn (OAc)₂ as a catalyst. This is one of the useful new catalyst that can be easily separated and are not contaminated by products. The Multi component Reaction (MCR) strategies offer significant advantages over conventional linear type by the formation of new molecule in a single synthetic operation without isolation of intermediate.¹This method offers several advantages including high yields, short reaction times, simple work up procedure and easy isolation.

Keywords: Aldehyde, Amine, Allyltributylstannane and Zinc acetate

INTRODUCTION

A reaction in which three or more reactants come together in a single reaction vessel to form a new product that contains portions of all the components is called multicomponent reaction (MCR). The MCR strategies offer significant advantages over conventional linear type by the formation of new molecule in a single synthetic operation without isolation of intermediate. Homoallylamines (Fig. 1) are fundamental building blocks in organic chemistry and their synthesis is an important industrial and synthetic goal. The homoallylamine fragment can be encountered in natural products, but often the homoallylamine is transformed to a range of products by fictionalization, reduction or oxidation of the double bond.



R, R¹ = aromatic, heteroaromatic, aliphatic and alicyclic substituents

Homoallylic amines are important intermediates in the synthesis of nitrogen containing compounds such as *N*-heterocycles, β -lactams,² β -amino acids,³ natural products and other biologically active compounds.^{4,5} Various catalytic procedures have been developed for the preparation of these homoallylic amines by coupling of an aldehyde, an amine (or an amide) with different types of allylic organometallics.

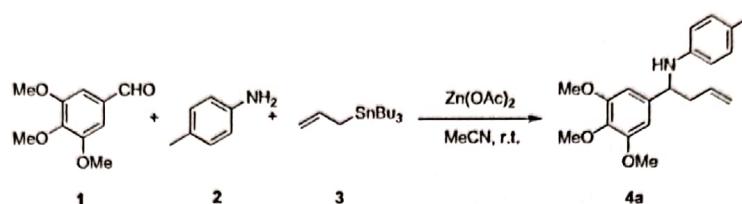
However, many of the methods have some drawbacks, which involve use of strong Lewis acids, prolonged reaction times, vigorous reaction conditions and low yields of products.

Multicomponent reactions (MCR) like Hantzsch,⁶ Biginelli,⁷ Mannich,⁸ Robinsons⁹ and Passerini¹⁰ reactions have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug like heterocyclic compounds. Homoallylic amines are excellent building blocks for the synthesis of numerous nitrogen containing natural products.¹¹

Therefore, there is an increasing interest in recent years, in developing environmentally benign, atom economic, catalytic processes and milder reaction conditions that employ unmodified aldehydes, amines and allylic compounds for multicomponent reactions. Keep in mind the above drawbacks, we have developed a mild and efficient method, in order to improve the efficiency of homoallyl amines synthesis using a mild and robust Lewis acid catalyst Zinc acetate [$\text{Zn}(\text{OAc})_2$]. In this juncture, we have used for one pot synthesis of homo allylamines by condensation of aldehydes, amines and allyl tributylstannane.

EXPERIMENT

In our experiment, equimolar amounts of 3,4,5-trimethoxybenzaldehyde(1), *p*-toluidine(2) and allyltributylstannane(3) were reacted in the presence of a catalytic amount (10%mol) of Zinc acetate in acetonitrile at room temperature to afford the corresponding product, 4-methyl-*N*-[1-(3,4,5-trimethoxy phenyl) but-3-enyl] benzene amine (4a) in excellent yields.

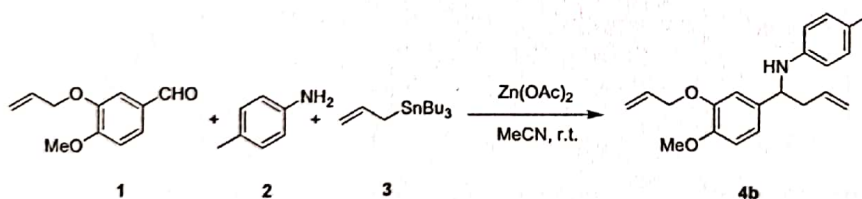


scheme-1

In this process the catalyst Zinc acetate plays a vital role in the activation of the carbonyl group to form the imine and in the activation of the imine to react with alkylating agent as shown in the scheme 1.

The obtained pure product (4a) was identified by their spectral data. The ^1H NMR spectra shows a singlet at δ 3.85 integrating for 9H protons of three methoxy groups, allylic protons at δ 5.70-5.90 as multiplet integrating for 1H and δ 6.35 ppm as doublet integrating for 2H and confirmative benzylic proton appears as multiplet at δ 4.15-4.25.

In the second experiment (Scheme-2), 3-(allyloxy)-4-methoxybenzaldehyde, *p*-toluidine and allyltributylstannane were reacted in the presence of a catalyst Zinc acetate to afford the corresponding product, *N*-[1-(3-(allyloxy)-4-methoxy phenyl) but-3-enyl]-4-methylbenzenamine (4b) in excellent yields.

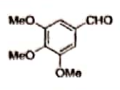

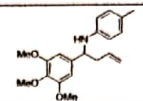
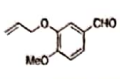

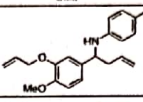
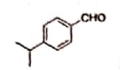

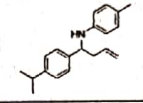
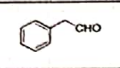

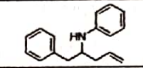
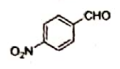

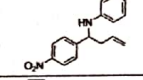
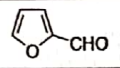

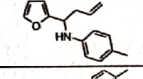
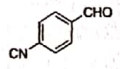

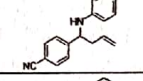
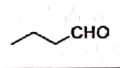

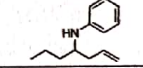
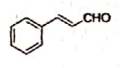

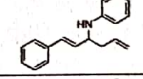
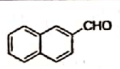

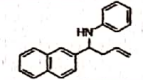
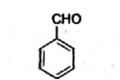

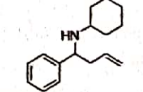
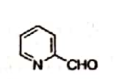

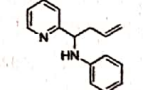
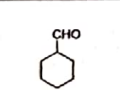

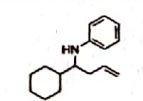
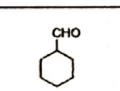

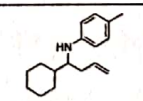


Scheme-2

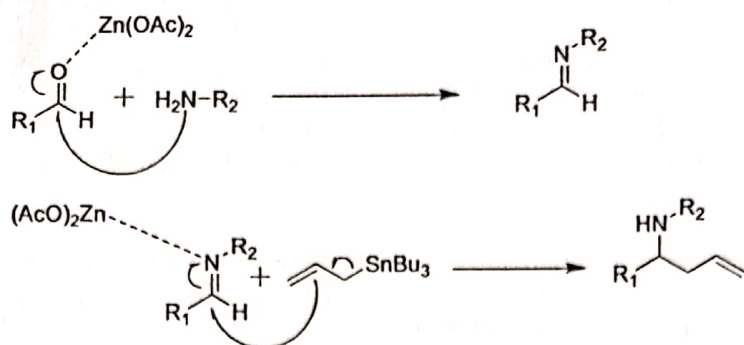
The obtained pure product (4b) was identified by their spectral data. The ^1H NMR spectra shows a singlet at δ 2.19 integrating for 3H of toluene methyl, a multiplet at δ 2.40-2.62 integrating for 2H of allyl methylene, a singlet at δ 3.85 integrating for 3H of methoxy group and a multiplet at δ 4.18-4.28 integrating for 1H of benzylic and a characteristic proton. A doublet at δ 4.55 integrating for 2H of allyloxy methylene, a doublet at δ 5.12 integrating for 2H of allyl olefin methylene and a triplet at δ 5.22 integrating for 2H of allyloxy olefin methylene. A multiplet at δ 5.68-5.80 integrating for 1H of allyl olefin methine and a multiplet at δ 5.98-6.18 integrating for 1H of allyloxy olefin methine respectively.

Encouraged by the result obtained with the above reaction, we have extended this procedure to various aldehydes and amines with the same quantity of allyltributylstannane and the catalyst in acetonitrile at room temperature (shown in Table - 1)

Table I: One-pot synthesis of homoallylic amines catalyzed by $Zn(OAc)_2$:

Entry	Aldehydes	Amine	Product (4a)	Time (h)	Yield (%)
a				3.0	95
b				5.0	90
c				4.0	89
d				6.0	87
e				7.0	84
f				3.0	92
g				5.0	85
h				6.0	80
i				6.0	84
j				5.0	87
k				7.0	81
l				6.0	80
m				7.0	80
n				7.0	82



A PLAUSIBLE MECHANISM:**Scheme 3**

The plausible reaction mechanism shows that the aldehyde reacts with amine to form imine. Thus formed imine undergoes nucleophilic addition by allyltributylstannane to afford the corresponding homoallylic amine derivatives. In this process the catalyst Zinc acetate plays a vital role in the activation of the carbonyl group to form the imine and in the activation of the imine to react with allylating agent as shown in the scheme 2.

GENERAL PROCEDURE:

To a stirred mixture of aldehyde (2mmol), amine (2mmol) and $Zn(OAc)_2$ (10 mol %) in MeCN (10 mL) was added allyltributylstannane (2mmol) at $0^\circ C$. The resulting reaction mixture was stirred at room temperature for a specified time as shown in the table-1. The progress of the reaction was monitored by TLC. After completion of the reaction as indicated by TLC, the mixture was quenched by adding crushed ice at $0^\circ C$ and extracted with EtOAc (2x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude products, which were purified by column chromatography using silica gel (60-120 mesh) by eluting with ethyl acetate-hexanes mixture (Table. I). The structures of all the products were confirmed by their 1H NMR, IR and mass spectroscopy data.

CONCLUSION

The objective of the present research work is to develop various new synthetic methodologies. Here we have developed a simple and efficient methodology for the synthesis of homoallylic amines derivatives. We reported $Zn(OAc)_2$ as a new catalyst for the above homoallylic amines derivatives, The new catalyst reduced the reaction time and the yields were very good. In conclusion, this method is very easy to handle environmentally benign and the recovery of the products is easy. The products obtained were characterized by IR, 1H NMR and Mass Spectra.

ACKNOWLEDGEMENTS

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Spectral data:

4-Methyl-N-[1-(3,4,5-trimethoxyphenyl)but-3-enyl]benzenamine(4a): Yellow solid. mp, 65-66°C. IR (neat): ν_{\max} cm.⁻¹ 3402, 2959, 2932, 2873, 1618, 1591, 1521, 1458, 1417, 1324, 1269, 1232, 1183, 1125, 1041, 1002, 959, 915, 835, 808, 712. ¹H NMR (CDCl₃, 300MHz): δ = 2.20 (3H, s), 2.38-2.48 (1H, m), 2.51-2.61 (1H, m), 3.85 (9H, s), 4.15-4.25 (1H, m), 5.12-5.22 (2H, m), 5.70-5.90 (1H, m), 6.35 (2H, d, J = 6.5 Hz), 6.85 (2H, q, J = 6.0 Hz), 7.10 (2H, dd, J = 7.5, 3.0 Hz). ESI-MS: m/z (%) 328 [M⁺+1] (70), 297 (10), 278 (12), 253 (10), 223 (10), 221 (100), 191 (12), 190 (20), 175 (10), 159 (10), 151 (10), 130 (10).

N-(1-(4-Allyloxy)-3-methoxyphenyl)but-3-enyl)-4-methylbenzenamine(4b): Liquid. IR (neat): ν_{\max} cm.⁻¹ 3418, 2923, 2755, 1598, 1515, 1460, 1422, 1266, 1146. ¹H NMR (CDCl₃, 300MHz): δ = 4.28 (1H, m), 4.55 (2H, d, J = 6.5 Hz), 5.12 (2H, d, J = 7.5 Hz), 5.22 (2H, t, J = 10.0 Hz), 5.40 (1H, d, J = 14.5 Hz), 5.68-5.80 (1H, m), 5.98-6.18 (1H, m), 6.35 (2H, d, J = 6.5 Hz), 6.55 (2H, d, J = 6.5 Hz), 6.75-6.95 (3H, m). ESI-MS: m/z (%) 324 [M⁺] (95), 306 (10), 265 (10), 249 (10), 237 (20), 223 (10), 218 (25), 217 (100), 207 (10), 176 (10), 175 (25), 158 (20), 147 (10), 124 (10).

N-[1-(4-Isopropylphenyl) but-3-enyl]-4-methylbenzenamine (4c): Brown liquid. IR (neat): ν_{\max} cm.⁻¹ 3405, 3015, 2962, 2926, 2869, 2730, 1702, 1611, 1577, 1518, 1461, 1421, 1305, 1265, 1213, 1171, 1108, 1054, 994, 918, 830, 727. ¹H NMR (CDCl₃, 300 MHz): δ = 1.20 (6H, s), 2.18 (3H, s), 2.45-2.65 (2H, m), 2.85-3.05 (1H, m), 4.25-4.35 (1H, m), 5.20 (2H, t, J = 6.5 Hz), 5.68-5.78 (1H, m), 6.35 (2H, d, J = 6.5 Hz), 6.85 (2H, d, J = 6.5 Hz), 7.10 (2H, d, J = 6.5 Hz), 7.25 (1H, d, J = 6.5 Hz), 7.40 (1H, d, J = 6.5 Hz). ESI-MS: m/z (%) 280 [M⁺+1] (100), 279 (15), 262 (20), 238 (35), 223 (10), 174 (10), 173 (20), 158 (10), 138 (10), 109 (10).

N-(1-Phenylpent-4-en-2-yl)benzenamine(4d): Yellow liquid. IR (KBr): ν_{\max} cm.⁻¹ 3412, 3054, 2965, 1639, 1602, 1518, 1314, 748, 750. ¹H NMR (CDCl₃, 300 MHz): δ 2.40-2.61 (1H, m), 2.86 (2H, d, J = 7.0 Hz), 4.12 (1H, brs), 4.36 (1H, dd, J = 5.4, 8.1 Hz), 5.08-5.14 (2H, m), 5.63-5.79 (1H, m), 6.46 (2H, d, J = 7.5 Hz), 6.61 (3H, t, J = 7.4 Hz), 7.05 (2H, t, J = 7.5 Hz), 7.16-7.22 (1H, m), 7.22-7.38 (4H, m). ESI-MS: m/z (%) 238 [M⁺] (100), 182, 141, 104, 77.

N-(1-(4-Nitrophenyl) but-3-enyl)benzenamine(4e): Yellow liquid. IR (KBr): ν_{\max} cm.⁻¹ 3410, 3077, 3021, 2979, 2914, 2853, 1640, 1603, 1518, 1344, 1289, 1108, 993, 854, 750. ¹H NMR (CDCl₃, 300 MHz): δ = 2.47-2.55 (1H, m), 2.59-2.66 (1H, m), 4.24 (1H, brs), 4.48 (1H, dd, J = 5.1 Hz), 5.18-5.24 (2H, m), 5.69-5.79 (1H, m), 6.423 (2H, d, J = 7.5 Hz), 6.69 (1H, t, J = 7.5 Hz), 7.09 (2H, t, J = 7.5 Hz), 7.55 (2H, d, J = 8.4 Hz), 8.179 (2H, d, J = 8.4 Hz).

N-[1-(Furan-2-yl) but-3-enyl]-4-methylbenzenamine (4f): Yellow syrup. IR (neat): ν_{\max} cm.⁻¹ 3415, 2924, 2859, 1618, 1518, 1442, 1300, 1260, 1218, 1183, 1150, 1074, 1005, 920, 808, 737. ¹H NMR (300 MHz, CDCl₃): δ = 2.21 (3H, s), 2.62 (2H, t, J = 6.0 Hz), 4.49 (1H, t, J = 6.0 Hz), 5.12 (2H, dd, J = 10.5, 6.0 Hz), 5.60-5.80 (1H, m), 6.08 (1H, s), 6.22 (1H, s), 6.45 (2H, d, J = 6.5 Hz), 6.89 (2H, d, J = 6.5 Hz), 7.31 (1H, s). ESI-MS: m/z (%) 228 [M⁺+1] (60), 226 [M⁺-1] (100), 190 (10), 158 (45), 144 (25), 102 (20).

4-[1-(*p*-Toluidino)but-3-enyl]benzotrile(4g): Thick syrup. IR (neat): ν_{\max} cm.⁻¹ 3401, 2924, 2855, 2227, 1615, 1519, 1460, 1411, 1300, 1265, 1112, 993, 921, 834, 809, 772. ¹H NMR (300 MHz, CDCl₃): δ = 2.20 (3H, s), 2.45 (1H, q, J = 5.0 Hz), 2.55-2.65 (1H, m), 4.33-4.41 (1H, m), 5.15-5.25 (2H, m), 5.65-5.80 (1H, m), 6.28 (2H, d, J = 6.5 Hz), 6.82 (2H, d, J = 6.5 Hz), 7.48 (2H, d, J = 6.5 Hz), 7.60 (2H, d, J = 6.5 Hz). ESI-MS: m/z (%) 263 [M⁺+1] (100), 261 (M⁺, 10) 247 (10), 225 (10), 210 (10), 182 (20), 168 (10), 149 (15), 144 (10), 108 (25).

N-(Hept-1-en-4-yl) benzenamine (4h): ¹H NMR (300 MHz, CDCl₃): δ = 0.91 (3H, t, J = 7.3 Hz), 1.32-1.62 (4H, m), 2.27-2.30 (2H, m), 3.83 (1H, t, J = 6.4 Hz), 5.05-5.09 (2H, m), 5.77-5.85 (1H, m), 6.57 (2H, d, J = 8.2 Hz), 6.65 (1H, t, J = 6.6 Hz), 7.15 (2H, t, J = 7.6 Hz).

(*E*)-N-(1-Phenylhexa-1,5-dien-3-yl)benzenamine(4i): Thick syrup. IR (neat): ν_{\max} cm.⁻¹ 3408, 3020, 2935, 1636, 1503, 1318, 969, 910, 748, 695. ¹H NMR (300 MHz, CDCl₃): δ 2.40-2.55 (2H, m), 3.90 (1H, brs),

4.01-4.15 (1H, m), 5.13-5.23 (2H, m), 5.70-5.80 (1H, m), 6.25 (1H, dd, $J = 5.0, 15.0$ Hz), 6.60-6.70 (4H, m), 7.15-7.35 (7H, m).

***N*-(1-(Naphthalene-2-yl) but-3-enyl)benzenamine(4j)**: Liquid. IR (KBr): ν_{\max} cm⁻¹ 3410, 3052, 2918, 1639, 1602, 1503, 1316, 920, 749. ¹H NMR (300 MHz, CDCl₃): δ 2.55-2.73 (2H, m), 4.26 (1H, brs), 4.53-4.57 (1H, t, $J = 6.9$ Hz), 5.14-5.26 (2H, m), 5.75-5.85 (1H, m), 6.56 (2H, d, $J = 8.4$ Hz), 6.63 (1H, t, $J = 6.9$ Hz), 7.03-7.10 (2H, m), 7.43-7.54 (3H, m), 7.80-7.86 (4H, m).

***N*-(1-Phenylbut-3-enyl)cyclohexanamine(4k)**: Brown syrup. IR (neat): ν_{\max} cm⁻¹ 3423, 3069, 3029, 2925, 2854, 1642, 1492, 1455, 1376, 1261, 1195, 1048, 915, 871, 800, 757. ¹H NMR (CDCl₃, 300MHz): δ = 0.78-0.98 (2H, m), 1.22-1.42 (7H, m), 1.65 (1H, s), 1.80 (1H, brs, NH), 2.05 (1H, s), 2.40-2.55 (2H, m), 4.70 (1H, t, $J = 6.0$ Hz), 5.15 (2H, t, $J = 6.0$ Hz), 5.70-5.85 (1H, m), 7.257.40 (5H, m), ESI-MS: m/z 230[M+1] (100).

***N*-(1-(Pyridin-2-yl) but-3-enyl) benzenamine(4l)**: Thick syrup, IR (neat): ν_{\max} cm⁻¹ 3409, 3057, 2931, 1608, 1579, 1518, 1455, 1304, 1271, 1148, 1091, 1012, 996, 916, 878, 743. ¹H NMR (CDCl₃, 300MHz): δ = 2.77-2.72 (2H, m), 4.44 (1H, brs), 4.55-4.52 (1H, m), 5.18-5.11 (2H, m), 5.80-5.72 (1H, m), 6.54 (2H, d, $J = 8.5$ Hz), 6.68-6.65 (1H, m), 7.10 (2H, t, $J = 8$ Hz), 7.17-7.14 (1H, m), 7.34 (1H, d, $J = 8$ Hz), 7.62-7.59 (1H, m), 8.60-8.59 (1H, m), ESI-MS: m/z 225[M+1] (100).

***N*-(1-Cyclohexylbut-3-enyl)benzenamine(4m)**: Yellow syrup. IR (neat): ν_{\max} cm⁻¹ 3409, 3075, 3018, 2924, 1639, 1601, 1505, 1321, 992, 912, 747. ¹H NMR (CDCl₃, 300MHz): δ = 1.00-1.28 (4H, m), 1.40-1.56 (6H, m), 2.12-2.38 (2H, m), 2.48-2.56 (1H, m), 4.06 (1H, dd, $J = 5.1, 12.9$ Hz), 3.50 (1H, brs), 5.00-5.08 (2H, m), 5.72-5.84 (1H, m), 6.56 (2H, d, $J = 8.7$ Hz), 6.62 (1H, t, $J = 7.2$ Hz), 7.12 (2H, dt, $J = 7.2, 8.7$ Hz).

***N*-(Cyclohexylbut-3-enyl-4-methylbenzenamine (4n)**: Yellow syrup. IR (neat): ν_{\max} cm⁻¹. 3415, 3075, 3018, 2924, 1639, 1601, 1515, 1321, 1260, 1183, 1150, 992, 912, 747, 691. ¹H NMR (CDCl₃, 300MHz): δ = 1.00-1.28 (5H, m), 1.40-1.56 (6H, m), 2.12-2.18 (2H, m), 2.21 (3H, s), 3.22 (1H, dd, $J = 5.1, 12.9$ Hz), 3.50 (1H, brs), 5.00-5.08 (2H, m), 5.72-5.84 (1H, m), 6.56 (2H, d, $J = 8.7$ Hz), 7.12 (2H, dt, $J = 7.2, 8.7$ Hz).

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