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Short Note

Efficient synthesis of novel 3,4,5-triarylisoxazole derivatives and its antifungal activity studies

Rajesha Shetty [a,*], *Syed Shafi* [b], *Yuvaraja Kuberan* [c]

[a] *Sr. Research Scientist, Syngene International Ltd, Biocon Group Company, Bangalore, Karnataka, India*
[b] *Professor and Head, Department of Chemistry, Thiruvallur University, Vellore, Tamilnadu, India*
[c] *Research Scholar, Department of Chemistry, Thiruvallur University, Vellore, Tamilnadu, India*

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ABSTRACT

Novel 3,4,5-triarylisoxazole derivatives were synthesised by Suzuki reaction of 4-bromo-3,5-diaryl isoxazoles with various boronic acid under microwave condition. The structures of the newly synthesised compounds are characterised by ^{1}H NMR, ^{13}C NMR, LC-MS and screened for their antifungal activity against *Aspergillus flavus* (NCIM No. 524), *Fusarium oxysporum* (NCIM No. 1072) and *Candida albicans* (NCIM No. 3102).

1. Introduction

Nitrogen containing heterocyclic compounds – especially isoxazole and its derivatives are broad spectrum of biologically active such as antimicrobial agents,[1] anti-inflammatory,[2] antifungal,[3] herbicidal,[4] antiviral,[5] analgesic, antitumour, cytotoxic, antipyretic and obesity.[6] We report in the present work the synthesis and biological activity of novel triarylisoxazole derivatives.

2. Chemistry

The required triarylisoxazole derivatives prepared from 2,4-difluorobenzaldehyde (1) in 5 steps. 2,4-dfluorobenazldehde was converted to corresponding oxime (2) by treating with hydroxylamine HCL, which on treatment with bromine and styrene yielded 3,5-diarylisoxazoline (3). 3,5-diarylisoxazoline was oxidised to corresponding isoxazole (4) by treating with NBS in carbon tetrachloride, which further brominated to 4-bromo-3,5-diarylisoxazole (5) by reacting with NBS in acetic acid at 120 °C. In the final step various boronic acids were coupled with 4-bromo-3,5-diarylisoxazole derivative using Suzuki condition and microwave irradiation to afford 3,4,5-triarylisoxazole (6) derivatives [Scheme 1]. The obtained yields of final compounds are mentioned in Table 1.

3. Experimental

All reagents were purchased from Aldrich and used as received. Dry THF, Ethanol, Toluene were supplied by

* *Corresponding author*. Tel.: +91 9845273314.
E-mail address: rjsh_shetty@rediffmail.com (R. Shetty).

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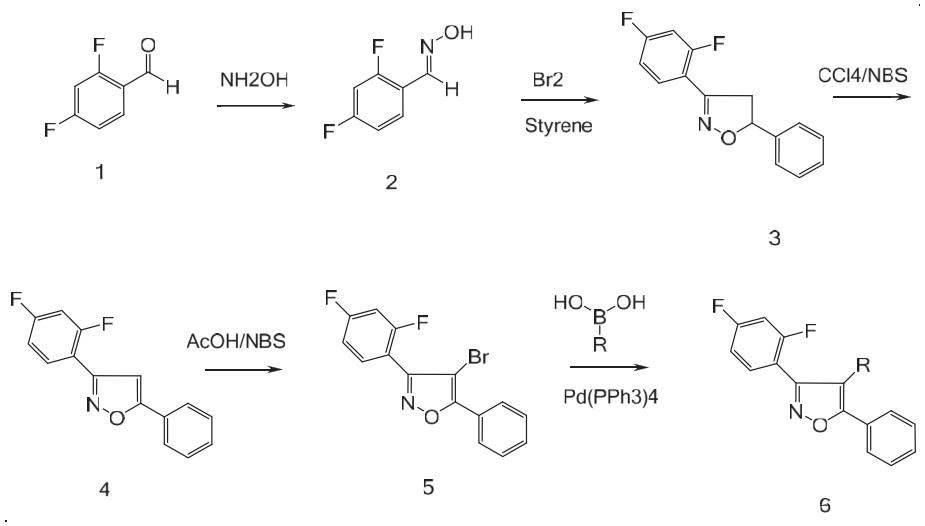

Scheme 1 – Synthesis of 3,4,5-triarylisoxazoles.

Spectrochem. All chemistry was performed under a nitrogen atmosphere using standard techniques. All the NMR spectra were measured using either Bruker AMX 400 instrument with 5 mm PABBO BB-1H tubes. 1H and 13C NMR spectra were measured for approximately 0.03 M solutions in d6-DMSO at 400 MHz with TMS as internal reference. The IR spectra were measured as potassium bromide pellets using a Perkin–Elmer 1600 series FTIR spectrometer. LCMS were obtained using Agilent 1200 series LC and Micro mass zQ spectrometer. Column chromatography was performed using a silica gel (230–400 mesh).

3.1. *2,4-Difluorobenzaldheyde oxime (2)*

To a solution of 2,4-difuororbenzaldehyde (25.0 g, 176.05 mmol) in THF/Water (1:1, 400 mL) was added $NaHCO_3$ (29.5 g, 351.19 mmol) in one lot. Hydroxylamine hydrochloride[7] (24.5 g, 352 mmol) was added portion wise and then RM was stirred at RT for 2 h. RM was diluted with diethyl ether (200 mL) and the organic layer was separated, washed with water and saturated brine solution, dried over Na_2SO_4, evaporated under reduced pressure. Yield of the product was 26.0 g (94%) as white solid. M. pt: 127.9–129.2 °C. Mol. Wt: 157.12; LCMS: 158.3(M^++1). ^{1}H NMR (CDCl3, 300 MHz) δ 8.33(s, 1H), 7.69(m, 1H), 6.89(m, 2H). ^{13}C NMR (CDCl3, 300 MHz): 165.6, 162.77, 159.2, 143.5, 128.2, 116.18, 112.26, 104.65.

3.2. *3-(2,4-Difluorphenyl)-5-phenyl-4,5-dihydroisoxazole (3)*

To a solution of 2,4-difluorobezaldehyde oxime (25.0 g, 159.23 mmol) in dichloromethane/aqueous 10% $NaHCO_3$ (3:2, 500 mL), was added bromine[8] (25.5 g, 159.37 mmol) drop wise at 0 °C. Once the bromine colour disappeared, styrene was added at 0 °C and then the RM was stirred at RT for 12 h. The organic layer was separated, washed with saturated brine solution, dried over Na_2SO_4, evaporated under reduced pressure. Crude product was triturated with petroleum ether; solid obtained was filtered and dried. Yield of the product was 36.0 g (87.3%) as white solid. M. pt: 66.6–67.7 °C. Mol. Wt: 259.25, LCMS: 260.1 (M+1). ^{1}H NMR (CDCl3, 400 MHz); δ 7.92(m, 1H), 7.36(m, 5H), 6.97(m, 1H), 6.89(m, 1H), 5.76(q, J = 5.26 Hz 1H), 3.85(m, 1H), 3.45 (m, 1H). ^{13}C NMR (CDCl3, 300 MHz): 165.6, 162.77, 159.2, 152.16, 140.59, 130.33, 128.77, 125.86, 112.34, 104.66, 82.86, 44.63.

3.3. *3-(2,4-Difluorophenyl)-5-phenylisoxazole (4)*

To the solution of 3-(2,4-difluorophenyl)-5-phenyl-4,5-dihydroisoxazole (25.0 g, 96.52 mmol) in carbon tetrachloride (300 mL) was added N-bromosuccinimide[9] (25.0 g, 140.45 mmol), in one lot at RT and then reaction mass was heated to 80 °C for 5 h. RM was cooled to RT, washed with water, saturated brine solution, dried over Na_2SO_4, and evaporated under reduced pressure. Crude product was triturated with cold petroleum ether; solid obtained was filtered and dried. Yield of the product was 20.0 g (80.6%) as white solid. M. pt: 103.4–104.8 °C. Mol. Wt: 257.23, LCMS: 258.1(M+1). ^{1}H NMR (CDCl3, 400 MHz); δ 8.12(m, 1H), 7.86(m, 2H), 7.47(m, 3H), 6.97(m, 3H). ^{13}C NMR (CDCl3, 300 MHz): 170.42, 165.6, 162.77, 15752, 130.26, 128.11, 127.22, 125.78, 112.3, 104.9, 99.61.

3.4. *4-Bromo-3-(2,4-difluorophenyl)-5-phenylisoxazole (5)*

To the solution of 3-(2,4-difluorophenyl)-5-phenylisoxazole (20.0 g, 77.82 mmol) in glacial acetic acid (200 mL) was added N-bromosuccinimide[10] (16.6 g, 93.25 mmol), in one lot at RT and then reaction mass was heated to 100 °C for 16 h. RM was cooled to RT and acetic acid was removed under reduced