Synlett S. Yaragorla et al. Letter

Alkaline-Earth-Catalyzed sp³ C–H Functionalization of Methyl Azaarenes and Its Use in a One-Pot Four-Component Synthesis of Azaarenyl Benzylpyrazolones

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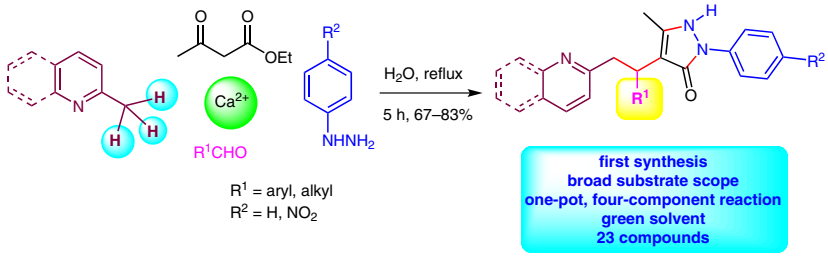


Received: 03.10.2015
Accepted: 23.10.2015
Published online: 23.12.2015
DOI: 10.1055/s-0035-1560385; Art ID: st-2015-d0790-l

Abstract The sp³ C–H functionalization of methyl azaarenes by using calcium triflate as the catalyst is described, together with its use in the first synthesis of azaarenyl benzylpyrazolones by a one-pot four-component reaction.

Key words nitrogen heterocycles, azaarenes, sp³ C–H functionalization, multicomponent reactions, pyrazolones

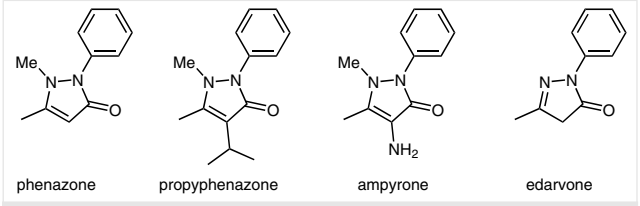


Figure 1 Representative examples of biologically active pyrazolones

The sp³ C–H functionalization of methyl azaarenes is an important method for constructing biologically important N-heterocyclic compounds.[1] Methyl azaarene derivatives are known to possess important biological activities;[2] for example, FZ41 and KHD161 act as promising HIV integrase inhibitors through a previously unknown mechanism,[3] and montelukast sodium is used as a potent antiasthma drug.[4] Chimanine B,[5] VUF 5017,[6] L-660,711,[7] and LY190154[8] are other biologically important azaarene derivatives. Methyl azaarenes are also key building blocks for the synthesis of 2-alkyl heterocyclic compounds.[9].

Pyrazolone derivatives have proved to be potent structural motifs in drug candidates. For example phenazone, propyphenazone, and ampyrone (Figure 1) are well-known antipyretic and antianalgesic drugs. Pyrazolone derivatives are also known to show antifungal, antimycobacterial, antibacterial, antiinflammatory, antitumor, antidepressant, and antitubercular activities.[10]

One-pot multicomponent reactions have a key role in the synthesis of heterocycles, generating molecular complexity in a single reaction vessel with concomitant atom and step economies.[11] The use of water as the reaction medium is always advantageous where possible.[12] Recently, calcium triflate has been explored as an alternative to transition-metal- and lanthanide-based catalysts, because of its greater abundance, non-toxicity, and stability towards moisture and air.[13,14] Our group has demonstrated that calcium triflate is an efficient catalyst for the Ritter reaction,[14c] and in the syntheses of pyranocoumarins,[14b] benzopyrans,[14b] benzylpyrazolyl coumarins,[14a] styryl azaarenes, and 2-aryl 1,3-bisazaarenes.[14]

Owing to the biological significance of both azaarene and pyrazolone derivatives, we considered that it might be useful to develop a method for the synthesis of a new class of azaarene–pyrazolone derivatives by using a one-pot multicomponent approach. In continuation of our research aimed towards the synthesis of biologically important molecules,[14] we report a straightforward method for the synthesis of methyl azaarene derivatives through benzylic C–H functionalization in a one-pot four-component approach with water as the solvent.

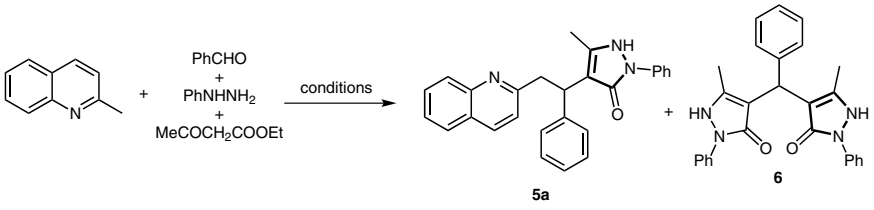
We first studied the reaction of quinaldine (**1a**; 2-methylquinoline), benzaldehyde, ethyl acetoacetate, and phenylhydrazine in the presence of 5 mol% calcium triflate and 5 mol% tetrabutylammonium hexafluorophosphate in refluxing water at 100 °C (Table 1). After five hours, the reaction was found to be complete and the desired product **5a** was isolated in 74% yield after column chromatography (Table 1, entry 3) together with 10% of the benzylbispyrazolone **6**. Product **5a** was characterized by means of ^{1}H and ^{13}C NMR

spectroscopy and mass spectrometry. Encouraged by this result, we attempted to optimize the reaction conditions by examining the roles of the catalyst, additive, and water. When the reaction was performed without the catalyst and solvent at 100 °C, no change was observed by TLC (entry 1), but when the reactants were heated to reflux in water under catalyst-free conditions, 35% of the desired product was formed, along with 25% of benzylbispyrazolone **6** (entry 2). Increasing the temperature to 120 °C (entry 4) did not improve the yield. We therefore increased the catalyst loading from 5 mol% to 10 mol%, and we observed an increase in yield to 80% (entry 5). When the amount of additive was also increased to 10 mol%, the same yield was obtained (entry 6). This suggested that the additive has little influence on the reaction; to confirm this, we heated the reactants to reflux in water in the presence of 10 mol% of calcium triflate, and we still obtained an 80% yield of the desired product **5a**, along with 9% of bispyrazolone **6** (entry 7). Therefore, these conditions were identified as optimal for the sp^3 C–H functionalization and for the one-pot four-component synthesis of methyl azaarene derivatives.

Having established the optimal conditions, we then investigated the substrate scope of the method (Table 2). Quinaldine (**1a**) reacted with 4-nitrobenzaldehyde and phenylhydrazine to give the azaarene derivative **5b** in 83% yield, along with 6% of the corresponding dimeric pyrazolone (Table 2, entry 2). Similarly, quinaldine (**1a**) reacted with 4-chloro-, 4-bromo-, or 4-fluorobenzaldehyde to give the corresponding azaarenyl pyrazolyl derivatives **5c**, **5d**, and **5e** in 83, 78 and 75% yield, respectively (entries 3–5). In the case of aldehydes with electron-releasing groups, 4-methoxybenzaldehyde and 4-methylbenzaldehyde gave the corresponding products **5f** and **5g** in 80 and 75% yields, respectively, whereas 3-hydroxybenzaldehyde gave **5h** in 81% yield. The hetaryl aldehydes pyridine-3-carbaldehyde and furfural also reacted at similar rates (5.5 hours) to give the corresponding products **5i** and **5j** in 80 and 69% yield, respectively. Having explored the scope of the substituted aromatic aldehydes in the method, we then examined the reactions of 7-chloroquinaldine (**1b**; 7-chloro-2-methylquinoline). When benzaldehyde was used with **1b** under the optimized reaction conditions, **5l** was obtained in 79% yield along with 8% of the corresponding bispyrazolone. We therefore examined the reactions of this substrate with a range of aromatic aldehydes to give products **5m**–**r** in good yields (entries 13–18). Hetaryl aldehydes also reacted with **1b** to give products **5s** and **5t** in 75 and 67% yield, respectively (entries 19 and 20). To examine the scope with respect to the phenylhydrazine derivative, we treated 4-nitrophenylhydrazine with **1b** and benzaldehyde under the same reaction conditions and obtained 75% of product **5u**.

Finally, we examined the participation of aliphatic aldehydes (Scheme 1). When quinaldine (**1a**) was treated with 2-methylpropanal, phenylhydrazine, and ethyl acetoacetate under the same catalytic conditions, product **5v** was obtained in 58% yield after six hours. Similarly, 7-chloroquinaldine (**1b**) with 2-methylpropanal gave product **5w** in 62% yield. Further exploration of the reactions of various aliphatic aldehydes and compounds with active methylene groups is ongoing.

Table 1 Optimization Studies for the Four-Component Synthesis of Azaarenyl Pyrazolone Derivative **5a**[a]

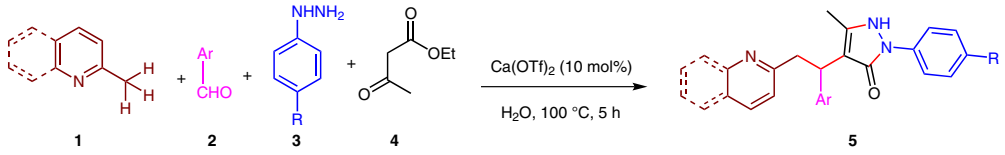


5a **6**

Entry	$Ca(OTf)_2$ (mol%)	Bu_4NPF_6 (mol%)	Solvent	Temp (°C)	Time (h)	Yield[b] (%) of **5a** (**6**)
1	0	0	–	100	20	nr
2	0	0	H_2O	100	15	35 (25)
3	5	5	H_2O	100	5	74 (10)
4	5	5	H_2O	120	5	74 (12)
5	10	5	H_2O	100	5	80 (10)
6	10	10	H_2O	100	5	80 (10)
7	10	0	H_2O	100	5	80 (9)
8	0	5	H_2O	100	15	35 (28)

[a] All reactants were used stoichiometric amounts.
[b] Isolated yield after column chromatography.

Table 2 One-Pot Four-Component Synthesis of Pyrazolone Derivatives **5** by Calcium-Catalyzed sp^3 C–H Functionalization of Methyl Azaarenes[a]



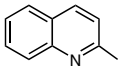
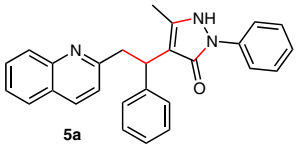
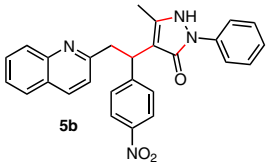
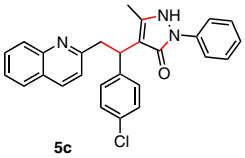
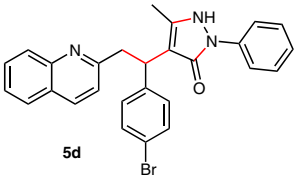
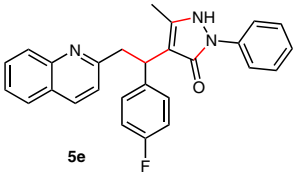
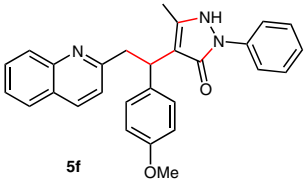
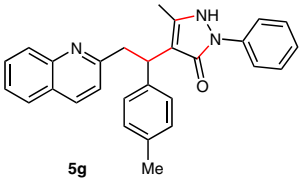
Entry	Azaarene	Ar	R	Product **5**	Yield[b] (%)	Mp (°C)
1	 **1a**	Ph	H	 **5a**	80	67–68
2	**1a**	4-$O_2NC_6H_4$	H	 **5b**	83	104–105
3	**1a**	4-ClC_6H_4	H	 **5c**	83	79–80
4	**1a**	4-BrC_6H_4	H	 **5d**	78	86–88
5	**1a**	4-FC_6H_4	H	 **5e**	75	74–75
6	**1a**	4-$MeOC_6H_4$	H	 **5f**	80	67–68
7	**1a**	4-MeC_6H_4	H	 **5g**	75	86–87

Table 2 (continued)

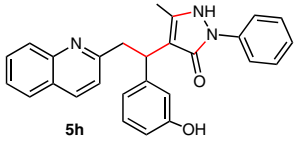
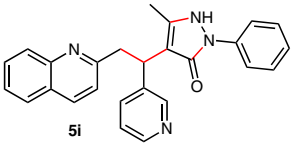
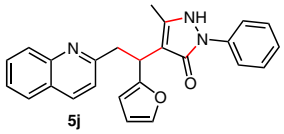
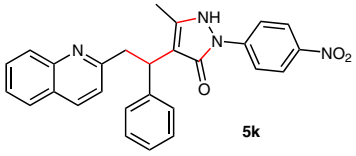
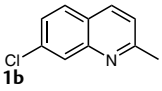
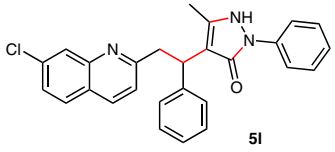
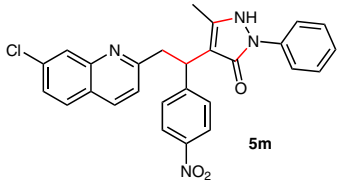
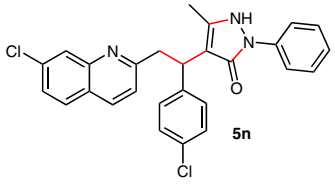
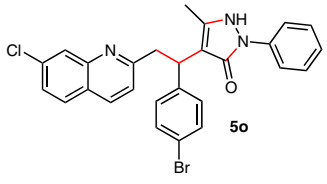
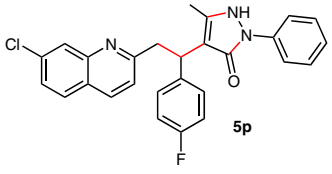
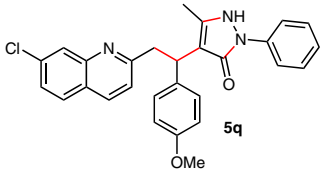
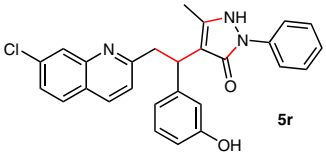
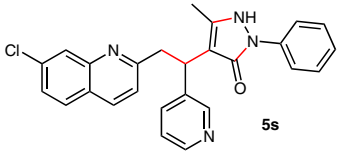
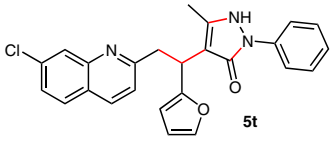
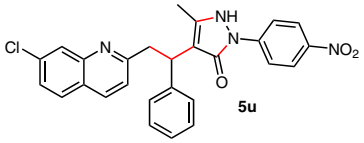
Entry	Azaarene	Ar	R	Product **5**	Yield[b] (%)	Mp (°C)
8	**1a**	3-HOC_6H_4	H	 **5h**	81	183–184
9	**1a**	3-pyridyl	H	 **5i**	80	60–61
10	**1a**	2-furyl	H	 **5j**	69	73–75
11	**1a**	Ph	NO_2	 **5k**	79	104–105
12	 **1b**	Ph	H	 **5l**	79	133–134
13	**1b**	4-$O_2NC_6H_4$	H	 **5m**	78	105–106
14	**1b**	4-ClC_6H_4	H	 **5n**	77	82–83
15	**1b**	4-BrC_6H_4	H	 **5o**	74	90–91
16	**1b**	4-FC_6H_4	H	 **5p**	78	82–83

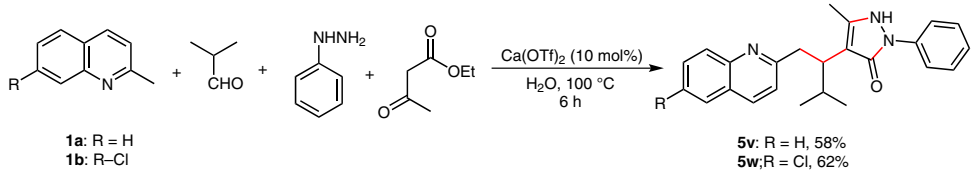
Table 2 (continued)

Entry	Azaarene	Ar	R	Product **5**	Yield[b] (%)	Mp (°C)
17	**1b**	4-$MeOC_6H_4$	H	 **5q**	74	77–78
18	**1b**	4-MeC_6H_4	H	 **5r**	73	106–107
19	**1b**	3-HOC_6H_4	H	 **5s**	75	62–64
20	**1b**	3-pyridyl	H	 **5t**	67	74–75
21	**1b**	Ph	NO_2	 **5u**	75	176–177

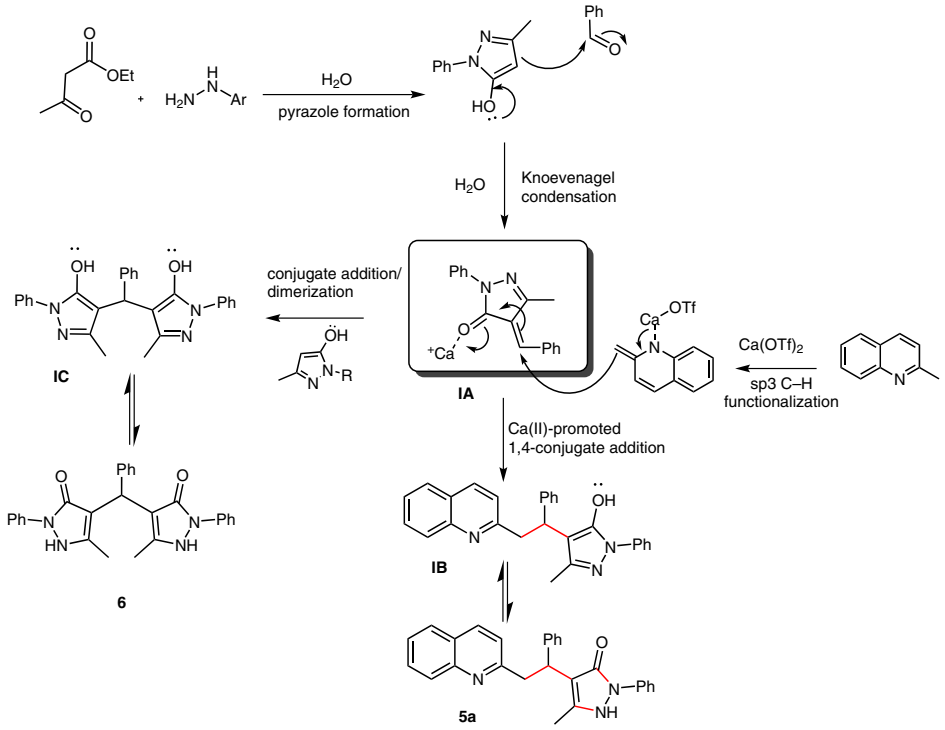
[a] All substrates were present in stoichiometric amounts except for ethyl acetoacetate (1.2 equiv); the mixture was refluxed in H_2O for 5 h with 10 mol% of catalyst.[15]
[b] Isolated yields after column chromatography.

A plausible mechanism for this one-pot four-component process is outlined in Scheme 2. Initially a pyrazolone is formed by condensation of the aryl hydrazine and ethyl acetoacetate; this undergoes Knoevenagel condensation with the aldehyde to give adduct **IA**. Adduct **IA** undergoes 1,4-conjugate addition with the calcium triflate activated methyl azaarene to give **IB**, which tautomerizes to the final product **5a**. Alternatively, adduct **IA** can undergo condensation with another molecule of the pyrazolone to give the bispyrazolone adduct **6** as byproduct.

In summary, an alkaline-earth-catalyzed benzylic C–H functionalization of azaarenes in a multicomponent synthesis of pyrazolone derivatives has been described for the first time. The use of water as the solvent and calcium triflate as the catalyst, the simple procedure, and the wide substrate scope are features of this protocol, leading to the first synthesis of this type of molecule.



Scheme 1 Reaction of 2-methylpropanal with quinaldines **1a** and **1b** in the calcium-promoted, one-pot, four-component synthesis



Scheme 2 Plausible mechanism for the calcium(II)-catalyzed sp^3 C–H functionalization and four-component synthesis

Acknowledgment

S.Y. acknowledges financial support from DST-India. R.D. and G.S. thank the CSIR and the Central University of Rajasthan, respectively, for their fellowships.

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(15) **2-Aryl-4-(1-Aryl-2-hetarylethyl)-5-methyl-1,2-dihydro-3*H*-pyrazol-3-ones 5a–u**; **General Procedure**
$Ca(OTf)_2$ (10 mol%) was added to a stirred solution of $MeCOCO_2Et$ (1.13 mmol), arylhydrazine **3** (0.942 mmol), aryl aldehyde **2** (0.934 mmol), and 2-methylazarene **1** (0.942 mmol) in H_2O (3 mL), and the mixture was heated to 100 °C. When the reaction was complete (TLC; ~5 h), the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a crude solid that was purified by column chromatography.
5-Methyl-2-phenyl-4-(1-phenyl-2-quinolin-2-ylethyl)-1,2-dihydro-3*H*-pyrazol-3-one (**5a**)
Pink solid; yield: 227.9 mg (80%); mp 67–68 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (t, *J* = 9 Hz, 2 H), 7.83 (d, *J* = 7.5 Hz, 2 H), 7.69–7.62 (m, 2 H), 7.63 (t, *J* = 7 Hz, 1 H), 7.44 (t, *J* = 7 Hz, 2 H), 7.17–7.02 (m, 7 H), 4.32 (d, *J* = 9 Hz, 1 H), 3.77 (dd, *J* = 2, 13.5 Hz, 1 H), 3.76 (t, *J* = 13.5 Hz, 1 H), 1.72 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.3, 148.5, 144.8, 144.3, 139.6, 138.3, 132.7, 130.6, 129.1 (2C), 128.6 (2C), 128.4, 127.8, 127.7 (2C), 126.8, 126.4, 126.2, 125.1, 122.9, 121.8 (2C), 100.8, 42.7, 42.1, 13.4.
4-[2-(7-Chloroquinolin-2-yl)-1-(4-nitrophenyl)ethyl]-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**5m**)
Brown solid; yield: 222.7 mg (78%); mp 105–106 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01–7.95 (m, 4 H), 7.8 (d, *J* = 7.5 Hz, 2 H), 7.66 (d, *J* = 8.5 Hz, 1 H), 7.45–7.38 (m, 3 H), 7.26 (d, *J* = 7.5 Hz, 2 H), 7.21–7.18 (m, 1 H), 7.06 (d, *J* = 8.5 Hz, 1 H), 4.48 (d, *J* = 9.5 Hz, 1 H), 3.77 (t, *J* = 13.5 Hz, 1 H), 3.66 (dd, *J* = 2.5, 14.0 Hz, 1 H), 1.74 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.3, 151.5, 150.7, 147.9, 146.5, 145.3, 139.2, 138.5, 137.2, 129.0, 128.8, 128.6, 128.4, 125.6, 125.5, 125.2, 123.7, 122.9, 122.0, 99.4, 42.0, 41.4, 13.3.