Res Chem Intermed (2013) 39:585–595
DOI 10.1007/s11164-012-0581-2

Selective *O*-deallylation of dihydropyrazoles by molecular iodine in the presence of active *N*-allyl and formyl groups

Vivek T. Humne · Kamal Hasanzadeh · Pradeep D. Lokhande

Received: 3 March 2012 / Accepted: 26 April 2012 / Published online: 16 May 2012

Abstract Selective *O*-deallylation of dihydropyrazoles has been achieved by use of iodine (10 mol%) in PEG-400 as ecofriendly solvent. Iodine (10 mol%) in dimethyl sulfoxide at 100 °C also afforded *O*-deallylation with aromatization compatible with highly reactive *N*-allyl and formyl groups. The function of iodine in the synthesis of substituted pyrazoles under different conditions is described.

Keywords Iodine · Dihydropyrazole · Deallylation · PEG-400

Introduction

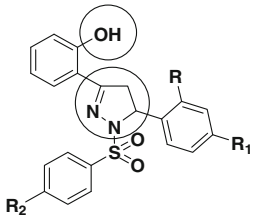
The design of new strategies for synthesis of *N*-containing heterocyclic compounds is essential in organic chemistry from a biological and pharmacological perspective. 4,5-Dihydropyrazoles and their corresponding aromatic pyrazoles are important heterocyclic compounds with a wide range of biological activity, for example anti-inflammatory [1], analgesic [2], antimicrobial [3], and insecticidal [4]. 2′-Hydroxy dihydropyrazoles are also widely used intermediates capable of undergoing a variety of transformations affording flavanone [5] and coumarin [6]-like natural products and organometallic complexes [7] with biological activity [8–11]. A variety of methods have been reported for synthesis of substituted pyrazoles [12–16]. Recently, transition-metal-catalyzed coupling of functionalized allenes with organic halides, leading to pyrazoles, has been reported [17]. The most practical method for obtaining substituted pyrazoles with favored regioselectivity is,

V. T. Humne (✉) · K. Hasanzadeh · P. D. Lokhande
Center for Advance Studies, Department of Chemistry, University of Pune, Pune 411 007, India
e-mail: vivekhumne@rediffmail.com

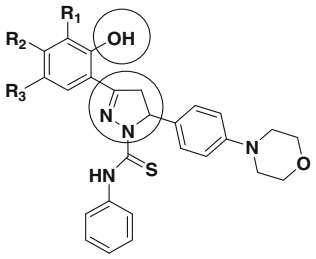
P. D. Lokhande
e-mail: pdlokhande@chem.unipune.ac.in

however, treatment of substituted chalcones with hydrazine hydrate or phenylhydrazine [18, 19].

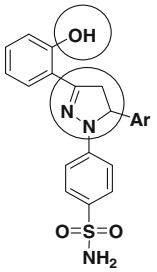
A literature survey revealed that the free hydroxyl group of 2′-hydroxy dihydropyrazoles is of crucial importance in the synthesis of heterocyclic groups. Appropriate selection of an efficient protecting group and selective deprotection are challenging tasks in organic chemistry. Use of allyl groups to protect the nitrogen and oxygen is becoming increasingly popular because of its less hindered nature and the ease of protection. Thus protection and deprotection of these groups is necessary and important. The deprotection of allyl ethers by use of transition metal catalysts, for example palladium [20–26], ruthenium(II) [27], iridium(I) [28, 29], titanium [30], and zirconium [31] has been reported.



MAO - inhibitor
Bioorg. Med. Chem. Lett., 2010, 20 132



Analgesic & Anti-inflammatory activities
Bioorg. Med. Chem. Lett.,2010, 20, 3721



Anticancer drug
Bioorg. Med. Chem. Lett., 2011, 21, 4301

Previous procedures have limited scope, are expensive, and loading of the catalyst is difficult. Oxidation of the resulting dihydropyrazoles is also a significant intellectual task [32–42]. Therefore, development of a method for deprotection under mild conditions with high selectivity is desirable.

Molecular iodine is convenient for pharmaceutical synthesis owing to its inexpensive, non-toxic, and environmentally benign characteristics. Iodine can also be easily removed from reaction systems [43–46] and is insensitive to air and moisture. We have successfully performed deallylation with oxidative ring closure in the synthesis of substituted flavones [47]. As part of a continuing study

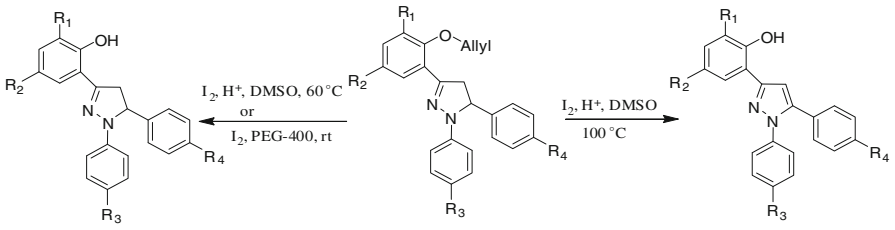
of iodine-mediated transformations in our laboratory [48–51], we became interested in the possibility of developing an easy and efficient method of deallylation of substituted dihydropyrazoles and isoxazoles. To the best of our knowledge, this paper is the first report of deallylation with aromatization of dihydropyrazoles and isoxazoles by use of catalytic amount of iodine (10 mol%) in dimethyl sulfoxide (DMSO) at ambient temperature. Selective *O*-deallylation, in the presence of *N*-allyl groups, has also been achieved by use of iodine (10 mol%) in poly(ethylene glycol) 400 (PEG-400) at room temperature, with good yield.

Results and discussion

The dihydropyrazoles were conveniently prepared by treatment of a variety of substituted 2′-hydroxy chalcones with hydrazine hydrate or phenyl hydrazine in methanol. To achieve the required substrate (Scheme 1, 1a–j), it was stirred with stoichiometric amounts of allyl bromide and potassium carbonate in dimethylformamide at room temperature. In the course of our investigation of the effect of the solvent used for deallylation, we found the reaction did not proceed in methanol, acetonitrile, dimethylformamide, dichloromethane, of diphenyl ether. However, DMSO was found to be efficient solvent. Thereafter, we investigated the amount of iodine required to catalyze the reaction. First, we used 5 mol% and then 1.5 mol iodine. No significant changes were observed at room temperature. On increasing the temperature to 60 °C, the *O*-deallylated product was isolated in excellent yield. It was observed that the time required for completion of the reaction was longer when 5 mol% iodine was used. However, 20 mol% iodine was found adequate for deallylation (Table 1, entry 2a–j). Use of 100 mol% iodine gave the deallylated (yield 51 %) and aromatized (yield 37 %) mixed product.

To optimize the reaction conditions, the temperature was increased to 100 °C. Under these conditions, uniquely, the deallylated, aromatized product was obtained in good yield by use of 20 mol% iodine (Table 1, entry 3a–j).

To check the utility of iodine in DMSO, a variety of substituted dihydropyrazoles and isaxozolines were used (Scheme 2). All aromatized product were isolated in good yields. Even in the presence of the formyl group in dihydropyrazole [51] (Table 1, entry 1f–j), deallylation with aromatization was achieved successfully by



2a-j **1a-j** **3a-j**

Scheme 1

Table 1 Selective deallylation and aromatization of substituted dihydropyrazoles

Entry	Substrate 1				Product 2		Product 3		
	R_1	R_2	R_3	R_4	Time[a] (min)	Yield (%)	Time[b] (min)	Yield (%)	Yield (%)
a	H	Cl	H	H	10	92[a]	35	74	87[b]
b	Cl	Cl	H	H	10	90[a]	30	76	84[b]
c	H	Me	H	H	25	88[a]	40	80	84[b]
d	H	Cl	H	Cl	10	92[a]	25	78	83[b]
e	Cl	Cl	H	Cl	10	90[a]	25	71	82[b]
f	H	Cl	CHO	OMe	15	92	30	83	85
g	H	H	CHO	H	10	90	35	84	82
h	H	H	CHO	OMe	15	90	35	81	77
i	H	H	CHO	Cl	10	89	30	89	81
j	H	Cl	CHO	Cl	10	93	25	86	76

[a] Reaction conducted in DMSO at 60 °C

[b] Reaction conducted in PEG-400 at room temperature

use of iodine in DMSO at 100 °C. Remarkably, the easily oxidizable formyl and highly active *N*-allyl groups remained unchanged in aromatization process.

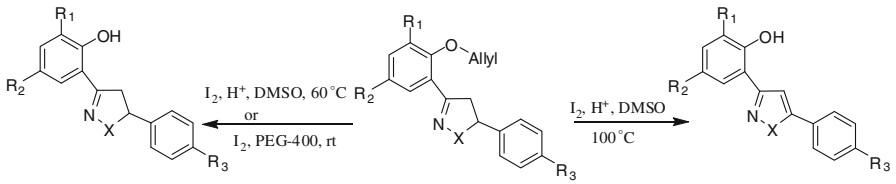
Use of DMSO at higher temperatures for the reaction resulted in decomposition. To avoid the requirement of high temperatures and to achieve selective *O*-deallylation, we investigated use of different solvents for the deallylation process. However, in ethylene glycol, the isolated product was obtained in low yield, with recovery of starting substrate at room temperature. Increasing the viscosity of solvent by using PEG-400 resulted in isolation of the selectively deallylated product in excellent yield. Use of 10 mol% iodine in PEG-400 as solvent afforded the *O*-deallylated product at room temperature (Scheme 1) (Table 2). Use of one equivalent of iodine resulted in almost the same yield and reaction time without formation of side products.

To investigate the generality and versatility of this new method of iodine-catalyzed deallylation, we studied the selective deallylation of *N*-allyl-substituted dihydropyrazoles in the presence of using iodine in PEG-400 as green reaction solvent (Scheme 2, 5g–j). It was observed that *N*-allyl groups were not affected whereas selective *O*-deallylation was achieved cleanly and smoothly for entries 4g–j (Table 3) by use of iodine in PEG-400 at room temperature. The *O*-deallylated product was obtained with excellent yield. The time required for completion of reaction was longer for isoxazoline (Table 3, entry 5a–f).

Table 2 Recycling of PEG-400 for deallylation of 1a with 10 mol% iodine as catalyst at room temperature

Run	1	2	3	4	5
Yield[a]	92	90	88	83	83

[a] All reactions were conducted with 1 mmol substrate



5a-j **4a-j** **6a-j**

Scheme 2

Table 3 Selective deallylation and aromatization of substituted *N*-allyl dihydropyrazoles and isoxazoles

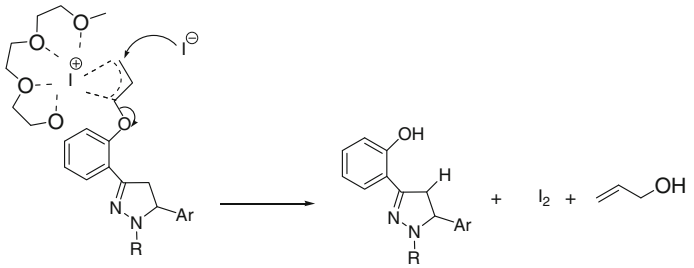
Entry	Substrate 4				Product 5			Product 6	
	R_1	R_2	R_3	X	Time[a] (min)	Yield (%)	Time[b] (min)	Yield (%)	Yield (%)
a	H	Cl	H	O	30	95	10	91	91
b	Cl	Cl	H	O	25	96	10	95	93
c	H	Me	H	O	15	95	20	88	87
d	H	Cl	H	O	25	91	15	92	89
e	Cl	Cl	H	O	30	90	15	91	93
f	H	Me	H	O	20	94	20	85	85
g	H	Cl	Cl	*N*-Allyl	30	89	10	92	79
h	Cl	Cl	Cl	*N*-Allyl	35	90	10	90	77
i	Br	Cl	Cl	*N*-Allyl	35	91	10	91	77
j	H	Me	Cl	*N*-Allyl	30	85	20	86	74

[a] Reaction conducted in PEG-400 at room temperature

[b] Reaction conducted in DMSO at 60 °C

To study the reusability of the solvent, the reaction mixture was extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated. The remaining mother liquor was subjected to vacuum distillation to remove water, leaving PEG behind in the container. The recovered PEG used five times without loss of its activity (Table 2).

A plausible mechanism of deallylation of substituted pyrazolines is depicted in Scheme 3. Gunduz et al. [52] reported that iodine and DMSO under acidic



1 **2**

Scheme 3 Plausible mechanism of deallylation of *O*-allyl dihydropyrazoles

conditions effectively produced the iodonium ion. Floyd et al. [53] regenerated the halogen from the combination of a halo acid and DMSO. On the basis of to this hypothesis, we believe molecular iodine in a polarized state in DMSO promoted the deallylation and aromatization process. The function of PEG is possibly to form a complex with the cation, much like a crown ether, and these complexes cause the anion to be activated. In addition, there is no need for any external phase transfer catalyst (PTC) or acidic medium to activate the oxygen atom of the ally ether. Initially, we assumed the deallylation mechanism was based on the iodine cation, which is stabilized by interaction with the oxygen of PEG. However, when potassium iodide or sodium iodide was used in the reaction, the deallylation product was not observed.

Similarly, tetraalkylammonium iodide did not give the expected product. On the basis of our results and the literature, a tentative mechanism for deallylation is proposed. As soon as iodine is added it activates the C=C bond and forms a three-membered iodonium intermediate, it is stabilized by interaction with the oxygen atom of PEG. The color of the solution remains unchanged, which suggest regeneration of the iodine. Formation of allyl alcohol in the reaction could not be traced. Finally, we believe PEG is not only acting as an efficient solvent but also as a PTC, causing the anion to be activated.

In conclusion, we have developed the sequential procedure for selective *O*-deallylation and aromatization of substituted pyrazolines and isoxozolines by using a catalytic amount of iodine either in PEG-400 at room temperature or in DMSO at different temperatures, in good yield and with easy workup. The attractiveness of this method is its tolerance of *N*-allyl and formyl groups of pyrazolines. The operational simplicity and economic viability of this method justify further study of this reaction.

Experimental

Allylic substrates were prepared by the conventional method. Analytical TLC was performed on Merck aluminium foil plates precoated with silica gel 60 F_{254}. IR spectra were recorded (in KBr pallets) on a Shimadzu spectrophotometer. ^{1}H NMR spectra were recorded (in $CDCl_3$) on a Varian Mercury 300 MHz spectrometer using TMS as internal standard. Mass spectra were recorded on Shimadzu-QP 5050 GC–MS spectrometer.

General procedure for synthesis of compounds 2a–j and 5a–j

To a solution of **1** (10 mmol) in PEG-400, iodine (10 mol%) was added and the reaction mixture was stirred at room temperature. After completion of the reaction (progress was monitored by TLC) the reaction mixture was poured into a saturated solution of sodium thiosulfate. The precipitate was isolated by filtration and washed with cold water. The crude product was crystallized from methanol.

Alternative procedure

To solution of **1** (10 mmol) in DMSO, iodine (10 mol%) was added and the reaction mixture was heated at 120 °C for 25–50 min (progress was monitored by TLC). After cooling, the reaction mixture was poured on to crushed ice. The precipitate was isolated by filtration and washed with methanol to remove excess iodine. The crude product was crystallized from methanol.

4-(3-(5-Chloro-2-hydroxyphenyl)-4,5-dihydro-5-(4-methoxyphenyl)pyrazol-1-yl)benzaldehyde (2f): mp 174–175 °C

IR (KBr) ν cm^{-1}: 3,144, 3,063, 2,931, 2,835, 2,742, 1,685, 1,595. ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 3.29 (*dd*, 1H, $J_1 = 17.4$ Hz, $J_2 = 5.7$ Hz), 3.78 (*s*, 3H), 3.96 (*dd*, 1H, $J_1 = 17.4$ Hz, $J_2 = 12.3$ Hz), 5.38 (*dd*, 1H, $J_1 = 12.3$ Hz, $J_2 = 5.7$ Hz), 6.87 (*d*, 2H, $J = 8.7$ Hz), 6.99–7.03 (*m*, 3H), 7.11 (*d*, 1H, $J = 2.7$ Hz), 7.17 (*d*, 2H, $J = 8.4$ Hz), 7.23–7.35 (*m*, 1H), 7.71 (*d*, 2H, $J = 8.7$ Hz), 9.76 (*s*, 1H), 10.46 (*s*, 1H). ^{13}C NMR (75 MHz, TMS, $CDCl_3$): *d* 44.1, 59.4, 61.9, 112.7, 114.2, 117.8, 119.9, 126.1, 127.0, 127.8, 130.2, 130.7, 132.5, 134.3, 147.1, 149.3, 157.6, 159.4, 190.8. MS *m/z* (%): 406 (M+) (100), 299 (91).

4-(4,5-Dihydro-3-(2-hydroxyphenyl)-5-phenylpyrazol-1-yl)benzaldehyde (2g): mp 164–165 °C

IR (KBr) ν cm^{-1}: 3,333, 3,163, 3,086, 2,924, 2,829, 2,750, 1,685, 1,595. ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 3.35 (*dd*, 1H, $J_1 = 17.4$ Hz, $J_2 = 5.7$ Hz), 4.03 (*dd*, 1H, $J_1 = 17.25$ Hz, $J_2 = 12.3$ Hz), 5.38 (*dd*, 1H, $J_1 = 12.15$ Hz, $J_2 = 5.4$ Hz), 6.90 (*t*, 1H, $J = 7.8$ Hz), 6.99 (*d*, 2H, 8.7 Hz), 7.07 (*d*, 1H, $J = 8.4$ Hz), 7.14 (*d*, 1H, $J = 7.8$ Hz), 7.28–7.38 (*m*, 6H), 7.70 (*d*, 2H, $J = 8.7$ Hz), 9.75 (*s*, 1H), 10.49 (*s*, 1H). ^{13}C NMR (75 MHz, TMS, CDCl3): *d* 43.4, 58.6, 112.3, 116.8, 117.1, 120.4, 126.4, 126.6, 126.9, 128.3, 129.8, 130.8, 131.3, 143.9, 149.5, 152.3, 159.2, 190.9. MS *m/z* (%): 342 (M+) (100), 265 (95).

4-(4,5-Dihydro-3-(2-hydroxyphenyl)-5-(4-methoxyphenyl)pyrazol-1-ylbenzaldehyde (2h): mp 178–179 °C

IR (KBr) ν cm^{-1}: 3,338, 3,005, 2,808, 2,727, 1,680, 1,584, 1,514 cm-1. ^{1}H NMR (300 MHz, TMS, CDCl3): δ 3.33 (*dd*, 1H, *J*1 = 17.55 Hz, *J*2 = 5.7 Hz), 3.75 (*s*, 3H), 4.00 (*dd*, 1H, *J*1 = 17.25 Hz, *J*2 = 12.3 Hz), 5.35 (*dd*, 1H, *J*1 = 11.7 Hz, *J*2 = 5.7 Hz), 6.86–6.94 (*m*, 3H), 7.01 (*d*, 2H, $J = 8.7$ Hz), 7.09 (*d*, 1H, $J = 8.4$ Hz), 7.15–7.21 (*m*, 3H), 7.32 (*t*, 1H, $J = 7.2$ Hz), 7.71 (*d*, 2H, $J = 8.7$ Hz), 9.76 (*s*, 1H), 10.52 (*s*, 1H). ^{13}C NMR (75 MHz, TMS, CDCl3): δ 43.9, 55.2, 61.5, 112.4, 114.7, 115.6, 116.7, 119.6, 126.7, 127.6, 128.0, 131.3, 131.6, 132.5, 147.4, 152.4, 157.2, 159.3, 190.3. MS *m/z* (%): 372(M+) (100), 265 (94).

4-(5-(4-Chlorophenyl)-4,5-dihydro-3-(2-hydroxyphenyl) pyrazol-1-yl)benzaldehyde (2i): mp 186–188 °C

IR (KBr) ν cm^{-1}: 3,155**,** 2,922, 1,678, 1,593. ^{1}H NMR (300 MHz, TMS, CDCl3): δ 3.32 (*dd*, 1H, $J1 = 19.05$ Hz, $J2 = 5.4$ Hz)**,** 4.04 (*dd*, 1H, $J1 = 17.1$ Hz, $J2 = 12.3$ Hz)**,** 5.37 (*dd*, 1H, $J1 = 12.15$ Hz, $J2 = 6$ Hz)**,** 6.92 (*t*, 1H, $J = 7.2$ Hz), 6.98 (*d*, 2H, $J = 8.7$ Hz), 7.09 (*d*, 1H, $J = 8.4$ Hz), 7.15 (*d*, 1H, $J = 8.4$ Hz), 7.22 (*d*, 2H, $J = 8.4$ Hz), 7.31–7.36 (*m*, 3H), 7.72 (*d*, 2H, $J = 9.9$ Hz), 9.78 (*s*, 1H), 10.44 (*s*, 1H). ^{13}C NMR (75 MHz, TMS, CDCl3): δ 43.7, 59.1, 112.9, 113.1, 115.8, 119.5, 124.3, 128.6, 128.9, 130.6, 131.1, 132.0, 132.5, 141.4, 148.3, 150.0, 159.8, 189.9. MS *m/z* (%): 376 (M+) (100), 265 (94).

4-(3-(5-Chloro-2-hydroxyphenyl)-5-(4-chlorophenyl)-4,5-dihydropyrazol-1-yl) benzaldehyde (2j): mp 190–192 °C

IR (KBr) ν cm^{-1}: 3,099, 3,033, 2,978, 2,815, 2,750, 1,687, 1,585. ^{1}H NMR (300 MHz, TMS, CDCl3): δ 3.29 (*dd*, 1H, $J1 = 17.4$ Hz, $J2 = 5.4$ Hz)**,** 4.00 (*dd*, 1H, $J1 = 17.55$ Hz, $J2 = 12$ Hz)**,** 5.40 (*dd*, 1H, $J1 = 12.15$ Hz, $J2 = 5.7$ Hz)**,** 6.98 (*d*, 1H, $J = 8.4$ Hz), 7.03 (*d*, 2H, $J = 8.7$ Hz), 7.10 (*d*, 1H, $J = 2.4$ Hz), 7.19–7.28 (*m*, 3H), 7.35 (*d*, 2H, $J = 8.4$ Hz), 7.73 (*d*, 2H, $J = 8.7$ Hz), 9.79 (*s*, 1H), 10.39 (*s*, 1H). ^{13}C NMR: 43.6, 61.5, 112.6, 116.6, 118.2, 124.3, 126.4 126.8, 128.6, 129.7, 131.0, 131.7, 134.2, 138.7, 146.9, 150.9, 155.7, 190.3. MS *m/z* (%): 410 (M+) (100), 299 (93).

2-(1-Allyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-4-chlorophenol (5g): mp 156–158 °C

IR (KBr) ν cm^{-1}: 3,123, 2,971, 2,848, 1,701, 1,585, 1,510. ^{1}H NMR (300 MHz, TMS, CDCl3): δ 3.27 (*dd*, 1H, $J_1 = 17.4$ Hz, $J_2 = 5.4$ Hz), 4.04 (*dd*, 1H, $J_1 = 17.4$ Hz, $J_2 = 12.3$ Hz, 4.60 (*m*, 2H), 4.87 (*dd*, 1H, $J_1 = 17$ Hz, $J_2 = 1.5$ Hz), 5.08 (*dd*, 1H, $J_1 = 17$ Hz, $J_2 = 1.2$ Hz), 5.37 (*dd*, 1H, $J_1 = 12.3$ Hz, $J_2 = 5.5$ Hz), 5.83–5.90 (*m*, 1H), 6.71 (*d*, 1H, $J = 8.2$ Hz), 7.06 (*d*, 2H, $J = 8.1$ Hz), 7.11 (*d*, 1H, $J = 8.2$ Hz), 7.22 (*d*, 2H, $J = 8.1$ Hz), 7.54 (*d*, 1H, $J = 2$ Hz). MS *m/z* (%): 346 (M+) (100), 348 (66), 347 (20).

2-(1-Allyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-4,6-dichlorophenol (5h): mp 167–169 °C

IR (KBr) ν cm^{-1}: 3,103, 3,059, 2,839, 2,744, 1,693, 1,600, 1,581, 1,496. ^{1}H NMR (300 MHz, TMS, CDCl3): δ 3.24 (*dd*, 1H, $J_1 = 17.1$ Hz, $J_2 = 5.2$ Hz), 4.05 (*dd*, 1H, $J_1 = 17.1$ Hz, $J_2 = 13.1$ Hz, 4.61 (*m*, 2H), 4.87 (*dd*, 1H, $J_1 = 17$ Hz, $J_2 = 1.5$ Hz), 5.08 (*dd*, 1H, $J_1 = 17$ Hz, $J_2 = 1.2$ Hz), 5.37 (*dd*, 1H, $J_1 = 12.3$ Hz, $J_2 = 5.1$ Hz), 5.83–5.90 (*m*, 1H), 7.0–7.08 (*m*, 3H), 7.22 (*d*, 2H, $J = 7.9$ Hz), 7.34 (*s*, 1H). MS *m/z* (%): 380 (M+) (100), 382 (98).

2-(1-Allyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-6-chloro-4-methylphenol (5i):mp 161–163 °C

IR (KBr) v cm^{-1}: 3,134, 2,920, 2,850, 1,693, 1,599, 1,510. ^1H NMR (300 MHz, TMS, CDCl3): δ 2.56 (*s*, 3H), 3.21 (*dd*, 1H, $J_1 = 16.9$ Hz, $J_2 = 4.7$ Hz), 3.99 (*dd*, 1H, $J_1 = 17.0$ Hz, $J_2 = 12.0$ Hz), 4.56 (*m*, 2H), 4.91 (*dd*, 1H, $J_1 = 16.9$ Hz, $J_2 = 1.7$ Hz), 5.1 (*dd*, 1H, $J_1 = 17$ Hz, $J_2 = 1.2$ Hz), 5.40 (*dd*, 1H, $J_1 = 12.5$ Hz, $J_2 = 5.2$ Hz), 5.83–5.90 (*m*, 1H), 7.0–7.1 (*m*, 3H), 7.22–7.225 (*m*, 2H).MS *m/z* (%): 360 (M+) (100), 362 (66), 361 (21).

General procedure for synthesis of compounds 3a–j and 6a–j

To a solution of **1** (10 mmol) in DMSO, iodine (10 mol%) was added. The reaction mixture was then heated at 120 °C for 25–50 min (monitored by TLC). After cooling, the reaction mixture was poured on to crushed ice. The precipitate was isolated by filtration and washed with methanol to remove excess iodine. The crude product was then crystallized from methanol.

4-(3-(5-Chloro-2-hydroxyphenyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzaldehyde (3f): mp 218–220 °C

IR (KBr) v cm^{-1}: 3,441, 3,134, 3,007, 2,837, 2,739, 1,701, 1,600, 1,508. ^1H NMR (300 MHz, TMS, $CDCl_3$): *d* 3.85 (*s*, 3H), 6.85 (*s*, 1H), 6.92 (*d*, 2H, 8.4 Hz), 7.21–7.26 (*m*, 3H), 7.50 (*d*, 2H, $J = 8.4$ Hz), 7.61 (*d*, 1H, $J = 7.5$ Hz), 7.72 (*d*, 1H, $J = 2.7$ Hz), 7.88 (*d*, 2H, $J = 8.4$ Hz), 10.03 (*s*, 1H), 11.76 (*s*, 1H). 13C NMR (75 MHz, TMS, CDCl3): *d* 55.3, 105.3, 114.3, 117.0, 118.6, 121.3, 124.1, 124.6, 126.1, 129.5, 130.1, 130.4, 134.8, 143.6, 144.4, 151.6, 154.7, 160.3, 190.8. MS *m/z* (%): 404 (M+) (100), 238 (31).

4-(3-(2-Hydroxyphenyl)-5-phenyl-1H-pyrazol-1-yl)benzaldehyde (3g): mp 189–191 °C

IR (KBr) v cm^{-1}: 3,419, 3,123, 2,971, 2,848, 1,701, 1,585, 1,510. ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 6.92 (*s*, 1H), 6.95 (*t*, 1H, $J = 7.8$ Hz), 7.07 (*d*, 1H, $J = 7.8$ Hz), 7.24–7.31 (*m*, 3H), 7.35–7.42 (*m*, 3H),7.52 (*d*, 2H, $J = 8.7$ Hz), 7.61 (*dd*, 1H, $J1 = 7.8$ Hz, $J2 = 1.8$ Hz), 7.92 (*d*, 2H, $J = 8.7$ Hz), 10.11 (*s*, 1H), 10.43 (*s*, 1H). ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 105.7, 115.3, 118.5, 118.8, 120.8, 127.3, 127.9, 128.0, 128.7, 129.2, 129.7, 133.3, 133.8, 141.6, 142.1, 152.1, 158.3, 191.1. MS *m/z* (%): 340 (M+) (100), 208 (42).

4-(3-(2-Hydroxyphenyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzaldehyde (3h): mp 196–198 °C

IR (KBr) v cm^{-1}: 3,446, 3,103, 3,059, 2,839, 2,744, 1,693, 1,600, 1,581, 1,496 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): *d* 3.85 (*s*, 3H), 6.86(*s*, 1H), 6.91 (*d*, 2H, $J = 8.7$ Hz), 6.96 (*t*, 1H, $J = 7.5$ Hz) 7.07(*d*, 1H, $J = 8.4$ Hz), 7.24(*d*, 2H,

$J = 8.4$ Hz), 7.28–7.31(*m*, 1H), 7.51(*d*, 2H, $J = 8.7$ Hz), 7.64(*dd*, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.5$ Hz), 7.88 (*d*, 2H, $J = 8{,}7$ Hz), 10.02 (*s*, 1H), 10.68(*s*, 1H). ^{13}C NMR (75 MHz, TMS, CDCl3): *d* 55.3, 105.4, 114.3, 115.7, 117.2, 119.4, 121.6, 124.5, 126.6, 129.9, 130.2, 130.4, 134.6, 143.8, 144.2, 152.7, 156.1, 160.2, 190.9. MS *m/z* (%): 370 (M+) (100), 238 (45).

4-(5-(4-Chlorophenyl)-3-(2-hydroxyphenyl)-1H-pyrazol-1-yl)benzaldehyde (3i): mp 209–211 °C

IR (KBr) ν cm^{-1}: 3,437, 3,134, 2,920, 2,850, 1,693, 1,599, 1,510. ^{1}H NMR (300 MHz, TMS, $CDCl_3$): 6.92 (*s*, 1H), 6.97 (*t*, 1H, $J = 8.1$ Hz), 7.07 (*d*, 1H, $J = 7.8$ Hz), 7.24–7.31 (*m*, 3H), 7.37 (*d*, 2H, $J = 8.4$ Hz), 7.49 (*d*, 2H, $J = 8.7$ Hz), 7.63 (*dd*, 1H, $J_1 = 7.9$ Hz, $J_2 = 1.5$ Hz), 7.90 (*d*, 2H, $J = 8.7$ Hz), 10.03 (*s*, 1H), 10.56 (*s*, 1H). ^{13}C NMR (75 MHz, TMS, $CDCl_3$): 106.0, 115.5, 117.3, 119.5, 124.6, 126.6, 127.8, 129.2, 130.1, 130.5, 134.9, 135.5, 143.1, 143.4, 152.9, 156.12, 190.7. MS *m/z* (%): 374 (M+) (100), 242 (52).

4-(3-(5-Chloro-2-hydroxyphenyl)-5-(4-chlorophenyl)-1H-pyrazol-1-yl)benzaldehyde (3j): mp 224–226 °C

IR (KBr) ν cm^{-1}: 3,423, 3,156, 2,994, 2,881, 1,756, 1,561, 1,497. ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 6.90 (*s*, 1H), 7.01 (*d*, 1H, $J = 9$ Hz) 7.20–7.27 (*m*, 3H) 7.38 (*d*, 2H, $J = 9$ Hz) 7.48 (*d*, 2H, $J = 8.7$ Hz) 7.59 (*d*, 1H, $J = 2.4$ Hz) 7.91 (*d*, 2H, $J = 8.7$ Hz) 10.03 (*s*, 1H) 10.55 (*s*, 1H). ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 106.0, 116.1, 118.6, 124.6, 124.8, 126.3, 127.5, 129.2, 129.7, 130.0, 135.1, 135.6, 138.2, 142.9, 143.6, 150.0, 154.6, 190.6. MS *m/z* (%): 408 (M+) (100), 242 (39).

Acknowledgment VTH thanks CSIR, New Delhi, India, for the award of a Senior Research Fellowship.

References

1. R. Sridhar, P.T. Perumal, S. Etti, G. Shanmugam, M.N. Ponnuswamy, V.R. Prabayathy, N. Mathivanan, Bioorg. Med. Chem. Lett. **14**, 6035 (2004)
2. E. Banoglu, M. Sukuroglu, B. Caliskan, S. Nacak, E. Aypar, M. Ark, Turk. J. Chem. **31**, 677 (2007)
3. Z.N. Siqqiqui, T.N.M. Musthafa, A. Ahmad, A.U. Khan, Bio. Med. Chem. Lett. **21**, 2860 (2011)
4. R.E. Sammelson, P. Caboni, K.A. Durkin, J.E. Casida, Bioorg. Med. Chem. **12**, 3345 (2004)
5. F. Kallay, G. Janzso, I. Koczor, Tetrahedron **21**, 19 (1965)
6. P. Lokhande, K. Hasanzadeh, S.G. Konda, Eur. J. Chem. **2**, 223 (2011)
7. K.V. Sharma, V. Sharma, U.N. Tripathi, J. Coord. Chem. **62**, 676 (2009)
8. R.S. Joshi, P.G. Mandhane, S.D. Diwakar, S.K. Dabhade, C.H. Gill, Bioorg. Med. Chem. Lett. **20**, 3721 (2010)
9. K.L. Stirett, J.A. Ferreres, V. Jayaprakash, B.N. Sinha, L.E.N. Quadri, Bioorg. Med. Chem. Lett. **18**, 2662 (2008)
10. A. Sahoo, S. Yabanoglu, B.N. Sinha, G. Ucar, A. Basu, V. Jayaprakash, Bioorg. Med. Chem. Lett. **20**, 132 (2010)
11. R. Bashir, S. Ovais, S. Yaseen, H. Hamid, M.S. Alam, M. Samim, S. Singh, K. Javed, Bioorg. Med. Chem. Lett. **21**, 4301 (2011)
12. S. Fustero, M. Sanchez-Rosell, P. Barrio, A. Simon-Fuentes, Chem. Rev. **111**, 6984 (2011)
13. K.V. Gothelf, K.A. Jorgensen, Chem. Rev. **98**, 863 (1998)

14. D.V. Vorobyeva, N.M. Karimova, I.L. Odinets, G.V. Röschenthaler, S.N. Osipov, Org. Biomol. Chem. **9**, 7335 (2011)
15. H.-L. Liu, H.-F. Jiang, M. Zhang, W.-J. Yao, Q.-H. Zhu, Z. Tang, Tetrahedron Lett. **49**, 3805 (2008)
16. R. Surmont, G. Verniest, N.D. Kimpe, Org. Lett. **12**, 4648 (2010)
17. J.D. Sieber, J.P. Morken, J. Am. Chem. Soc. **128**, 74 (2006)
18. A. Levai, J. Heterocyl. Commun. **5**, 151 (1999)
19. F. Manna, F. Chimenti, A. Bolasco, D. Secci, B. Bizzarri, O. Befani, P. Turini, B. Mondovi, S. Alcaro, A. Tafi, Bioorg. Med. Chem. Lett. **12**, 3629 (2002)
20. O. Dangles, F. Guibe, G. Balavoine, S. Lavielle, A. Marquet, J. Org. Chem. **52**, 4984 (1987)
21. M. Honda, H. Morita, I. Nagakura, J. Org. Chem. **62**, 8932 (1997)
22. T. Opaltz, H. Kunz, Tetrahedron Lett. **41**, 10185 (2000)
23. R. Vutukuri, P. Bharathi, Z. Yu, K. Rajashekaran, P.H. Tiran, S. Thayumanavan, J. Org. Chem. **68**, 1146 (2003)
24. S. Chandrashekar, C.R. Reddy, R.J. Rao, Tetrahedron **57**, 3435 (2001)
25. H. Murakami, T. Minami, F. Ozawa, J. Org. Chem. **69**, 4482 (2004)
26. G. Mora, O. Piechaczyk, X.F. Le Goff, P. Le Floch, Organometallics **27**, 2565 (2008)
27. K.C. Nicolaou, C.W. Hummel, N.J. Bockovich, C.-H. Wong, Chem. Commun. 870 (1991)
28. J.J. Oltvoort, C.A.A. Van Boeckel, J.H. De Koning, J.H. Van Boom, Synthesis **4**, 305 (1981)
29. S.J. Hecker, M.L. Minich, K. Lackey, J. Org. Chem. **55**, 4904 (1990)
30. M. Ohkubo, S. Mochizuki, T. Sano, Y. Kawaguchi, S. Okamoto, Org. Lett. **9**, 773 (2007)
31. K.P. Charry, G.H. Mohan, D.S. Iyengar, Chem. Lett. **11**, 1223 (1999)
32. W.A. Gladstone, R.O.C. Norman, Chem. Commun. 1536 (1966)
33. I. Bhatnagar, M.V. George, Tetrahedron **24**, 1293 (1968)
34. Y.R. Huang, J.A. Katzenellenbogen, Org. Lett. **18**, 2833 (2000)
35. L.I. Smith, K.L. Haward, J. Am. Chem. Soc. **65**, 159 (1943)
36. R.P. Dodwadmath, T.C. Wheeler, Proc. Ind. Acad. Sci. **2A**, 438 (1955)
37. S.P. Singh, D. Kumar, O. Prakash, R.P. Kappor, Syn. Commun. **27**, 2683 (1997)
38. N. Nakamichi, Y. Kawashita, M. Hayashi, Synthesis **7**, 1015 (2004)
39. N. Nakamichi, Y. Kawashita, M. Hayashi, Org. Lett. **4**, 3955 (2002)
40. G. Bianchi, P. Grunanger, Tetrahedron **21**, 817 (1965)
41. G. Bianchi, M. De Amici, J. Chem. Res. Synop. 311 (1979)
42. D. Azarifar, B. Maleki, K. Mohammadi, Heterocycles **71**, 683 (2007)
43. M. Jereb, D. Vrazic, M. Zupan, Tetrahedron **67**, 1355 (2011)
44. H. Toga, S. Iida, Synlett **14**, 2159 (2006)
45. A.N. French, T. Wirth, Chem. Soc. Rev. **33**, 354 (2004)
46. M. Girardin, P.G. Alsabeh, S. Lauzon, S.J. Dolman, S.G. Ouellet, G. Hughes, Org. Lett. **11**, 1159 (2009)
47. P.D. Lokhande, S.S. Sakate, K.N. Taksande, B. Navghare, Tetrahedron Lett. **46**, 1573 (2005)
48. P.D. Lokhande, B.Y. Waghmare, S.S. Sakate, Indian J. Chem. **44B**, 2338 (2006)
49. V.T. Humne, S.G. Konda, K. Hasanzadeh, P.D. Lokhande, Chinese Chem. Lett. **22**, 1435 (2011)
50. S.G. Konda, V.T. Humne, P.D. Lokhande, Green Chem. **13**, 2354 (2011)
51. P.D. Lokhande, K. Hasanzadeh, J. Chem. Pharm. Res. **3**, 105 (2011)
52. M. Gündüz, S. Bilgiç, O. Bilgiç, D. Özöğüt, Arkivoc **13**, 115 (2008)
53. M.B. Floyd, M.T. Du, P.F. Fabio, J. Org. Chem. **50**, 5022 (1985)