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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

A novel series of homoallylic amines as potential antimicrobials

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Abstract An efficient catalytic three-component reaction of aldehydes, amines, and allyltributylstannate has been successfully developed to produce homoallylic amines at 25°C, in excellent yields, in the presence of 1 mol% of trifluoroacetic acid an inexpensive and environmentally friendly catalyst. Newly synthesized compounds were confirmed by spectral studies. Compound **3o** was characterized by single crystal X-ray analysis. All the compounds were also screened for their antimicrobial activity. Halogen-substituted compounds namely **3d**, **3g**, **3n**, and **3o** have showed excellent antibacterial activity.

Keywords Homoallylic amines · Allyltributyl stannate · CF_3COOH · Antibacterial activity

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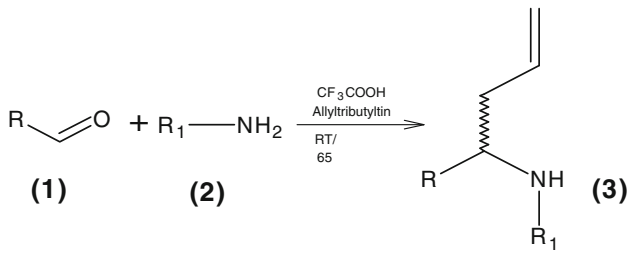
Introduction

Homoallylic amines are valuable intermediates in organic synthesis (Yamaguchi *et al*., 1985) as starting materials in the preparation of biologically active substances (Moser *et al*. 1982), as resolving agents (James 1989) and as chiral auxiliaries for asymmetric synthesis (Sabine and Horst, 1991). They are used for the synthesis of β-amino acids (Xie *et al*., 1989), as well as β-lactams (Wright *et al*., 2000a, b) and HIV-protease inhibitors (Bloch 1998). The homoallylic amine moiety is not widely present in natural products, however, compounds like eponemycin (Schmidt and Schmidt 1994), which exhibits potent activity against B16 melanoma cells, or a depsipeptide cryptophycin 337 (Russell *et al*., 2000), which is an analog of a potent antitumor compound cryptophycin, contain this subunit.

On the other hand, homoallylic amines are excellent building blocks for the synthesis of numerous nitrogen-containing natural products (Puentes and Kouznetsov 2002), Chiral homoallylic amines were utilized as the key intermediates in the preparation of many natural products, such as an amino-sugar vancosamine isolated from vancomycin (Wright *et al*., 2000a, b), a spirocycle alkaloid alichlorine isolated from a Japanese sponge *Halichondria okadai* Kadota (Ciufolini *et al*., 1989), an alkaloid from *Prosopis africana*, desoxoprosopinine (Felpin and Lebreton 2003), and many others. With the utilization of ring-closing metathesis methodology, numerous piperidine alkaloids can be easily prepared from the corresponding aminodienes (Voigtmann and Blechert 2000). Preparation of β-amino acids is of particular interest to medicinal and bioorganic chemists as various β-amino acid moieties can be found in taxoids, β-lactam antibiotics, and other compounds.

In general, Homoallylic amines are prepared either by the addition of organometallic reagents to imines or by

nucleophillic addition of allylsilanes, allyltin, allylboron, or allyl germane reagents to imines (Keck and Enholm, 1985) in the presence of catalysts such as $LiClO_4$, [(Yadav *et al*., 2002), $Sn(OTf)_3$ (Manoj Pandey *et al*., 2005), $Bi(OTf)_3{\cdot}nH_2O$ (Ollevier *et al*., 2003), $PdCl_2(PPh3)_2$ (Nakamura *et al*., 1996). Recently, $HClO_4$–SiO_2 (Nagarapu *et al*., 2007) have been employed for this transformation. However, most of the synthesis protocols reported so far requires long reaction times, stringent conditions, and highly toxic reagents/catalysts (Ponnaboina and Kim, 2009) the catalysts are often expensive and tedious to prepare. The reactions are often characterized by low yields. Therefore, there is a need for the development of simple, convenient, and environmentally benign approaches for the synthesis of homoallylic amines.



Scheme 1 Synthetic route for the Homoallylic amines

Results and discussion

Synthesis

The reaction of benzaldehyde, 1-naphthylamine, and allyltributyl in the presence of 0.1 equivalents CF_3COOH in acetonitrile at 25°C resulted in the formation of the homoallylic amines in 68–98% yield. The scope and generality of this process is illustrated with respect to different substrates. Aromatic, aliphatic, cyclic and heterocyclic aldehydes reacted smoothly with different amines to afford the corresponding homoallylic amines in high to excellent yields of the products within 25–60 min, whereas ketones did not yield any product even after long reaction times (15–29 h.) Synthetic route has been presented in Scheme 1.

Compounds containing an electron withdrawing group on the aldehydes reacted more efficiently resulting with higher yields, e.g. **3f.** Amines bearing an electron donating group also favored the reaction under the standard reaction conditions to give products less than 1 h, e.g. **3c**. Furthermore, acid-sensitive aldehyde, furfuraldehyde worked well without any decomposition under the reaction conditions because of low concentration of acid and at ambient temperature. Enolizable aldehydes, such as cyclohexanecarboxaldehyde also produced the corresponding homoallylamines in good yields. In all cases, no homoallylic alcohol (the adduct of aldehyde and allyltributyltin) was obtained under these reaction conditions due to rapid formation and activation of imines in the presence of catalytic amount of CF_3COOH. Results are summarized in Table 1.

Table 1 Newly synthesized homoallylic amines

S. no	R	R^1	Reaction time (min)	Yield (%)
3a	Benzaldehyde	Napthylamine	30	95
3b	Benzofuran-2-aldhyde	3,4-Diflurobenzylamine	35	90
3c	Cyclopropanecarboxaldehyde	4-t-Butylaniline	30	98
3d	2,4-Difluorobenzaldehyde	2,4,5-Trifluoroaniline	45	89
3e	Benzofuran-2-aldhyde	Napthylamine	30	90
3f	2,4-Difluoro-benzaldehyde	4-t-Butylaniine	45	95
3g	2-Fluoro-5-methoxy benzaldehde	3-Fluoroaniline	45	82
3h	Cyclopropane carboxaldehyde	4-Fluoro-3-trifluoromethylaniline	30	85
3i	Cyclohexane carboxaldehyde	4-Morpholinobenzenamine	60	78
3j	Cyclohexane carboxaldehyde	2,5-Dimemethylaniline	30	88
3k	2-Allyloxy benzaldehyde	4-(4-Chlorophenoxy)benzenamine	45	75
3l	5-(2-Chlorophenyl)furan-2-carbaldehyde	4-(4-Chlorophenoxy)benzenamine	60	73
3m	1-Acetyl-1H-indole-3-carbaldehyde	Benzo[d]thiazol-7-amine	60	68
3n	2,4-Difluorobenzaldehyde	2,4-Difluoroaniline	45	75
3o	2,6-Difluorobezaldehyde	4-Chloro-3-fluoroaniline	30	78
3p	Thiophen-3-carboxaldehyde	4-Cyanoaniline	45	68
3q	3-Ethoxybenzaldehyde	4-Fluoroaniline	30	72

Characterization

All aldehydes, amines, allyltributyltin, CF_3CO_2H, and solvents are purchased from commercial sources and all the aldehydes and solvents were distilled before use. Reactions were monitored on TLC by comparison with the starting materials. Yields refer to the isolated yields of the products after purification by flash chromatography. ^{1}H-NMR, ^{13}C-NMR were recorded on 400 MHz Brucker spectrometer, Elemental analysis was performed on a Thermo Finnigan FLASH EA 1112 CHN analyzer. Melting points were recorded (uncorrected) on a Buchi Melting Point B-545 apparatus.

All the reactions are monitored by mass analysis of crude reaction mixture and by TLC using ethylacetate: hexane as eluent. An unambiguous structure proof of compound **3** was achieved by an examination of the crystal structure of compound **3o** (Fun *et al*., 2009). Figure 1 shows a crystal structure of compound **3o**. In the crystal structure, weak intermolecuar N–H···F hydrogen bonds link molecules into centrosymmetric dimers which are arranged in molecular sheets parallel to the ac plane.

Antimicrobial studies

All the newly synthesized compounds were screened for their antibacterial activity. For this, *Staphylococcus aureus, Bacillus subtilis, Escherichia coli*, and *Pseudomonas aeruginosa* microorganisms were employed. Antimicrobial study was assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method (Collee *et al*., 1989). Several colonies of *S. aureus, B. subtilis, E.coli*, and *P. aeruginosa* were picked off a fresh isolation plate and inoculated in corresponding tubes containing 5 mL of trypticase soya broth. The broth was incubated for 6 h at 37°C until there was visible growth. Mc Farland No.5 standard was prepared by adding 0.05 ml of 1% w/v $BaCl_2{\cdot}2\ H_2O$ in Phosphate Buffered saline (PBS) to 9.95 ml of 1% v/v H_2SO_4 in PBS. The growth of all the four cultures was adjusted to Mc Farland No.5 turbidity standard using sterile PBS. This gives a 10^8 cfu/ml suspension. The working inoculums of aforementioned four different microorganisms containing 105 cfu/ml suspension was prepared by diluting the 108 cfu/ml suspension, 10^3 times in trypticase soya broth.

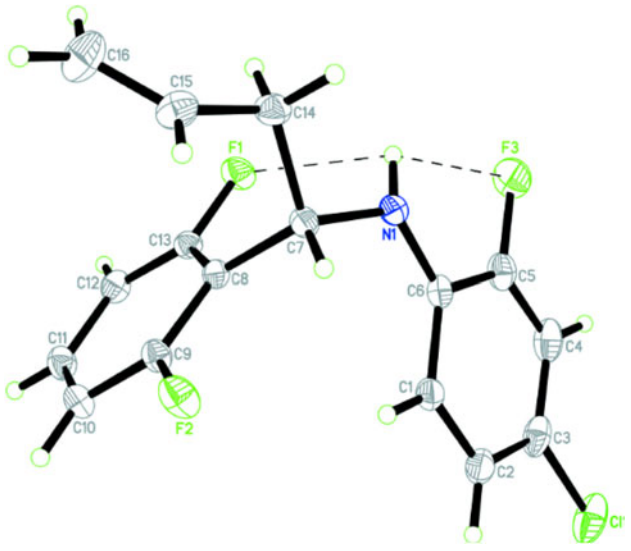


Fig. 1 The structure of **3o**, showing 50% probability displacement ellipsoids and the atom-numbering scheme. (Figure reproduced from Acta Cryst 2009, E65 o1027–o1028)

Preparation of anti-microbial suspension (50 μg/ml)

Dissolved 0.5 mg of each compound in 10 ml of trypticase soya broth to get 50 μg/ml. This suspension was filter sterilized in syringe filters.

Preparation of dilutions

In all, for each of the 11 anti-microbial compounds and standard antimicrobial i.e. Ceftriaxone, 24 tubes of 5 ml capacity were arranged in four rows with each row containing six tubes. Then, 1.9 ml of trypticase soya broth was added in the first tube in each row and 1 ml in the remaining tubes. Now, 100 μl of filtered anti-microbial suspension was added to the first tube in each row and after mixing the content, 1 ml was serially transferred from these tubes to the second tube in each of the rows. The contents in the second tube of each of the rows were mixed and transferred to the third tube in each of the rows. This serial dilution was repeated till the sixth tube in each of the rows. This provided anti-microbial concentrations of 50, 25, 12.5, 6.25, 3.125, 1.6125 μg/ml in the first to sixth tube, respectively, in each row. Finally, 1 ml of 10^5 cfu/ml of *S. aureus, B. subtilis, E. coli,* and *P. aerogenosa* suspension were added to the first, second, third, and fourth rows of tubes, respectively. Along with the test samples and Ceftriaxone (standard), the inoculums control (without anti-microbial compound) and broth control (without antimicrobial compound and inoculum) were maintained. All the test sample and control tubes were then incubated for 16 h at 37°C. The results are summarized in Table 2.

Interpretation

After incubation, the tubes showing no visible growth was considered to be representing the MIC. The details of results are furnished in Table 2. Inoculum control showed visible growth, whereas the broth control showed no growth.

Table 2 Antibacterial activity data in MIC (μg/ml)

Compound no.	*S. aureus*	*B.subtilis*	*E.coli*	*P.aeruginosa*
3a	25	25	25	25
3b	1.6125	3.125	3.125	3.125
3c	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations
3d	1.6125	1.6125	1.6125	1.6125
3e	1.6125	1.6125	25.00	Growth in all concentrations
3f	3.125	3.125	3.125	3.125
3g	1.6125	1.6125	1.6125	1.6125
3h	1.6125	1.6125	Growth in all concentrations	Growth in all concentrations
3i	6.250	6.250	6.250	25
3j	6.250	12.5	12.5	12.5
3k	3.125	3.125	6.250	25.00
3l	3.125	3.125	3.125	3.125
3m	12.5	12.5	12.5	12.5
3n	1.6125	1.6125	1.6125	1.6125
3o	3.125	1.6125	1.6125	1.6125
3p	6.250	6.250	3.125	6.250
3q	3.125	3.125	3.125	3.125
Ceftriaxone (Standard)	3.125	1.6125	1.6125	1.6125
Inoculum control	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations
Broth control	No growth	No growth	No growth	No growth

Experimental

General procedure

To a mixture of aldehyde (10 mmol), amine (10 mmol), and allyltributyltin (10 mmol) in acetonitrile (5 ml), CF_3COOH (1 mmol) was added. The reaction mixture was stirred at 25°C under nitrogen atmosphere for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC and mass analysis, the reaction mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were concentrated in vacuum and purified by flash chromatography to afford the pure homoallylic amines.

*Naphthalene-1-y-(1-phenyl–but-3-enyl)-amine (**3a**)*

(TLC, Pet-ether/EtOAc, 1:1, $Rf = 0.5$), Thick liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, 24°C):$\delta = 2.72$–2.83 (m, 2H, CH_2), 4.55–4.61 (m, 1H,CH), 5.18–5.22 (d, 1H, $J = 16$ Hz), 5.31–5.36 (m, 1H, CH_2), 5.80–5.90 (m, 1H, CH_2), 6.36 (br. s, 1H, NH), 7.14–7.27 (m, 4H, Ar-H), 7.31–7.38 (m, 2H, Ar-H), 7.41–7.78 (m, 4H, Ar-H), 7.93–7.7.95 (m, 1H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 43.4$, 57.0, 106.3, 117, 118.6, 119.7, 123.4, 124.7, 125.6, 126.2, 127.0, 128.7, 128.9, 134.2, 134.7, 141.8, 143.0. LCMS (97.9%, Method; 0.1% HCOOH; ACN, Flow 1 ml/min, Column C 18 75 × 4.6 mm 5 μm, RT = 3.4 min, $m/z = 274$ [M+H]+). Anal. Calc. for $C_{20}H_{19}N$: C 87.91, H 6.96, N 5.13. Found: C 87.9, H 6.95, N 5.11%.

*(1-Benzofuran-2-yl-but-enyl)-(3,5-difluoro-benzyl)-amine (**3b**)*

(TLC, Pet-ether/EtOAc, 1:1, $Rf = 0.4$), Thick liquid. 1H-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 2.59$–2.75 (m, 2H, CH_2), 3.71–3.75 (m, 1H,), 3.83–3.3.92 (m, 2H, CH_2), 5.08–5.17 (m, 2H, CH_2), 5.71–5.81 (m, 1H, CH), 6.64 (s, 1H, NH), 6.77–6.84 (m, 2H, Ar-H), 7.24–7.37 (m, 3H, Ar-H), 7.48–7.50 (m, 1H, Ar-H), 7.55–7.57 (m, 1H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 39.12$, 44.3, 55.4, 103.4, 104, 110.9, 111, 118, 120.7, 122, 123, 128, 131.13, 134.2, 154.8, 158, 159.8, 162. LCMS (96.3%, Method; 0.1% HCOOH; ACN, Flow 1 ml/min, Column C 18 75 × 4.6 mm 5 μm, RT = 1.0 min, $m/z = 314$ [M+H] +). Anal. Calc. for $C_{19}H_{17}F_2NO$; C 72.84, H 5.43, N 4.47. Found: C 72.82, H 5.44, N 4.45%.

*(4-tert-Butyl-phenyl)-(1-cyclopropyl-3-but-enyl)-amine (**3c**)*

(TLC, Pet-ether/EtOAc, 1:1, $Rf = 0.6$), Thick liquid. 1H-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 0.330.35$ (m, 2H, CH_2), 0.50 (m, 2H, CH_2), 1.09 (m, 1H, CH), 1.29 (s, 9H, t-butyl), 2.44–2.47 (m, 2H, CH_2), 2.95–2.97 (m, 1H, CH),

3.5 (bs, 1H, NH), 5.12 (m, 2H, CH_2), 5.97–5.99 (m, 1H, CH), 6.60–6.62 (d, 2H, $J = 8$ Hz, Ar-H),7.237.24 (d, 2H, $J = 8$ Hz, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 2.6$, 3.40, 16, 31.6, 39.7, 56.8, 113, 117, 125.9, 135.2, 139.9, 145.4. LCMS (95%, Method; 0.1% HCOOH; ACN, Flow 1 ml/min, Column C 18 75 × 4.6 mm 5 µm, RT = 4.1 min, $m/z = 244$ [M+H]+). Anal. Calc. for $C_{17}H_{25}N$;C 83.95, H 10.29, N 5.76. Found: C 83.97, H 10.26, N 5.75%.

*[1-(2,4-Difluorophenyl)-but-3-enyl]-(2,4,5-trifluoro-phenyl)-amine (**3d**)*

(TLC, Petether/EtOAc, 1:1, $Rf = 0.4$), Thick liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 2.47$–2.2.63 (m,2H, CH_2), 4.13–4.26 (m, 2H, 2CH), 5.20–5.24 (m, 2H, CH_2), 5.70–5.77 (m, 1H, CH), 6.11–6.5 (m, 1H, Ar-H), 6.84–6.88 (m, 1H, Ar-H), 7.09-7.73 (m, 3H, Ar-H). 13C-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 42.9$, 56.5, 101, 104, 115, 117, 119, 122, 132, 139, 139.7, 144, 147, 150. LCMS (94.6%, Method; 0.1% HCOOH; ACN, Flow 0.8 ml/min, Column C 18 75 × 4.6 mm 5 µm, RT = 3.8 min, $m/z = 312$ [M−H]). Anal. Calc. for C16H12F5 N;C 61.34, H 3.83, N4.47. Found: C 61.33, H 3.84, N 4.45%.

*(1-Benzofuran-2-yl-but-3-eny)-napthalen-1-yl-amine (**3e**)*

(TLC, Pet-ether/EtOAc, 1:1, $Rf = 0.5$), Thick liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 2.93$ (t, 2H, $J = 8$ Hz, CH_2), 4.90 (t, 1H, $J = 4$ Hz, CH), 5.35 (m, 2H, CH_2), 5.94 (m, 1H, CH), 6.64 (m, 1H, Ar-H), 7.23–7.29 (m, 2H, Ar-H), 7.44–7.50 (m, 5H, Ar-H), 7.8(m, 1H, Ar-H), 7.90 (m, 1H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 39.2$, 51.69, 102, 106, 111, 118, 119, 120, 123, 124, 125.2, 126, 128, 133, 134, 154.3, 158. Anal. Calc. for $C_{22}H_{19}NO$; C 84.35, H 6.07, N 4.47. Found: C 84.32, H 6.06, N 4.46%.

*(4-tert-Butyl-phenyl)-[1-(2, 4-difluoro-phenyl)-but-3-eny]-amine (**3f**)*

(TLC, Pet-ether/EtOAc, 1:1, $Rf = 0.54$), Thick liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 1.36$ (s, 9H, t-butyl), 2.52 (m, 2H, CH_2), 4.35 (q, 1H, $J = 8$ Hz, CH), 5.29 (m, 2H, CH_2), 6.02 (m, 1H, Ar-H), 6.52 (d, 2H, $J = 8$ Hz, Ar-H), 7.18–7.23 (m, 4H, Ar-H), 7.32 (m, 1H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 31.6$, 33.7, 43.3, 56.77, 113, 115, 117, 118, 122, 125, 134, 140, 141, 144, 150. LCMS (90%, Method; 0.1% HCOOH; ACN, Flow 0.8 ml/min, Column C 18 75 × 4.6 mm 5 µm, RT = 4.3 min, $m/z = 316$ [M+H]+). Anal. Calc. for $C_{20}H_{23}F_2N$; C 76.19, H 7.30, N 4.44. Found: C 76.16, H 7.28, N 4.42%.

*[1-(2-Fluoro-6-methoxy-phenyl)-but-3-enyl]-(3-fluorophenyl)-amine (**3g**)*

(TLC, Petether/EtOAc, 1:1, $Rf = 0.7$), Thick liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 2.4$ (m, 1H, CH_2), 2.5 (m, 1H, CH_2), 3.6 (s, 3H, –OCH_3), 4.59 (t, 1H, $J = 4$ Hz, CH), 5.1 (m, 2H, CH_2), 5.6 (m, 1H, CH), 6.1 (dd, 1H, $J = 4$ Hz, Ar-H), 6.39 (m, 2H, Ar-H), 6.6 (m, 1H, Ar-H), 6.7 (m, 1H, Ar-H), 6.9 (m, 2H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 40.9$, 51.2, 55.8, 100.2, 104.4, 112.8, 113, 115, 116, 127, 128, 130, 133, 148, 152. LCMS (90%, Method; 0.1% HCOOH; ACN, Flow 0.8 ml/min, Column C 18 75 × 4.6 mm 5 µm, RT = 3.5 min, $m/z = 290$ [M+H]+). Anal. Calc. for $C_{17}H_{17}F_2NO$; C 70.59, H 5.88, N 4.84. Found: C 70.60, H 5.85, N 4.83%.

*(1-Cyclopropyl-but-3-enyl)-(4-fluoro-3-trifluoromethyl-phenyl)-amine (**3h**)*

(TLC, Petether/EtOAc, 1:1, $Rf = 0.8$), Thick liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 0.33$–0.35 (m, 2H, CH_2), 0.50 (m, 2H, CH_2), 2.4 (q, 2H, $J = 8$ Hz, CH), 2.9 (q, 1H, $J = 8$ Hz, CH), 5.2 (m, 2H, CH_2), 5.9 (m, 1H, CH), 6.68 (t, 1H, $J = 4$ Hz, Ar-H), 6.76 (t, 1H, $J = 4$ Hz, Ar-H), 7.0 (m, 1H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 2.8$, 3.1, 15.8, 39.3, 57, 110, 117.2, 118, 118.5, 121.5, 134, 144, 153. LCMS (93.5%, Method; 0.1% HCOOH; ACN, Flow 1.0 ml/min, Column C 18 75 × 4.6 mm 5 µm, RT = 1.9 min, $m/z = 272$ [M–H]). Anal. Calc. for $C_{14}H_{15}F_4N$; C 61.54, H 5.49,N 5.13. Found: C 61.57, H 5.47, N 5.11%.

*(1-Cyclohexyl-but-3-enyl)-(4-morpholin-4-yl-phenyl)-amine (**3i**)*

(TLC, Pet-ether/EtOAc, 1:1, $Rf = 0.3$), Thick liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 1.0$–1.32 (m, 4H, $2CH_2$), 1.5 (m, 2H, CH_2), 1.6–1.8 (m, 5H, CH_2), 2.2 (m, 2H, CH_2), 2.95–3.3 (bs, 4H, –NCH_2), 3.75 (m, 4H, –OCH_2), 5.2 (m, 2H, CH_2), 5.75 (m, 1H, CH), 6.5–7.0 (bs, 4H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 26.8$, 29.5, 35.6, 41.2, 51.0, 58.2, 68.9, 114.1, 116, 118, 128, 129, 142. LCMS (96%, Method; 0.1% HCOOH; ACN, Flow 0.8 ml/min, Column C 18 75 × 4.6 mm 5 µm, RT = 3.9 min, m/z = 315 [M+H]+). Anal. Calc. for $C_{20}H_{30}N_2O$; C 76.43, H 9.55, N 8.92. Found: C76.41, H 9.54, N 8.91%.

*(1-Cyclohexyl-but-3-enyl)-(2,5-dimethyl-phenyl)-amine (**3j**)*

(TLC, Pet-ether/EtOAc, 1:1, $Rf = 0.5$), Thick liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 1.1$–1.3 (m, 5H,

CH_2), 1.7 (m, 1H, CH_2), 1.75 (m, 1H, CH_2), 1.82 (m, 3H, CH_2), 1.92 (d, 1H, $J = 12$ Hz, CH_2), 2.15 (s, 3H, Ar-CH_3), 2.3 (m, 1H, CH_2), 2.35 (s, 3H, Ar-CH_3), 2.42 (m, 1H, CH_2), 3.9 (q, 1H, $J = 4$ Hz, CH), 5.12(m, 2H, CH_2), 5.8 (m, 1H, CH), 6.48 (d, 2H, $J = 8$ Hz, Ar-H), 6.97 (d, 1H, $J = 8$ Hz, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 17.2$, 21.7, 26.5, 26.7, 29.5, 35.8, 41.2, 57.0, 110.8, 116.4, 117.1, 117.5, 130.2, 135.2, 135.7, 136.6. LCMS (96%, Method; 0.1% HCOOH; ACN, Flow 0.8 ml/min, Column C 18 75 × 4.6 mm 5 μm, RT = 3.9 min, $m/z = 258$ [M+H]+). Anal. Calc. for $C_{18}H_{27}N$; C 84.05, H 10.51, N 5.45. Found: C 84.02, H 10.50, N 5.43%.

*[1-(2-Allyloxy-phenyl)-but-3-enyl]-[4-(4-chloro-phenoxy)-phenyl]-amine (**3k**)*

(TLC, Petether/EtOAc, 1:1, $Rf = 0.5$), Thick liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 2.55$ (m, 1H, CH_2), 2.75 (m, 1H, CH_2), 4.3 (bs, 1H, NH), 4.68 (t, 2H, $J = 4$ Hz, –OCH_2), 5.3 (m, 1H, CH), 5.36–5.39 (m, 2H, CH_2), 5.51 (d, 1H, $J = 16$ Hz, CH), 5.84 (d, 1H, $J = 13.6$ Hz, CH_2), 5.9 (m, 1H, CH), 6.13–6.20 (m, 1H, Ar-H), 6.54 (d, 2H, $J = 12$ Hz, CH), 6.82–6.9 (m, 4H, Ar-H), 6.9 (m, 2H, Ar-H), 7.2 (m, 3H, Ar-H), 7.39 (d, 1H, $J = 8$ Hz, Ar-H). ^{13}C-NMR (400 M Hz, $CDCl_3$, 24°C): $\delta = 40.6$, 52.0, 68.5, 11.6, 114.2, 117.0, 117.6, 118.2, 120.8, 123, 126.5, 127.1, 127.7, 130.2, 130, 133.2, 135.2, 144.2, 147.0, 155.6, 157.7. LCMS (98%, Method; 0.1% HCOOH; ACN, Flow 1.0 ml/min, Column C 18 75 × 4.6 mm 5 μm, RT = 2.6 min, m/z = 406 [M+H]+). Anal. Calc. for $C_{25}H_{24}ClNO_2$; C 73.98, H 5.92, N 3.45. Found: C 73.97, H 5.90, N3.44%.

*[4-(4-Chloro-phenoxy)-phenyl]-{1-[5-(2-chloro-phenyl)-furan-2-yl]-but-3-enyl}-amine (**3l**)*

(TLC, Pet-ether/EtOAc, 1:1, $Rf = 0.5$), Thick liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 2.7$ (bs, 2H, CH_2), 4.50 (t, 1H, $J = 4$ Hz, CH), 5.0 (m, 2H, CH_2), 5.6 (m, 1H, CH), 6.25 (s, 1H, Ar-H), 6.76 (m, 2H, Ar-H), 7.16 (m, 4H, Ar-H), 7.18 (d, 1H, $J = 4$ Hz, Ar-H), 7.23 (m, 3H, Ar-H), 7.3 (m, 1H, Ar-H), 7.35 (d, 1H, $J = 4$ Hz, Ar-H), 773 (d, 1H, $J = 4$ Hz, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 40$, 60, 100, 111.6, 118.5, 118.8, 120, 126, 127.6, 127.9, 129, 129.4, 130.7, 133.5, 144.5, 149, 150, 157. Anal. Calc. for $C_{26}H_{21}Cl_2NO_2$; C 69.33, H 4.67, N 3.11. Found: C 69.34, H 4.65, N 3.10%.

*1-{3-[1-(Benzothiazol-7-ylamino)-but-3-enyl]-indol-1-yl}-ethanone (**3m**)*

(TLC, Petether/EtOAc, 1:1, $Rf = 0.2$), Thick liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 2.5$ (s, 1H, CH_3), 2.72 (m, 1H, CH_2), 2.88 (m, 1H, CH_2), 4.78 (q, 1H, $J = 4$ Hz, CH), 5.26 (m, 2H, CH_2), 5.85 (m, 1H, CH), 6.87 (d, 1H, $J = 8$ Hz, Ar-H), 7.0 (s, 1H, Ar-H), 7.27–7.41 (m, 3H, Ar-H), 7.7 (m, 1H, Ar-H), 7.89 (d, 2H, $J = 8$ Hz, Ar-H), 8.46 (bs, 1H, NH), 8.67 (s, 1H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 26.9$, 40.4, 50.4, 103.8, 105, 105.7, 115.1, 117.0, 118.9, 122.5, 123.6, 123.7, 123.8, 125.5, 128, 134, 135.7, 136.6, 145.6, 146.1, 168.6.LCMS (76%, Method; 0.1% HCOOH; ACN, Flow 1.0 ml/min, Column C 18 75 × 4.6 mm 5 μm, RT = 3.7 min, $m/z = 362$ [M+H]+). Anal. Calc. for $C_{21}H_{19}N_3OS$: C 69.81, H 5.26, N 11.63. Found: C 69.79, H 5.25, N 11.60%.

*(2, 4-Difluoro-phenyl)-[1-(2,4-difluoro-phenyl)-but-3-enyl]-amine (**3n**)*

(TLC, Petether/EtOAc, 1:1, $Rf = 0.6$), Thick liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, 24°C), $\delta = 2.5$–2.6 (m, 2H, CH_2), 4.3 (bs, 1H, NH), 4.69 (m, 1H, CH), 5.24 (m, 2H, CH_2), 5.74 (m, 1H, CH), 6.34 (m, 1H, Ar-H), 6.59 (m, 1H, Ar-H), 6.64–6.87 (m, 3H, Ar-H), 7.3 (m, 1H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 41.2$, 50.7, 103, 110, 11.4, 112.9, 119.0, 125.2, 128.5, 131.6, 133.4, 149.6, 152.1, 153.3, 155.6, 160.7 LCMS (94.7%, Method; 0.1% HCOOH; ACN, Flow 0.8 ml/min, Column C 18 75 × 4.6 mm 5 μm, RT = 3.9 min, $m/z = 295.9$ [M+H]+). Anal. Calc. for $C_{16}H_{13}F_4N$; C 65.08, H 4.41, N4.75. Found: C 65.10, H 4.39, N 4.73%.

*(4-Chloro-2-fluoro-phenyl)-[1-(2,6-difluoro-phenyl)-but-3-enyl]-amine (**3o**)*

(TLC, Petether/EtOAc, 1:1, $Rf = 0.65$), White Solid; m.p. 126-127°C. ^{1}H-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 2.72$ (m, 1H, CH_2), 2.87 (m, 1H, CH), 4.95 (m, 1H, CH), 5.28 (m, 1H, CH_2), 5.71 (m, 2H, CH_2, NH), 5.81(m, 1H, CH), 6.68 (m, 1H, Ar-H), 6.8–6.9 (m, 4H, Ar-H), 7.2 (m, 1H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$): $\delta = 39.5$, 48.3, 111.6, 113.0, 115.3, 117.5, 118.3, 121.2, 124.4, 128.9, 129.0, 133.7, 152, 160, 162.5. LCMS (99.5%, Method; 0.1% HCOOH; ACN, Flow 0.8 ml/min, Column C 18 75 × 4.6 mm 5 μm, RT = 4.2 min, $m/z = 311.9$ [M+H]+). Anal.Calc. for $C_{16}H_{13}ClF_3N$: C 61.64, H 4.17, N 4.49. Found: C 61.61, H 4.14, N 4.47%.

*4-(1-Thiophen-2-yl-butylamino)-benzonitrile (**3p**)*

(TLC, Pet-ether/EtOAc, 1:1, $Rf = 0.5$), Thick liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 2.7$ (m, 2H, CH_2), 4.77 (m, 1H, CH), 5.2 (m, 2H, CH_2), 5.7 (m, 1H, CH), 6.56 (d, 2H, $J = 8$.Hz, Ar-H), 6.97 (d, 2H, $J = 4$ Hz, Ar-H), 7.20 (d, 1H, $J = 4$ Hz, Ar-H), 7.38 (d, 2H, $J = 8$ Hz, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$): $\delta = 42.6$, 52.7, 99.4,

113.1, 119.3, 120.3, 124.0, 124.4, 127.0, 133.3, 133., 146.6, 150.1. LCMS (96.0%, Method; 0.1% HCOOH; ACN, Flow 0.8 ml/min, Column C 18 75 × 4.6 mm 5 μm, RT = 2.6 min, $m/z = 355$ [M+H]+). Anal. Calc. for $C_{15}H_{14}N_2S$; C 70.87, H 5.51, N 11.02. Found: C 70.85, H 5.50, N 11.01%.

*[1-(3-Chloro-phenyl)-but-enyl]-(3-ethoxy-phenyl)-amine (**3q**)*

(TLC, Pet-ether/EtOAc, 1:1, $Rf = 0.56$), Thick liquid ^{1}H-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 1.43$ (t, 3H, $J =$ 6.8 Hz, CH_3), 2.5 (m, 2H, CH_2), 4.04 (m, 2H, –OCH_2), 4.3 (bs, 1H, NH), 4.35 (m, 1H, CH), 5.2 (m, 2H, CH_2), 5.8 (m, 1H, CH), 6.37 (q, 1H, $J = 5.6$ Hz, Ar-H), 6.62 (d, 1H, $J = 8$ Hz, Ar-H), 6.64 (m, 1H, Ar-H), 6.79 (m, 1H, Ar-H), 6.8–7.0 (m, 3H, Ar-H), 7.26 (m, 1H, Ar-H). ^{13}C-NMR (400 MHz, $CDCl_3$, 24°C): $\delta = 15.8$, 43.0, 56.9, 63.4, 111.6, 112.5, 112.7, 117.32, 118.5, 129.7, 134.3, 134.7, 144.6, 148.4, 148.4, 159.3. LCMS (95.8%, Method; 0.1% HCOOH; ACN, Flow 1.0 ml/min, Column C 18 75 × 4.6 mm 5 μm, RT = 4.0 min, $m/z = 302$ [M+H]+). Anal. Calc. for $C_{18}H_{20}ClNO$: C 71.64, H 6.63, N 4.64. Found: C 71.65, H 6.61, N 4.61%.

Conclusions

This article describes a convenient and efficient process for the synthesis of homoallylic amines though a three components coupling of various aldehydes and amines with allyltributyltin in the presence of catalytic amount of CF_3COOH. In addition to its simplicity, efficiency, and mild reaction conditions, this method provides high to excellent yields of products in a short period which makes it a useful and attractive process for the synthesis of homoallylic amines of synthetic importance. Newly synthesized compounds were characterized by 1H-NMR, 13C-NMR, Mass spectrometry, IR studies, and elemental analyses. Compound **3o** was analyzed for its molecular structure by single crystal X-ray crystallography. All the newly synthesized compounds were screened for antibacterial activity by MIC method. Among the screened samples, **3a**, **3i**, **3j**, **3k**, **3m**, and **3p** have showed very poor antibacterial property against all bacterial strains. Compounds **3d**, **3g**, **3n**, and **3o** have showed excellent antibacterial activity at 1.6125 μg/ml concentration against all microorganisms as compared to the standard drug Ceftriaxone. Interestingly, all the above four biologically active molecules are halogen substituted, which is accounted for their significant antibacterial activity. Compound **3h** which is also trifluoro substituted is active against *S. aureus* and *B. subtilis*, however, which has not showed any activity against other two bacterial strains. Remaining compounds showed moderate antibacterial activity.

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