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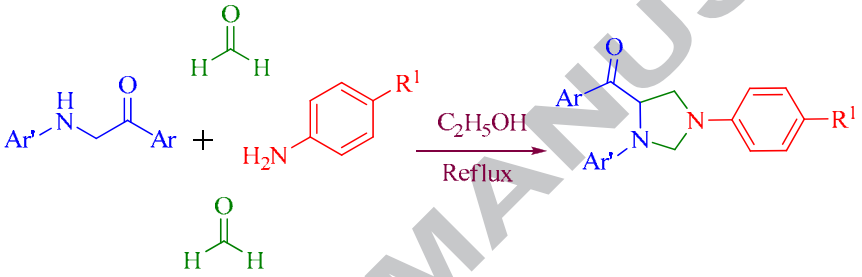

Synthesis of unsymmetrical (1,3-diarylimidazolidin-4-yl) (aryl)methanone *via* Mannich reaction

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Abstract

An atom-efficient, catalyst-free and environment friendly approach towards the synthesis of 1,3,4-trisubstituted imidazolidines (**4a**–**4p**) through a multicomponent reaction involving monophenacyl anilines **1**, aromatic amines **2** and formaldehyde **3** has been developed. The reaction proceeds in refluxing ethanol providing higher yields of the imidazolidines.

Keywords: Imidazolidines; Multicomponent reaction; Mannich reaction; Monophenacyl anilines; Nucleophilic addition.

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Heterocycles stand for a privileged scaffold within the realm of medicinal and biological chemistry. Among the nitrogen heterocycles highly-substituted, five-membered systems with two nitrogen atoms, such as imidazole, imidazoline and imidazolidine include numerous natural products and pharmaceutical lead.[1] Imidazolidines are broad class of bioactive pentagonal heterocyclic compounds with diverse biological activity such as antibacterial, antitubercular, antifungal, antiHIV, antileishmanial, antinociceptive, antiinflammatory and analgesic activity.[2] Imidazolidines are also found to posses antimicrobial, anti-Trypanosoma cruzi[3] and schistosomicidal properties,[4] hypnotic[5] and hypoglycaemic effects.[6,1d] They can be employed as precursors for medicinally important imidazolidin-2-ones,[7] chiral 1,2-diamines[8] and substituted imidazolidine-2,4-diones[9]. Some of the medicinally important compounds having imidazolidine skeleton are shown in Fig. 1. As the imidazolidines have a very reactive methylene group, they may further be functionalized through condensation with aromatic aldehydes.[1d]

The popular method available for the preparation of symmetrical imidazolidines involves the condensation of vicinal diamines with formaldehyde / arylaldehyde in presence of different catalysts[10] with subsequent transformations. The reaction of diethyl oxalate with one equivalent of two different primary amines followed by hydride reduction and condensation reaction with formaldehyde[11] resulted in unsymmetrical imidazolidines, which can also be accessed by some other methods.[12]

Mannich reaction, being one of the most important carbon-carbon bond forming reaction,[13] has been employed in the synthesis of several heterocyclic compounds.[14] As a multicomponent reaction, Mannich reaction can be used to generate a library of compounds with a wide range of structural variations in each categories for biological screening.[15] Multicomponent reaction has been employed as a tool for the eco-friendly approach to the

synthesis of various heterocyclic compounds in our laboratory.[16] In continuation, the construction of the imidazolidine ring through a novel protocol has been planned in the present investigation. Despite the availability of numerous methods for the synthesis of imidazolidines, only one report carries information about 1,3-diaryl-4-aroyl substituted imidazolidine, wherein the compound has been obtained as a byproduct in poor yield.[17]

A retrosynthetic approach reveals that this compound could be accessed from monophenacyl aniline and that prompted us to take up the present investigation. Thus the target imidazolidine, 1,3-diaryl-4-aroyl substituted imidazolidine **4**, was aimed at by refluxing a mixture of substituted monophenacyl aniline **1**, substituted aniline **2** and formaldehyde solution **3** in the ratio of (1:1:2) for 3 h in ethanol (Scheme 1).[18] Solvents such as water, acetonitrile, dimethylformamide, tetrahydrofuran, methanol and toluene were tested for their suitability in this reaction. The cleanest conversion with highest yield was achieved when refluxing the above mixture in ethanol for 3 h (Table 1). It was also proposed to consider the possibility of carrying out a pseudo five-component reaction, using aniline and phenacyl bromide to generate the monophenacyl aniline. Hence a mixture of two moles of aniline, phenacyl bromide and excess formaledyde was subjected to the reaction condition. The reaction did not go on the expected line. It is noteworthy that whatever be the ratio of formaldehyde solution with reference to the other substrates (1 or 2 or excess), only the imidazolidine **4** was obtained. Using the optimal conditions, differently substituted monophenacyl anilines with different anilines were employed to create a library of 1,3-diarylimidazolidin-4-yl) (aryl)methanone **4** in 77-94% yield (Table 2, See Supporting Information for characterization data). It must be mentioned that whenever 4-nitroaniline was used as the component **2**, the reaction has not led to the corresponding **4**.

The structures of the imidazolidines **4** were established from ^{1}H, ^{13}C and two dimensional NMR spectral data as illustrated for a representative example **4d** (Fig. 2 & Fig 3). The methylene hydrogens in between the nitrogen atoms appear as a pair of doublets at 4.72 ppm and 5.07 ppm with a coupling constant of 2.4 Hz. The poor geminal coupling could be due to the attached hetero atoms.

The mechanism for the formation of **4** has been envisaged in Scheme 2 in which two possible paths, route A and B, have been suggested. The imine **5** formed by the reaction of substituted aniline **2** with formaldehyde **3** could have undergone Mannich type reaction with the enolic form of monophenacyl aniline **1** resulting in **6.** **6** could have reacted with formaldehyde ultimately yielding 1,3-diarylimidazolidin-4-yl)(aryl)methanone **4** after dehydration. The initial formation of *N*-hydroxylmethyl derivative **7** has been proposed in route B. **7** undergoes reaction with imine **5** resulting in the imidazolidine derivative **4**.

Thus a simple methodology for the synthesis of unsymmetrical imidazolidines through Mannich type reaction using ethanol as a solvent has been developed. The proposed strategy makes use of readily available low cost substrates with no catalyst.

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18. General procedure for the synthesis of (1,3-diarylimidazolidin-4-l)(aryl)methanone: A mixture of monophenacyl aniline (1 mmol), substituted aniline (1 mmol) and excess formaldehyde solution (0.5 mL) in ethanol (10 mL) was refluxed for 3 h. After completion of the reaction (TLC), the yellow solid was filtered off and further purified by recrystallization from ethanol to yield pure **4**. Characterization data of (3-(4-chlorophenyl)-1-p-tolylimidazolidin-4-

yl)(phenyl)methanone (**4d**): Isolated as colourless solid; m.p. 160 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.27 (s, 3H, CH_3), 3.76 (dd, 1H, J = 8.7, 2.4 Hz, CH_2), 3.99 (t, 1H, J = 8.7 Hz, CH), 4.72 (d, 1H, J = 2.4 Hz, CH_2), 5.07 (d, 1H, J = 2.4 Hz, CH_2), 5.49 (dd, 1H, J = 8.7, 2.4 Hz, CH_2), 6.46 (d, 2H, J = 8.7 Hz, Ar-H), 6.56 (d, 2H, J = 8.4 Hz, Ar-H), 7.08 (d, 2H, J = 8.4 Hz, Ar-H), 7.17 (d, 2H, J = 8.7 Hz, Ar-H), 7.53 (t, 2H, J = 7.8 Hz, Ar-H), 7.63 (t, 1H, J = 7.8 Hz, ArH), 8.03 (d, 2H, J = 7.8 Hz, Ar- H).^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 20.3, 50.7, 62.3, 66.7, 112.8, 113.3, 122.7, 127.6, 128.4, 129.0, 129.2, 129.8, 133.9, 134.4, 143.4, 143.6, 196.9. Anal. Calcd for $C_{23}H_{21}ClN_2O$: C, 73.30; H, 5.62; N, 7.43%. Found C, 73.42; H, 5.55; N, 7.54%.

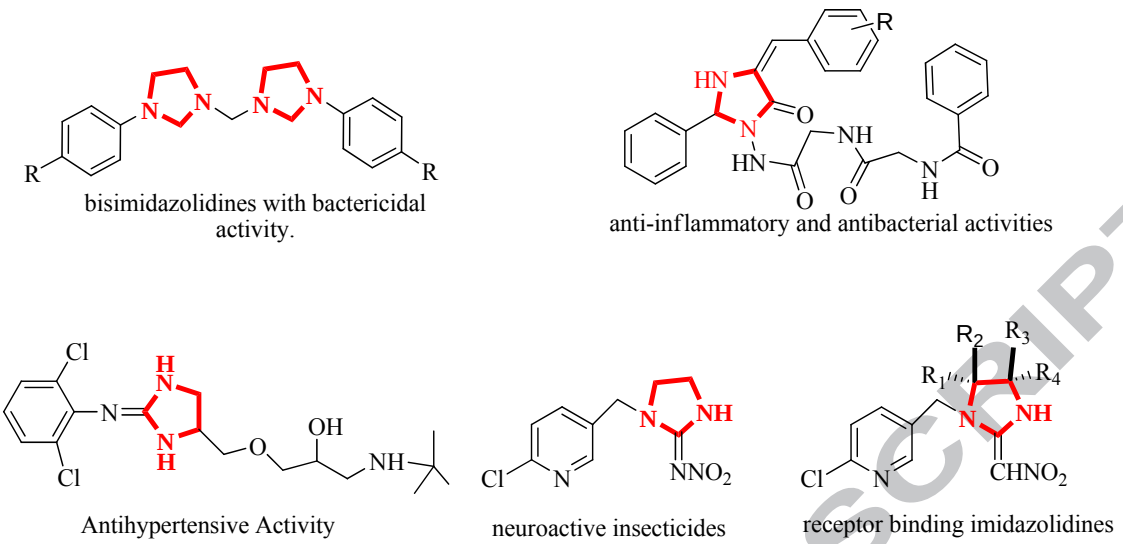


Figure 1. Medicinally important imidazolidine derivatives.

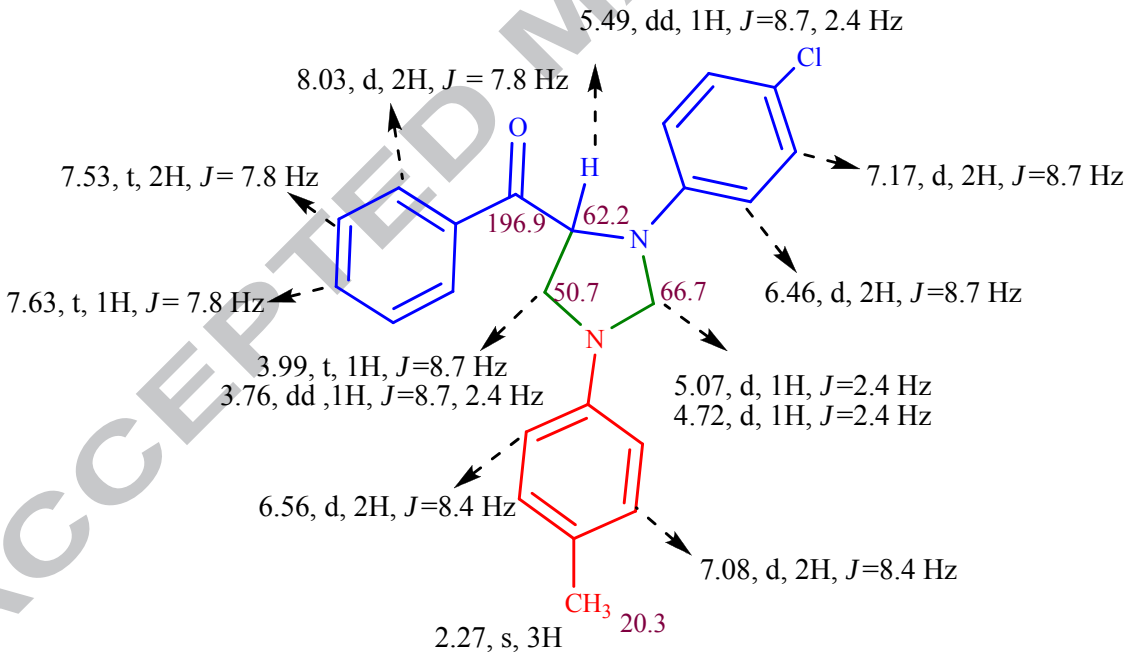


Figure 2. Selected ^{1}H and ^{13}C chemical shifts of compound **4d.**

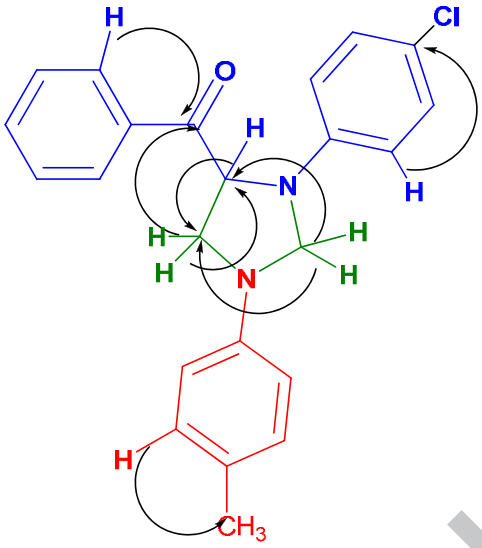


Figure 3. Selected HMB Correlations of **4d.**

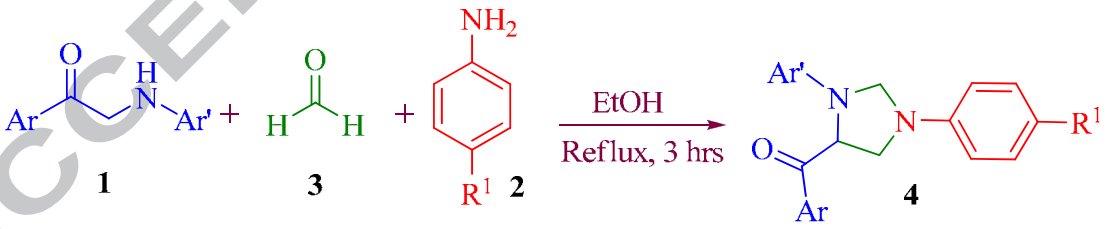
Table 1. Solvent effect on the multicomponent reaction for the formation of **4a.**

Entry	Solvent	Time (hrs)	Yield (%)
1	EtOH	3	94[b]
2	CH_3CN	3	56[a]
3	Water	3	76[b]
4	THF	3	45[a]
5	Toluene	3	60[b]
6	Dioxane	3	No reaction
7	MeOH	3	65[b]
8	DMF	3	No reaction
9	Solvent-free	3	No reaction

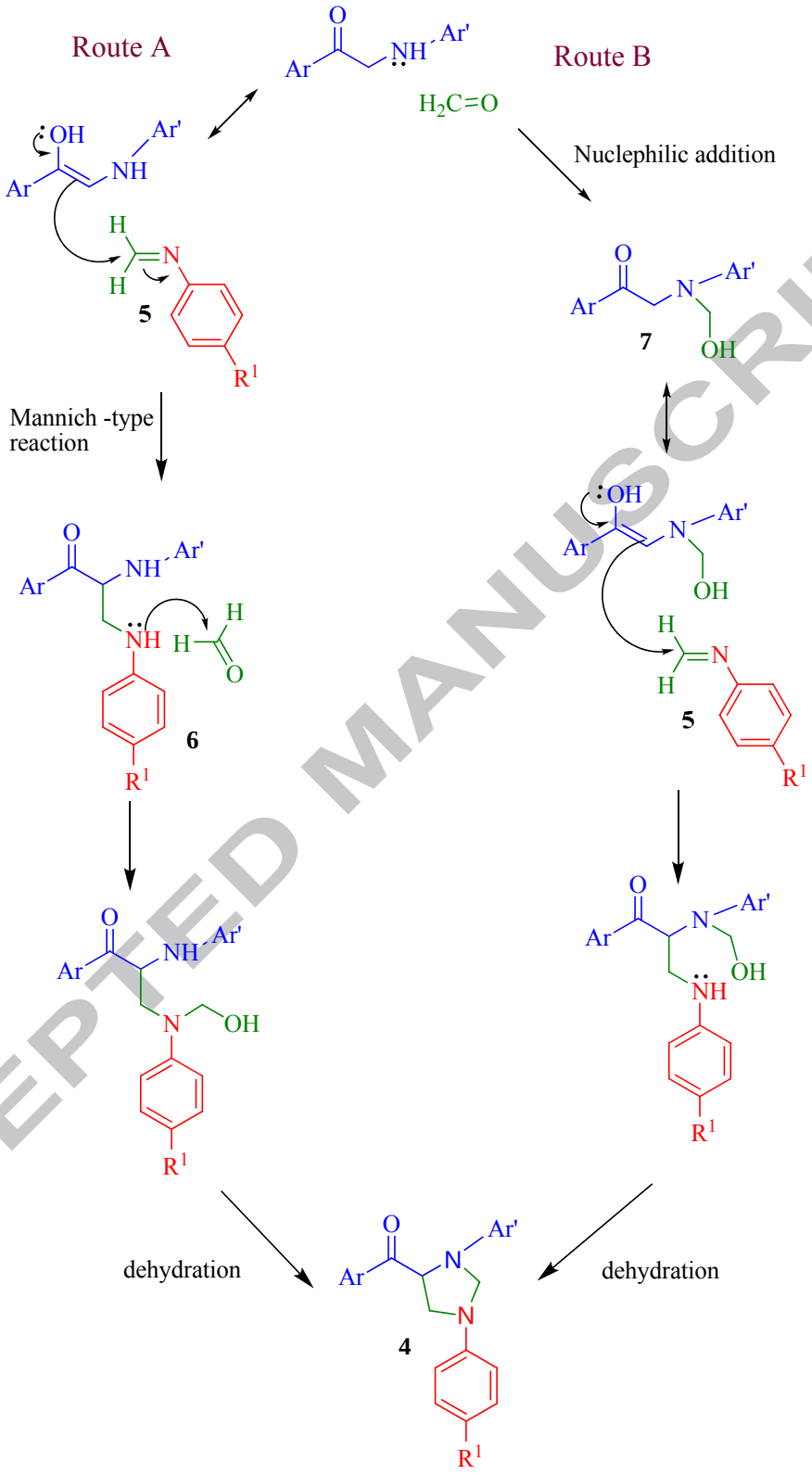
[a]Isolated yield after purification by column chromatography.
[b]Isolated yield by filtration and recrystallisation.

Table 2. Synthesis of compounds **4.**

Entry	compound	Ar	Ar'	R^1	Yield (%)	mp (˚C)
1	**4a**	Phenyl	4-Methylphenyl	CH_3	94	155
2	**4b**	Phenyl	4-Methylphenyl	Cl	78	157
3	**4c**	Phenyl	4-Methylphenyl	F	92	171
4	**4d**	Phenyl	4-Chlorophenyl	CH_3	85	160
5	**4e**	Phenyl	4-Chlorophenyl	Cl	86	158
6	**4f**	Phenyl	4-Chlorophenyl	F	89	159
7	**4g**	4-Chlorophenyl	4-Methylphenyl	CH_3	82	175
8	**4h**	4-Chlorophenyl	4-Methylphenyl	Cl	85	162
9	**4i**	4-Chlorophenyl	4-Methylphenyl	OCH_3	77	145
10	**4j**	4-Chlorophenyl	4-Chlorophenyl	CH_3	82	161
11	**4k**	4-Chlorophenyl	4-Chlorophenyl	OCH_3	78	155
12	**4l**	4-Cyanophenyl	4-Methylphenyl	CH_3	90	168
13	**4m**	4-Cyanophenyl	4-Methylphenyl	F	85	164
14	**4n**	4-Phenylphenyl	Phenyl	CH_3	85	163
15	**4o**	4-Phenylphenyl	4-Methylphenyl	CH_3	83	165
16	**4p**	2-Naphthyl	4-Methylphenyl	CH_3	82	166



Scheme 1. Synthesis of (1,3-diarylimidazolidin-4-yl)(aryl)methanone.



Scheme 2. Plausible mechanism for the formation of (1,3-diarylimidazolidin-4-yl)(aryl)methanone.