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Catalyst-free synthesis of 1,2,4,5-tetrasubstituted imidazoles from arylamins, benzonitriles, arylglyoxals, and Meldrum's acid

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ABSTRACT

An efficient and catalyst-free for the synthesis of 1,2,4,5-tetrasubstituted imidazoles has been developed using a one-pot, two-step reaction of arylamins, benzonitriles, arylglyoxals, and Meldrum's acid. All the products were obtained in good to excellent yields and their structures were established from their spectroscopic data.

Imidazoles are one of the most important five-membered ring heteroaromatic nitrogen-bearing compounds that show a broad range of pharmaceutical and industrial applications. Imidazole derivatives have a various biological activity such as antitumor,[1] antibacterial,[2] anti-HIV,[3] antiviral,[4] anti-allergic,[5] antioxidant,[6] anti-inflammatory,[7] antifungal,[8] and antiparasitic,[9] which have indicated them as new candidates in cancer therapy.[10] Moreover, they can be found in many important drugs such as Omeprazole, Eprosartan, and Trifenagrel having functionalized imidazole motif.[11] Therefore, a broad utility range has made imidazoles prime synthetic targets thereby accentuating the need to develop newer synthetic routes for imidazole derivatives.

A number of methods have been developed for the synthesis of 1,2,4,5-tetrasubstituted imidazoles. These compounds are generally synthesized in a four-component condensations of a 1,2-diketone derivative with an aldehyde, primary amine, and ammonium acetate using Cu(II) nitrate impregnated zeolite,[12] $FeCl_3{\cdot}6H_2O$,[13] SiO_2:BF_3,[14] SiO_2:$NaHSO_4$,[15] CAN,[16] *p*-toluene sulfonic acid,[17] molecular iodine,[18] heteropolyacid,[19] SiO_2:SnO_2,[20] bioglycerol-based carbon,[21] and the magnetic ionic liquid.[22] In addition, they can also be accessed by the condensation of a 1,2-diketone with an aryl nitrile and primary amine under microwave irradiation,[23] by hetero-Cope rearrangement,[24] and by *N*-alkylation of trisubstituted imidazoles.[25] However, many of these procedures are associated with one or more disadvantages such as the use of hazardous organic solvents, longer reaction times, tedious work-up procedure, expensive reagents, and large amounts of catalysts which would eventually result in the generation of large amounts of toxic waste.

It is known that the arylglyoxals undergoes multicomponent domino reactions have played an important role in the total synthesis of natural products. To illustrate this point, Jiang et al. have discovered a novel ABC_2 type domino reaction of arylglyoxal with electron-rich pyrazol-5-amines and aromatic amines, leading to the formation of pyrazolo[4′,3′:6,7]azepino[5,4,3-*cd*]indoles and pyrazolo[3,4-*b*]-pyridines under microwave heating.[26] Also, they were synthesized pyrazolo[3,4-*b*]pyridine derivatives from arylglyoxals, pyrazol-5-amines, aromatic amines, 4-hydroxy-6-methyl-2*H*-pyran-2-one, and cyclohexane-1,3-diones,[27] or synthesis of pyrazolo-fused 1,7-naphthyridines, 1,3-diazocanes, and pyrroles from arylglyoxals and pyrazol-5-amines,[28] and synthesis of oxazolo[5,4-*b*]indoles by using arylglyoxals with cyclic enaminones and amino acids.[29] In addition, bi-electrophilic centers of arylglyoxals were simultaneously utilized for the synthesis of biologically active compounds. For examples, synthesis of functionalized quinoxalines by the cyclocondensation of bi-electrophilic centers of arylglyoxals and aryl 1,2-diamine *via* a oxidation process using $BiCl_3/SiO_2$,[30] PVPP·OTf,[31] magnetic Fe_3O_4 nanoparticles,[32] iodine-catalyzed,[33] $Pd(OAc)_2$ or $RuCl_2(PPh_3)_3$-TEMPO,[34] and MnO_2.[35] With this background in mind, we describe in this study a one-pot, two-step synthesis of 1,2,4,5-tetrasubstituted imidazoles from the reaction of arylamins, benzonitriles, Meldrum's acid with arylglyoxals under catalyst-free conditions (Table 1).

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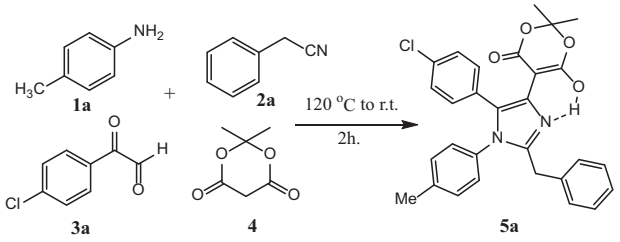
Table 1
Optimization of the reaction conditions[a].



Entry	Solvent Second step	Temp. (°C) First step/Second step	Yield (%)[b]
1	MeOH	120/r.t.	30
2	H_2O	120/r.t.	40
3	MeCN	120/r.t.	50
4	DMF	120/r.t.	58
5	H_2O:EtOH (1:1)	120/r.t.	60
6	EtOH	r.t./r.t.	55
7	EtOH	80/r.t.	70
8	EtOH	120/r.t.	96
9	EtOH	120/r.t.	90[c]

[a] Reaction conditions: **1a** (1.2 mmol), **2a** (1.0 mmol), **3a** (1.5 mmol), **4** (1.0 mmol), and reaction time was 2 h.
[b] Isolated yields.
[c] Reaction time was 6 h.

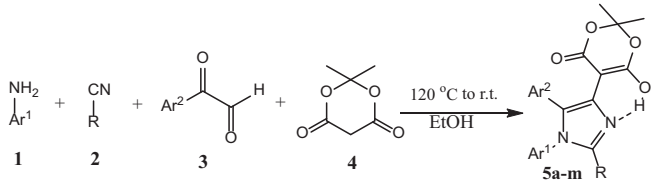
To find the optimized conditions, we studied the synthesis of 5-(2-benzyl-5-(4-chlorophenyl)-1-(*p*-tolyl)-1*H*-imidazol-4-yl)-6-hydroxy-2,2-dimethyl-4*H*-1,3-dioxin-4-one **5a** from the reaction of 4-methylaniline **1a** (1.2 mmol), benzyl cyanide **2a** (1.0 mmol), 4-chlorophenylglyoxal **3a** (1.5 mmol), and Meldrum's acid **4** (1.0 mmol) under a variety of conditions without any catalyst (Table 2).

The first step reaction was started using 4-methylaniline **1a**, and benzyl cyanide **2a** for construction of the corresponding intermediate at 120 °C for 1 h under solvent-free conditions. After cooling the reaction medium to room temperature at the second step, ethanol (5.0 mL), 4-chlorophenylglyoxal **3a**, and Meldrum's acid **4** were added to the intermediate. The reaction mixture was then stirred at room temperature. After completion of the reaction during 1 h, the reaction furnished the desired product, 5-(2-benzyl-5-(4-chlorophenyl)-1-(*p*-tolyl)-1*H*-imidazol-4-yl)-6-hydroxy-2,2-dimethyl-4*H*-1,3-dioxin-4-one **5a**. Therefore, the best reaction conditions for the synthesis of 1,2,4,5-tetrasubstituted imidazole **5a** was found to be an one-pot, two-step reaction of 4-methylaniline (1.2 mmol), benzyl cyanide (1.0 mmol), 4-chlorophenylglyoxal (1.5 mmol), and Meldrum's acid (1.0 mmol) at ambient temperature in ethanol for the second step and the product **5a** was obtained in 96% yield after 2 h (Table 1, entry 8).

Under the optimized reaction conditions, a series of 1,2,4,5-tetrasubstituted imidazole derivatives **5a**–**m** were synthesized (Table 2). To explore the scope of this novel transformation, then various arylamins **1**, benzonitriles **2**, arylglyoxals **3**, and Meldrum's acid **4** were utilized under the same reaction conditions. From the results shown in Table 2, we could see that all of the reactions proceeded smoothly to afford the corresponding products **5a**–**m** in excellent yields.

All the synthesized compounds were unknown to the best of our knowledge and were characterized by ^{1}H and ^{13}C NMR, IR, CHN analysis and melting points. For instance, the ^{1}H NMR spectrum of the compound **5a** consisted of two singlet at δ = 0.96 and 1.38 ppm for the methyl groups in the Meldrum's acid. The methyl and the methylene group protons were discernible as a singlet at δ = 2.36 and 4.19 ppm respectively. The aromatic protons resonated in the region δ = 6.96–7.71 ppm, and a broad singlet that integrated for one hydrogen was observed at δ = 14.76 ppm for the hydroxy proton. The ^{13}C NMR spectrum of compound **5a** exhibited 22 distinct signals in agreement with the proposed structure. In the IR spectrum, the hydroxyl and the carbonyl lactone absorption were observed at 3448 and 1674 cm^{-1}. Partial assignments of these

Table 2
Synthesis of 1,2,4,5-tetrasubstituted imidazoles in ethanol at room temperature.



Entry	Product	Ar^1	R	Ar^2	Time (h)	Yield (%)[a]
1	**5a**	4-$CH_3C_6H_4$	$CH_2C_6H_5$	4-ClC_6H_4	2	96
2	**5b**	4-$CH_3C_6H_4$	$CH_2C_6H_5$	4-$CH_3C_6H_4$	2	80
3	**5c**	4-$CH_3C_6H_4$	$CH_2C_6H_5$	C_6H_5	3	83
4	**5d**	4-$CH_3C_6H_4$	$CH_2C_6H_5$	4-$NO_2C_6H_4$	2	87
5	**5e**	4-$CH_3C_6H_4$	$CH_2C_6H_5$	4-$CH_3OC_6H_4$	3	82
6	**5f**	4-$CH_3OC_6H_4$	2-ClC_6H_4	4-ClC_6H_4	1.5	96
7	**5g**	4-$CH_3OC_6H_4$	2-ClC_6H_4	4-$CH_3C_6H_4$	2	82
8	**5h**	4-$CH_3C_6H_4$	$CH_2C_6H_5$	4-BrC_6H_4	1.5	90
9	**5i**	C_6H_5	2-ClC_6H_4	4-ClC_6H_4	2	92
10	**5j**	C_6H_5	2-ClC_6H_4	4-$CH_3C_6H_4$	3	81
11	**5k**	4-ClC_6H_4	2-ClC_6H_4	4-$CH_3OC_6H_4$	3	78
12	**5l**	4-$CH_3C_6H_4$	2-ClC_6H_4	4-BrC_6H_4	1.5	94
13	**5m**	4-$CH_3C_6H_4$	C_6H_5	4-ClC_6H_4	1.5	91

[a] Isolated yields.