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An efficient regioselective copper catalyzed multi-component synthesis of 1,3-disubstituted pyrazoles

Akula Raghunadh [a,*], Suresh Babu Meruva [a], Ramamohan Mekala [a], K. Raghavendra Rao [a], Thalishetti Krishna [a], R. Gangadhara Chary [a], L. Vaikunta Rao [b], U. K. Syam Kumar [c,*]

[a] Technology Development Centre, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd, Miyapur, Hyderabad 500 049, India
[b] Department of Chemistry, GIS, Gitam University, Visakhapatnam, India
[c] Integrated Product Development, Innovation Plaza, Dr. Reddy's Laboratories Ltd, Batchupally, Hyderabad 500 049, India

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ABSTRACT

An efficient synthesis of unsymmetrically substituted 1,3-pyrazole derivatives has been developed via three-component coupling reaction involving 3-(dimethylamino)-1-phenylprop-2-en-1-one, hydrazine, and aryl halides in one pot process exhibiting high regioselectivity. The pyrazole synthesis proceeds via a sequential series of reactions such as Michael addition, heterocyclization, dehydration, and Ullmann cross-coupling.

Considerable efforts have been made in the recent past both in academia as well as industry for the development of small molecule based drug discovery program. In this small molecule based drug development program, *N*-aryl pyrazole derivatives have been continuously evaluated for their biological properties and thus found wide spread utilization in pharmaceutical and agrochemical industries.[1] Many substituted pyrazole derivatives have found applications in antibacterial, anticonvulsant, analgesic, antimicrobial,[2] anti-inflammatory,[3] anti-diabetic, sedative, antirheumatic, anticancer, and antitubercular drugs,[4] either available or different stages of clinical development. In addition to these, 1,5-diarylpyrazole derivatives exhibit non-nucleoside HIV-1 reverse transcriptase inhibitor activity[5] as well as COX-2 inhibitor activity.[6] Celecoxib (**1**), Sulfaphenazole (**2**), CDPPB (**3**), Linazolac (**4**), Mepiprazole (**5**), and Rimonabant (**6**)[7] are some of the pyrazole based drugs available today in the market (Fig. 1).

Because of varied biological properties of 1,3-disubstituted pyrazole derivatives, number of methodologies have been exemplified in the literature for their synthesis.[8] Most of the syntheses of *N*-arylpyrazole derivatives utilize cyclocondensation of 1,3-dicarbonyl compound and propargylic ketones with *N*-aryl hydrazines.[9] Harrity and co-workers reported the cycloaddition of 4-iodosydnones with terminal alkynes that proceeds with excellent regiochemistry to provide 5-iodopyrazoles.[10] Dissanayake and Odom reported a multicomponent coupling of alkynes with isonitriles, and mono aryl hydrazines catalyzed by $Ti(NMe_2)_2(pypyr)_2$ to provide pyrazoles in excellent yields.[11] Junjappa and co-workers reported the cyclocondensation of aryl hydrazines with either α-oxoketene dithioacetals or β-oxodithioesters for the regioselective synthesis of 1-aryl-3,4-substituted/annulated-5-(methylthio)-pyrazoles and 1-aryl-3-(methylthio)-4,5-substituted/annulated pyrazoles.[12] The tandem amine-exchange/heterocyclization of enaminones is also successfully utilized for the regioselective synthesis of 1,5-diarylpyrazole derivatives.[13] Other notable methodologies employed for the synthesis of *N*-arylpyrazole derivatives include the 1,3-dipolar cycloaddition of (phenylsulfiny1)- and (phenylsulfonyl)alkenes with l-(chlorobenzal)-2-phenylhydrazine,[14] and N-arylation in the presence of copper and iron, as well as $Cu(OAc)_2{\cdot}H_2O$ mediated conditions.[15]

The development of new methodologies for the synthesis of pyrazole derivatives is always in demand. Herein we describe a straight forward novel transition-metal catalyzed multi-component reaction strategy for the regioselective synthesis of 1,3-disubstituted pyrazole derivatives in good to excellent yields. The synthesis of 1,3-disubstituted pyrazole derivatives utilizes enaminone **7**,[16] hydrazine **9**, and aryl halide **8**, the reaction was

* Corresponding authors. Tel.: +91 4044658701 (A.R.).
E-mail address: raghunadha@drreddys.com (A. Raghunadh).

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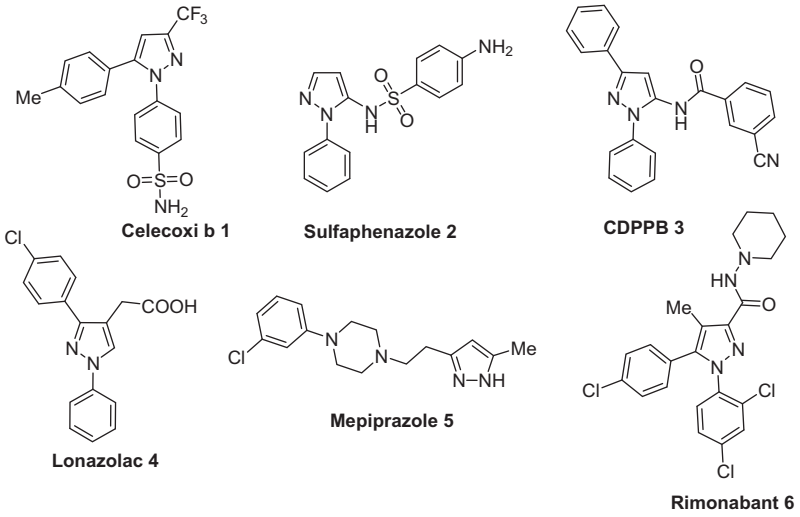
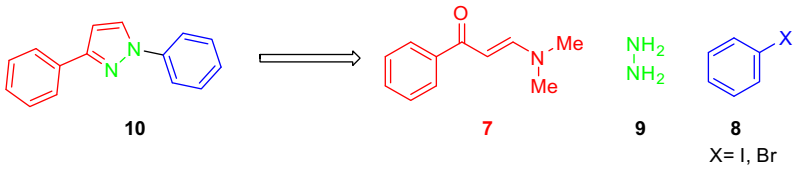
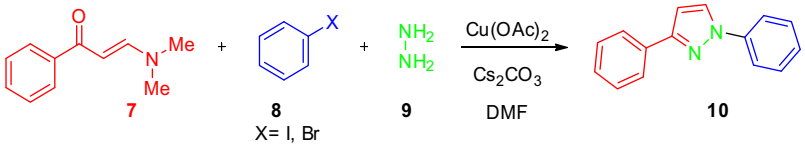


Figure 1. Biologically active pyrazole derivatives.



Scheme 1. Retrosynthesis of **10**.



Scheme 2. One-pot three-component synthesis of 1,3-disubstituted pyrazole.

conveniently carried out in one pot in the presence of Cs_2CO_3 and Cu catalyst in DMF at elevated temperature (Scheme 1).

The retrosynthetic strategy employed for the synthesis of 1,3-disubstituted pyrazoles is depicted in Scheme 1. The pyrazole could be easily obtained by the reaction of enaminone **7** with hydrazine **9** in polar aprotic solvents. The so-formed pyrazole in situ reacts with aryl halide **8** in the presence of Cu(II) catalyst to afford the 1,3-disubstituted pyrazole under Ullmann reaction conditions in a one pot process (see Scheme 2).

The synthesis of 1,3-disubstituted pyrazole derivative was initiated with enaminone **7**, hydrazine hydrate (**9**), and iodobenzene **8** in the presence of copper catalyst and a base. For the identification of suitable copper catalyst as well as base, catalyst screening reactions were carried out in DMF employing various bases. The best result was obtained when the reaction was performed in the presence of $Cu(OAc)_2{\cdot}H_2O$ using Cs_2CO_3 as the base. Initially the reaction was carried out with 1 equiv of $Cu(OAc)_2{\cdot}H_2O$; however during further studies, the quantity of $Cu(OAc)_2{\cdot}H_2O$ for N-arylation reaction was successfully optimized with 10 mol %. Further reduction in the quantity of $Cu(OAc)_2{\cdot}H_2O$ resulted in prolonged reaction time as well as incompletion of the N-arylation reaction. In order to improve the yields further, the reaction was attempted in polar aprotic solvents such as DMSO, 1,4-dioxane, 2-MeTHF as well as CPME. However the required product was obtained in diminished yields. During further studies on reaction parameters, temperature of the reaction was found to have high impact in this three-component coupling reaction. The reactions conducted at lower temperatures (less than 70 °C) afforded the required product in lower yields, and the reaction stopped at pyrazole[17] without proceeding for the required N-arylation reaction. When the reaction was carried out at elevated temperatures (80–90 °C) over

Table 1
Catalyst and solvent screening

Entry	Catalyst	Solvent	Base	Yield (%)
1	CuI	DMF	Cs_2CO_3	30
2	$CuBr_2{\cdot}2H_2O$	DMF	Cs_2CO_3	40
3	CuO	DMF	Cs_2CO_3	55
4	CuI + $[Cu(OAc)_2]$	DMF	Cs_2CO_3	65
5	$Cu(OAc)_2{\cdot}H_2O$	DMF	Cs_2CO_3	84
6	$Cu(OAc)_2{\cdot}H_2O$	DMF	K_2CO_3	54
7	$Cu(OAc)_2{\cdot}H_2O$	DMF	Na_2CO_3	35
8	$Cu(OAc)_2{\cdot}H_2O$	DMF	K_3PO_4	40
9	$Cu(OAc)_2{\cdot}H_2O$	DMF	Cs_2CO_3	0[a]
10	$Cu(OAc)_2{\cdot}H_2O$	DMF	Cs_2CO_3	15[b]
11	$Cu(OAc)_2{\cdot}H_2O$	DMSO	Cs_2CO_3	68
12	$Cu(OAc)_2{\cdot}H_2O$	1,4-Dioxane	Cs_2CO_3	43

Optimized reaction conditions: 0.1 equiv of $Cu(OAc)_2{\cdot}H_2O$, 3.5 equiv of Cs_2CO_3, and DMF.

[a] Reaction conducted at 30–35 °C.

[b] Reaction conducted at 65 °C.