

Chemistry & Biology Interface

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Research Paper

An Efficient Synthetic route for new pyrazoles bearing thiazolyl moieties

Prashant D. Netankar, Dinesh L. Lingampalle, Vasant B. Jagrut, Dhanaji V. Jawale and Ramrao A. Mane*

*Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004 India.

Received 22 May 2012; Accepted 24 June 2012

Keywords: Pyrazole, Thiosemicarbazide, PEG-400, Molecular sieves.

Abstract: An efficient synthetic protocol for the synthesis of new 1-((1-phenyl-3-aryl-1*H*-pyrazol-4-yl)methylene))-2-(4-arylthiazol-2-yl)hydrazines (5a-j) has been developed using 4-formyl pyrazoles as precursors. The route provides simple work up and gives better yields of the intermediates and the titled products.

Introduction

Thiazoles are well explored as therapeutic agents. The medicaments namely Famotidine,^[1] Pramipexole,^[2] Fentizac,^[3] Niridazole,^[4] and Clomethiazole^[5] are having thiazole ring system as a scaffold. Pyrazole is a class of heterocyclic compounds possessing significant pharmacological activities including anticancer, antitubercular, anticonvulsant, antiamoebic, antimicrobial, anti-inflammatory, antiviral, antiarrhythmic, antidepressant, antidiabetic, analgesic, antipyretic, muscle relaxant, and hypertensive.^[6-23] It is also revealed that there is scanty information on the synthesis of molecules having thiazolyl and pyrazolyl nuclei bridged by active pharmacophores.

Keeping this scope in mind and in continuation with our earlier interest^[24-27] in synthesizing new bioactive heterocycles, it was therefore planned to synthesize the titled new 1-((1-phenyl-3-aryl-1*H*-pyrazol-4-yl)methylene)-2-(4-aryl thiazol-2-yl)hydrazines with hope to obtain the molecules with intensified activities.

Results and discussion

Attempts were made to synthesize the target heterocycles from readily available precursors. Efforts were directed to carry the cyclocondensations, used for building the thiazole / pyrazole system. While optimizing the synthetic route, we acrossed some difficulties in synthesizing the titled compounds from freshly prepared 4-formyl substituted pyrazoles^[28]. In one of the attempts thiosemicarbazide was condensed with phenacyl chlorides following Hantzsch

method and the obtained intermediates were then separately condensed with substituted 4-formyl pyrazoles. It was noticed that by this route the products obtained were found to be the titled 1-((1-phenyl-3-aryl-1H-pyrazol-4-yl)methylene))-2-(4-arylthiazol-2-yl)hydrazines (Scheme 2). It was recorded that this route requires longer time and for completion of the two steps the reactions have to be run at refluxed conditions.

To modify this route and to make it more convenient in another attempt, first the 4-formyl pyrazoles **1** were subjected with thiosemicarbazide **2** in ethanol at 70 °C in the presence of activated molecular sieves. It was noticed that the condensation was completed within one hour, resulting into intermediates, 1-((1-phenyl-3-aryl-1H-pyrazol-4-yl)methylene) thiosemi carbazides (**3a-f**) with good to moderate yields (Scheme 1). The intermediates **3a-f** in subsequent step when cyclocondensed with phenacyl chlorides **4** in PEG-400 at room temperature gave high yields of the titled products, 1-((1-phenyl-3-aryl-1H-pyrazol-4-yl)methylene))-2-(4-arylthiazol-2-yl)hydrazines **5a-j** (Scheme 2). The cyclocondensation was found to be completed within 4-5 hr.

The modified route has been found to be more convenient as it has following advantages, i) reaction is relatively rapid, ii) gives better yields of intermediates and products, iii) medium and molecular sieves are recyclable and iv) needs simple workup in isolating the products.

Experimental

IR spectra were recorded on Jasco FTIR using KBr disc. ¹H NMR spectra were scanned on Bruker Advance II FT at 400 MHz using TMS as internal standard. Chemical shifts are expressed in δppm, DMSO *d*₆ was used as a medium. Mass

spectra were recorded on JEOL SX 102 / DA-600 mass spectrometer. Elemental analyses were performed on CHNS auto analyzer, Thermo Finnigan. Melting points of all the compounds were determined by open capillary method and are uncorrected. The purity of intermediates and final products were confirmed by chromatographic technique and the structures were established and confirmed using the spectral and elemental data.

General procedure for the Synthesis of 1-((1-phenyl-3-aryl-1H-pyrazol-4-yl)methylene) thiosemicarbazides (**3a-f**).

1-Phenyl-3-aryl-1H-pyrazole-4-carbaldehydes (0.025 mole), thiosemicarbazide (0.025 mole) and activated molecular sieves of size 4 Å⁰ (3 g) were refluxed in dry ethanol (25 ml) for 1hr. The progress of the reaction was monitored by TLC. On the completion of the reaction, the hot reaction mass was filtered and ethanol was removed from the filtrate by vacuum distillation. The residual mass was poured in ice cold water. The separated solid product was filtered, dried and crystallized from ethanol. The physical parameters of the products are incorporated in Table 1.

Spectral data of the intermediates (3)

Compound 3a: IR (KBr, cm⁻¹): 3330 (NH₂ asymmetric stretching), 3257 (NH₂ symmetric stretching), 3149 (CH aromatic stretching), 1662 (C=N) and 1101 (C-N stretching). ¹H NMR (400 MHz, DMSO- *d*₆, δ ppm): 7.35 to 7.90 (m, 12 H, ArH and NH₂), 8.22 (s, 1H, pyrazolyl-H), 9.17 (s, 1H, -CH=N-) and 11.31 (s, 1H, NH, exchangeable with D₂O). MS (Scanning mode ES⁺): m/z 322 (M⁺).

Compound 3b: IR (KBr, cm⁻¹): 3322 (NH₂ asymmetric stretching), 3218(NH₂ symmetric stretching), 3163 (CH aromatic

stretching), 1647 (C=N) and 1123 (C-N stretching). ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 2.43 (s, 3H, CH_3), 7.31 to 7.85 (m, 11 H, ArH and NH_2), 8.13 (s, 1H, pyrazolyl-H), 8.89 (s, 1H, $-\text{CH}=\text{N}-$) and 10.91 (s, 1 H, NH, exchangeable with D_2O). MS (Scanning mode ES+): m/z 336 (M^+).

Compound 3c: IR (KBr, cm^{-1}): 3341 (NH_2 asymmetric stretching), 3263 (NH_2 symmetric stretching), 3152 (CH aromatic stretching), 1651 (C=N) and 1101 (C-N stretching). ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 3.68 (s, 3H, OCH_3), 7.41 to 7.97 (m, 11 H, ArH and NH_2), 8.13 (s, 1H, pyrazolyl-H), 9.32 (s, 1H, $-\text{CH}=\text{N}-$) and 10.79 (s, 1H, NH, exchangeable with D_2O). MS (Scanning mode ES+): m/z 352 (M^+).

General procedure for the synthesis of Synthesis of 1-((1-phenyl-3-aryl-1H-pyrazol-4-yl)methylene))-2-(4-arylthiazol-2-yl)hydrazines (5a-j).

1-((1-phenyl-3-aryl-1H-pyrazol-4-yl)methylene) thiosemicarbazides (3a-f) (0.01 mole) and phenacyl chlorides (4) (0.01 mole) were dissolved in PEG-400 (15 ml) and the solution was stirred at room temperature for 5 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mass was poured in ice cold water and the separated solid was filtered, dried and crystallized from ethanol. The physical parameters of the products are incorporated in Table 2.

Spectral data of the titled products:

Compound 5a: IR (KBr, cm^{-1}), 3728 (N-H stretching), 3059 (CH aromatic stretching) and 1120 (CN stretching). ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 7.26 to 7.99 (m, 16H, ArH and thiazolyl-H), 8.16 (s, 1H, pyrazolyl-H), 8.87 (s, 1H $-\text{CH}=\text{N}-$) and 11.93 (s, 1H, NH, exchangeable with D_2O). MS (Scanning mode ES+): m/z 422 (M^+).

Compound 5b: IR (KBr, cm^{-1}), 3689 (N-H stretching), 3032 (CH aromatic stretching) 2917 (CH aliphatic stretching) and 1132 (C=N stretching). ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 2.39 (s, 3H, CH_3) 6.92 to 7.53 (m, 13H, ArH and thiazolyl-H), 8.10 (s, 1H, pyrazolyl-H), 8.19(s, 1H $-\text{CH}=\text{N}-$) and 11.21 (s, 1H, NH, exchangeable with D_2O). MS (Scanning mode ES+): m/z 472 (M^+).

Compound 5c: IR (KBr, cm^{-1}), 3666 (N-H stretching), 3030 (CH aromatic stretching) 2956 (CH aliphatic stretching) and 1143 (C=N stretching). ^1H NMR (400 MHz, DMSO- d_6 , δ ppm) 3.82 (s, 3H, CH_3), 6.92 to 7.53 (m, 13H, ArH and thiazolyl-H), 8.10 (s, 1H, pyrazolyl-H), 8.19 (s, 1H $-\text{CH}=\text{N}-$) and 11.21 (s, 1H, NH, exchangeable with D_2O). MS (Scanning mode ES+): m/z 488 (M^+).

Compound 5d: IR (KBr, cm^{-1}), 3597 (N-H stretching), 3112 (OH Aromatic) 3047 (CH aromatic stretching) 2976 (CH aliphatic stretching) and 1137 (C=N stretching). ^1H NMR (400 MHz, DMSO- d_6 , δ ppm) 6.8 to 7.65 (m, 13H, ArH and thiazolyl-H), 8.31 (s, 1H, pyrazolyl-H), 8.1 (s, 1H $-\text{CH}=\text{N}-$), 9.43 (bs, 1H, $-\text{OH}$) and 10.90 (s, 1H, NH, exchangeable with D_2O). MS (Scanning mode ES+): m/z 474 (M^+).

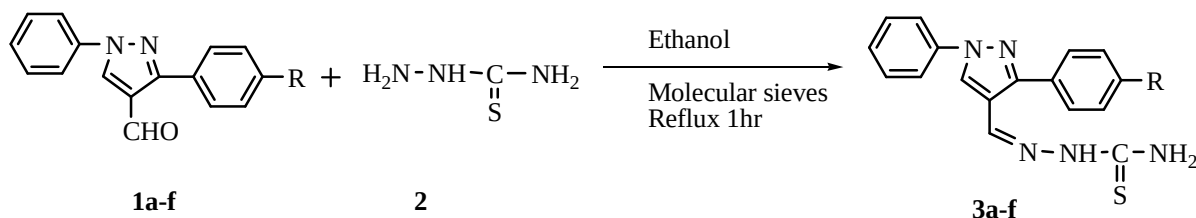
Compound 5e: IR (KBr, cm^{-1}), 3612 (N-H stretching), 3023 (CH aromatic stretching) 2964 (CH aliphatic stretching) and 1145 (C=N stretching). ^1H NMR (400 MHz, DMSO- d_6 , δ ppm) 2.41 (s, 3H, $-\text{CH}_3$), 3.35 (s, 3H, $-\text{SO}_2\text{CH}_3$) 6.9 to 7.95 (m, 14H, ArH and thiazolyl-H), 8.43 (s, 1 H, pyrazolyl-H), 8.17 (s, 1 H $-\text{CH}=\text{N}-$), and 11.10 (s, 1H, NH, exchangeable with D_2O). MS (Scanning mode ES+): m/z 514 (M^+).

Conclusion

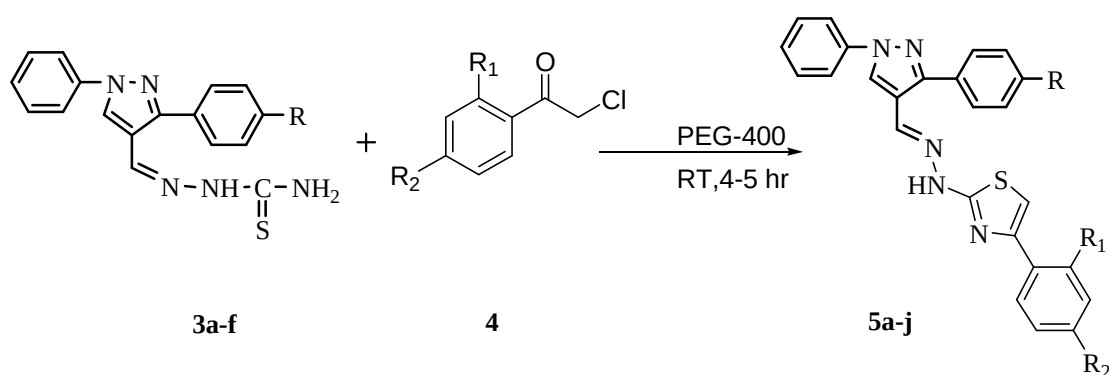
A convenient synthetic route has been developed for the synthesis of new pyrazoles

bearing thiazolyl moieties. Condensation of formyl pyrazoles with thiosemicarbazide is carried in ethyl alcohol in the presence of activated molecular sieves. The use of PEG-

400 to promote the cyclocondensation leading to thiazoles has been well explored. The developed route is simple and high yielding.



Scheme I Synthesis of 1-((1-phenyl-3-aryl-1H-pyrazol-4-yl)methylene) thiosemicarbazides (**3a-f**).



Scheme II Synthesis of 1-((1-phenyl-3-aryl-1H-pyrazol-4-yl)methylene))-2-(4-arylthiazol-2-)hydrazines (**5a-j**)

Table II: Physical parameters of compounds **3a-f**

Entry	R	Time (min)	Yields ^a (%)	M.P. (°C)
3a	H	50	91	209-211
3b	CH ₃	50	92	180-183
3c	OCH ₃	65	89	181-183
3d	OH	55	88	213-215
3e	NO ₂	40	87	274-276
3f	F	55	88	211-213

^aIsolated yields

Table II: Physical data of Compounds **5a-j**

Entry	R	R ₁	R ₂	Time (hr)	Yields ^a (%)	M.P. (°C)
5a	H	H	H	4.15	85	92-94
5b	CH ₃	F	F	4.30	84	150-152

5c	OCH ₃	F	F	5.00	87	147-149
5d	OH	F	F	4.40	89	167-169
5e	CH ₃	H	SO ₂ CH ₃	4.45	79	211-213
5f	F	F	F	4.50	85	130-132
5g	NO ₂	F	F	4.15	81	156-158
5h	OCH ₃	H	SO ₂ CH ₃	5.00	84	220-221
5i	OH	H	SO ₂ CH ₃	4.30	83	179-180
5j	NO ₂	H	SO ₂ CH ₃	4.50	87	209-211

^aIsolated yields

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