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A Green & Facile synthesis of diethyl 4-aryl-2,6-bis((arylsulfonyl)methyl)-1,4-dihydropyridine-3,5-dicarboxylate using Montmorillonite K-10 as a catalyst and their antifungal studies

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ABSTRACT

A multicomponent reaction of ethyl-3-oxo-4-(arylsulfonyl)butanoates , aromatic aldehydes and ammonium acetate using Montmorillonite K-10 as a catalyst provided a series of novel diethyl 4-aryl-2,6-bis((arylsulfonyl)methyl)-1,4-dihydropyridine-3,5-dicarboxylate. This synthetic approach provides an example of a green and facile synthesis under mild reaction condition with considerable yield and purity. The compounds synthesised were evaluated for their antifungal studies

INTRODUCTION

The well-known Hantzsch synthesis is as old as about one and half century is a one-pot multi-component reaction that led to the formation of dihydropyridines via the reaction of aldehyde, two equivalents of a *β*-keto ester, and nitrogen source such as ammonium acetate [1] Various reaction conditions were followed, performing the reaction in solvents like in acetic acid, water, or in ethanol. Of late Lewis acid, base, biocatalysts, organocatalysts, and ionic liquids were used as catalysts in the synthesize of 1,4-dihydropyridines [2-9]. Apart from the conventional methods various other methods like micro-wave irradiation, under solvent-free and catalyst-free conditions were successfully carried out [10].

Many Dialkyl 1,4-dihydro-2,6-dimethylpyridine- 3,5-dicarboxylates **1** moieties have been well established as an important drugs in the medical field especially in the treatment of angina and hypertension.Few examples that are commercially available are given in the figure **1**, Amlodipine **2**, Felodipine **3**, Isradipine **4**, Lacidipine **5**, Nicardipine **6**, Nifedipine **7**, Nimodipine **8**, Nitrendipine **9**. Their therapeutic uses as an efficient calcium channel blockers and thus decrease the passage of the transmembrane calcium current, which leads to a long lasting relaxation of the heart muscle with the reduction in the heart contraction were well established. has been proven that their therapeutic success is related to their efficacy to bind to calcium channels and consequently to decrease the passage of the transmembrane calcium current, associated in smooth muscle with a long lasting relaxation and in cardiac muscle with a reduction of contractility throughout the heart [11-13].

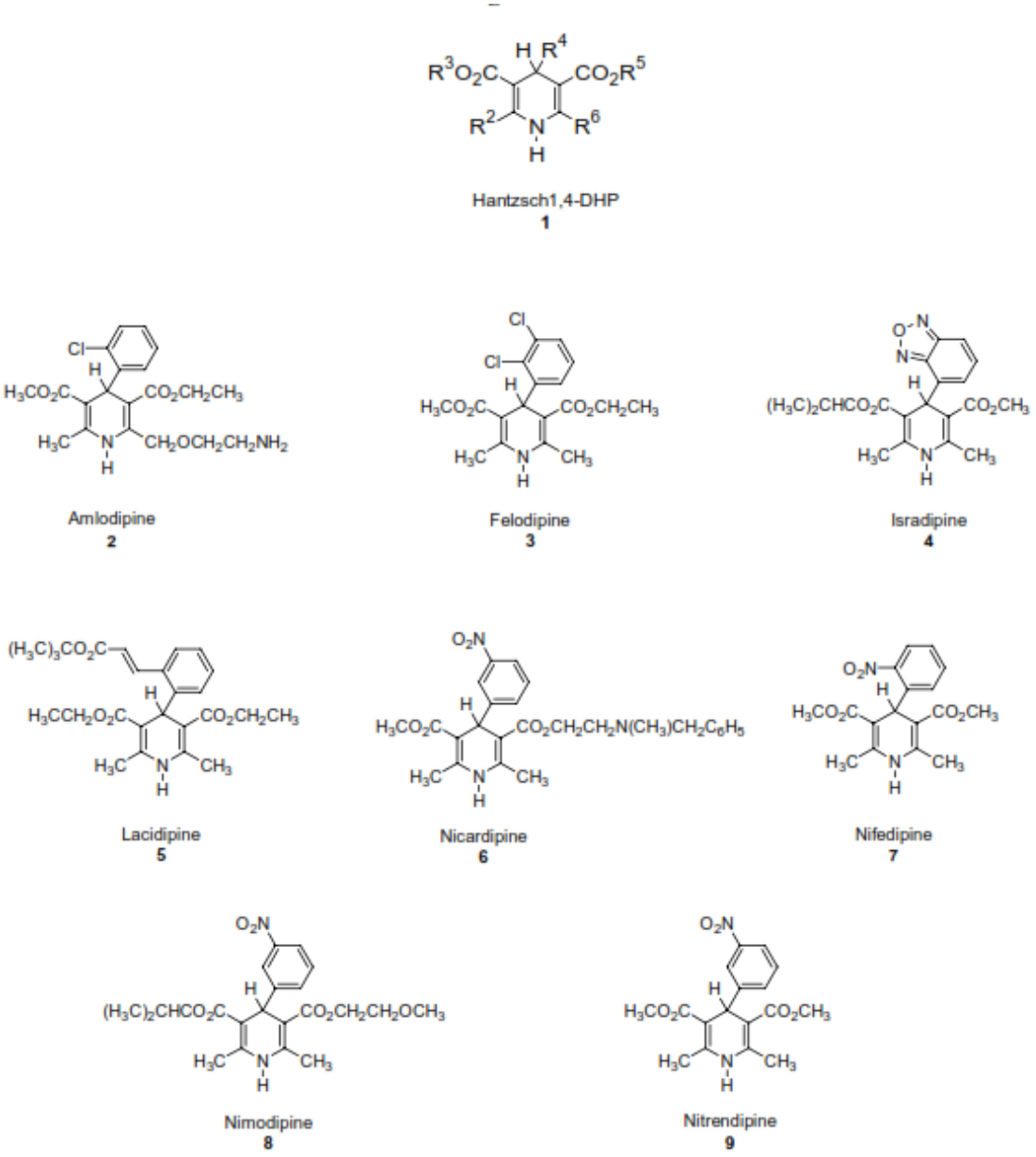
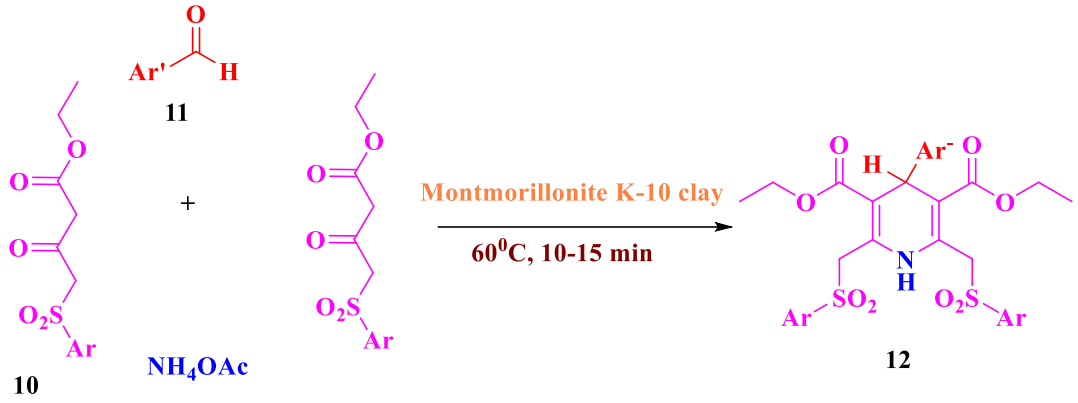


Figure 1: Dialkyl 1,4-dihydro-2,6-dimethylpyridine- 3,5-dicarboxylates derivatives used as the potential drugs

RESULTS & DISCUSSSION:

In the Present work a multicomponent reaction of ethyl-3-oxo-4-(arylsulfonyl)butanoates , aromatic aldehydes and ammonium acetate using Montmorillonite K-10 as a catalyst provided a series of novel diethyl 4-aryl-2,6-bis((arylsulfonyl)methyl)-1,4-dihydropyridine-3,5-dicarboxylate **(Scheme 1)**. This synthetic approach provides an example of a green and facile synthesis under mild reaction condition with considerable yield and purity. The compounds synthesised were evaluated for their antifungal studies.



Scheme 1: Synthesis of diethyl 4-aryl-2,6-bis((arylsulfonyl)methyl)-1,4-dihydropyridine-3,5-dicarboxylate.

A mixture ethyl-3-oxo-4-(arylsulfonyl)butanoates **10** (2 mmol). Derivatives of aldehydes **11**,(1 mmol), ammonium acetate (1.2 mmol), along with Montmorillonite K-10 as a catalyst was taken in a small boiling tube for the required amount of period. After a period of 10-15 min., the completion of the reaction was monitored by using TLC. when the reaction completed, the mixture was dissolved in minimum amount of ethanol, filtered and the filtrate was poured in water, filtered and washed with cold ethanol. The crude solid was purified by a short column chromatography on silica gel employing ethyl acetate-petroleum ether (1:4 v/v) as eluent to obtain pure product **12**.
The yield and reaction time was given in the **Table 1**.

Table 1 Synthesis of compound **12**

Code	Ar	Ar'	Reaction Time (min)	Yield (%)	m.p (°C)
12a	C_6H_5	*p*-$MeOC_6H_4$	10	85	222-223
12b	C_6H_5	*p*-MeC_6H_4	10	92	218-219
12c	C_6H_5	*p*-ClC_6H_4	12	88	205-206
12d	C_6H_5	*p*-FC_6H_4	10	87	215-216
12e	*p*-Me-C_6H_4	*p*-$MeOC_6H_4$	15	95	228-229
12f	*p*-Me-C_6H_4	*p*-MeC_6H_4	10	83	198-199
12g	*p*-Me-C_6H_4	*p*-Cl-C_6H_4	12	90	203-204
12h	*p*-ClC_6H_4	*p*-$MeOC_6H_4$	12	78	195-196
12i	*p*-ClC_6H_4	*p*-MeC_6H_4	14	84	225-226
12j	*p*-ClC_6H_4	*p*-ClC_6H_4	10	90	185-186
12k	*p*-ClC_6H_4	*p*-FC_6H_4	15	91	210-211

The structure of these diethyl 4-aryl-2,6-bis((arylsulfonyl)methyl)-1,4-dihydropyridine-3,5-dicarboxylate is in accord with elemental analyses and ^1H, ^{13}C and 2D NMR spectroscopic data as illustrated for a representative example **12b**. In the ^1H NMR spectrum of **12b**, The -CH_2 hydrogens (methylene hydrogens of ester function) appeared as quartet at 4.02 ppm (*J* = 6Hz Hz), which showed HMBCs with C-9 at 93.2 and C-10 at 35.0 ppm. The methylene hydrogens of the ester function appeared as a quartet at 3.88 ppm which showed HMBC with ester carbonyl at 164.1 ppm and CH_3 carbon at 13.9 ppm..The carbonyl carbon C-6 that appears at 193.3 ppm showed HMBC correlation with C-11&12hydrogens at 0.95 ppm. (**Figures 2 & 3**). After the addition of the D_2O, the peak at 6,82 disappears, which shows the presence of -NM group.

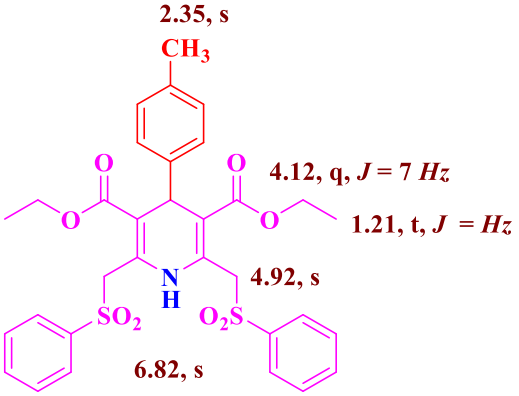


Figure 2. Selected ^1H NMR values for compound 12b

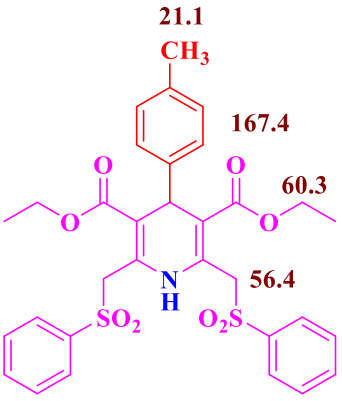


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Figure 3. Selected ^{13}C NMR values for compound 12b

Anti-Fungal Studies

Compounds synthesised were investigated for antifungal studies. Most of the compounds show considerable activity against all the organisms tested. Compounds **12a, 12b, 12e** and **12h** were found to be almost equipotent to that of reference drug kanamycin (**Table 2**).

Table 2: Antifungal activity of diethyl 4-aryl-2,6-bis((arylsulfonyl)methyl)-1,4-dihydropyridine-3,5-dicarboxylate 12

S.No	Comp	*Aspergillus Niger*				*Trichoderma*				*Candida albicans*			
		Concn. (mmol)				Concn. (mmol)				Concn. (mmol)			
		25	50	75	100	25	50	75	100	25	50	75	100
1	**12a**	++	++	+++	++++	+	+	++	++	++	++	+++	+++
2	**12b**	_	_	++	++	+	++	+++	+++	_	+	+	++
3	**12c**	+	+	++	++	_	_	_	_	_	_	_	_
4	**12d**	++	++	++	+++	_	_	_	++	+	+	++	++
5	**12e**	++	+++	+++	++++	+	+	++	++	_	_	+	++
6	**12f**	_	_	_	_	+	++	++	+++	_	_	_	_
7	**12g**	+	++	++	+++	_	_	_	_	_	_	_	_
8	**12h**	_	_	_	++	+	++	+++	+++	+	+	++	+++
9	**12i**	_	+	+	++	_	_	+	+	_	_	_	_
10	**12j**	+	++	++	+++	_	_	_	_	_	_	_	_
11	**12k**	_	_	++	++	+	++	+++	+++	_	+	+	++
12	***Kanamycin***	++	++	+++	+++	++	+++	+++	++++	+	++	+++	+++

CONCLUSION

In this article we described a multicomponent reaction of ethyl-3-oxo-4-(arylsulfonyl)butanoates , aromatic aldehydes and ammonium acetate using Montmorillonite K-10 as a catalyst provided a series of novel diethyl 4-aryl-2,6-bis((arylsulfonyl)methyl)-1,4-dihydropyridine-3,5-dicarboxylate. This synthetic approach provides an example of a green and facile synthesis under mild reaction condition with considerable yield and purity. The compounds synthesised were evaluated for their antifungal studies. Many compounds shows considerable antifungal activity.

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