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EFFICIENT SYNTHESIS OF 2,4,5-TRISUBSTITUTED IMIDAZOLES USING SILICOTUNGSTIC ACID AS CATALYST

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ABSTRACT

Objective: One-pot multicomponent reactions (MCRs) that convert more than two reactants directly into their products are of interest to chemists, owing to conserving atom economy and fostering the benign synthesis of organic compound like 2,4,5-trisubstituted Imidazoles derivatives. were efficiently synthesized by the reaction of benzyl/benzoin, ammonium acetate, and aromatic aldehydes in the presence of Silicotungstic acid as catalyst in ethanol.

Materials and Methods: 2,4,5-trisubstituted Imidazoles derivatives were efficiently synthesized by the reaction of benzyl/benzoin, ammonium acetate, and aromatic aldehydes in the presence of Silicotungstic acid as catalyst in ethanol under reflux.

Result: The syntheses of 2,4,5-triarylimidazoles using various benzaldehyde, benzil, ammonium acetate in the presence of a catalytic amount of silicotungstic acid (7.5 %) under reflux using ethanol as solvent.

Conclusion: The attractive features of this process are mild reaction conditions, short reaction times, easy isolation of products, and excellent yields.

Keywords: Multi-component reaction, Silicotungstic Acid, 2,4,5-trisubstituted Imidazoles derivatives, One pot.

INTRODUCTION One-pot multicomponent reactions (MCRs) that convert more than two reactants directly into their products are of interest to chemists, owing to conserving atom economy and fostering the benign synthesis of organic compounds. MCRs are part of the latest advanced solutions for decreasing the discovery and development times for new drugs, and potentially reducing the development costs and complexity in the process. Thus, useful structural variations can be increased [1, 2].

Substituted imidazoles have gained remarkable importance as pharmaceutical agents with antitumor [3], and antiinflammatory actions [4], antibacterial agents [5] herbicides [6], fungicides [7], inhibitors of P38 MAP kinase [8] as well as inhibitors of mammalian 15-LOX [9]. In addition to this, imidazoles are substantially used in the synthesis of ionic liquids [10]. They are also used in photography as photosensitive compounds [11]. Hence, Due to their great importance, many synthetic strategies have been developed. In 1882, Radziszewski and Japp reported the first synthesis of the imidazole from 1,2-dicarbonyl compound, various aldehydes and ammonia, to obtain the 2,4,5-triphenylimidazoles [12].

Recently, there are several methods reported in the literature for the synthesis of 2,4,5-triaryl-1*H*-imidazoles from benzyl/benzoin, aldehydes and ammonium acetate using different catalyst such as Keggintype heteropolyacid [13], $Yb(OTf)_3$ [14], iodine [15], PEG-400 [16], L-proline [17] $Y(TFA)_3$ [18], poly(AMPS-co-AA) [19],Tannic acid [20], $SbCl_3$[21],Rochelle Salt[22], nanoporous material (SBA-Pr-SO_3H) [23], $NiCoFe_2O_4$ [24], La0.5 Pb0.5MnO_3 [25] and 4 Å molecular sieves with titanium(IV) [26]. In recent years, silicotungstic acid has been successfully used as a acid catalyst for various organic synthetic transformations such as bis(indolyl)methane synthesis [27], alkylation of benzene with olefins [28], production of acrolein from glycerol [29], indole Michael addition [30], 1,2-dihydroquinones [31]and synthesis of oxindole derivatives [32]. We wish now to report a new usage of silicotungstic acid as an impressive, inexpensive and easily handling acid catalyst for the synthesis of 2,4,5-trisubstituted Imidazoles derivatives via the condensation reaction of benzyl/benzoin, ammonium acetate, and aromatic aldehydes at reflux temperature.

MATERIALS AND METHODS

Experimental

All the melting points were determined in open capillaries in an paraffin bath and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR using KBr discs. 1H NMR spectra were recorded on Mercury plus Varian in DMSO or $CDCl_3$ at 500 MHz using TMS as an internal standard. Mass spectra were recorded on Micromass Quattro II using electrospray Ionization technique. The progress of the reactions was monitoredby TLC.**General experimental procedure synthesis of 2,4,5-triaryl-1*H*-imidazole (4a-l).** A mixture of an aromatic aldehyde (1 mmol), benzyl/benzoin (1 mmol), ammonium acetate (2.5 mmol) and silicotungstic acid (7.5 mol %) in ethanol (15 ml) was stirred at reflux temperature for 3.5~7 hr. The progress of the reaction was monitored by TLC. After completion of reaction conversion, the reaction mixture was cooled to room temperature and poured on crushed ice. The obtained crude solid product was filtered, dried and crystallized from ethanol.

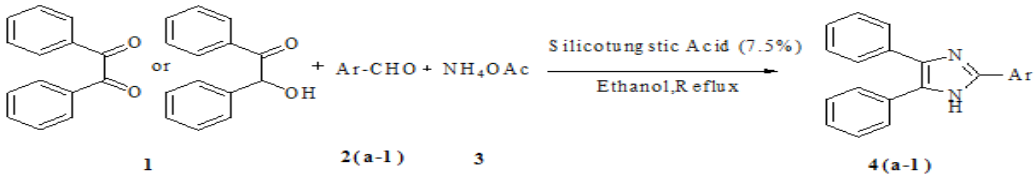
RESULTS AND DISCUSSION

In continuation of our research work on the development of novel synthetic methodologies, we would like to report a highly efficient route for the synthesis of 2,4,5-triaryl imidazoles catalyzed by an commercially available, inexpensive, mild catalyst silicotungstic acid.

Here we wish to report a very simple and general method for the syntheses of 2,4,5-triarylimidazoles (4**a-l**) in the presence of a catalytic amount of silicotungstic acid under reflux using ethanol as solvent (Scheme 1) considered as a standard model reaction. As an example, we examined the reaction among 4-chlorobenzaldehyde, benzil, ammonium acetate, and silicotungstic acid (7.5mol %) using ethanol as solvent under reflux condation.

To evaluate the effect of solvent, we have screened different solvents such as chloroform, acetonitrile, dichloromethane,

tetrahydrofuran, dioxane, methanol, ethanol, ethanol:water (1:1) at reflux temperature. Ethanol stand out as the solvent of choice among the solvents tested because of the rapid conversion and excellent yield (97%) of desired product, whereas the product formed in lower yields (25~80%) by using other solvents (Table 1, Entry 1~8). In case of the protic solvents the yields are better than aprotic solvent. (Table 1, Entry 6~8).



Scheme 1: Synthesis of 2,4,5-triarylimidazoles (4a-l)

Table 1: Screening of solvents for the synthesis of 4a

Entry	Solvent	Yield(%)
1	Chloroform	45
2	Acetonitrile	40
3	Dichloromethane	47
4	Tetrahydrofuran	42
5	Dioxane	25
6	Methanol	75
7	Ethanol	94
8	Ethanol:Water(1:1)	80

To determine the optimum concentration of catalyst, we have investigated the model reaction at 2.5, 5, 7.5 and 10 mol% of silicotungstic acid in ethanol at reflux temperature. The product was obtained in 63, 85, 94 and 94% yield, respectively. This indicates that the use of 7.5 mol% of silicotungstic acid is sufficient to promote the reaction forward (Table 2).

Table 2: Effect of concentration of silicotungstic acid

Entry	Concentration (mol %)	Yield (%)
1	2.5	63
2	5	85
3	7.5	94
4	10	94

To study the generality of this process, variety of examples were illustrated for the synthesis of 2,4,5-triaryl imidazoles and results are summarized in Table 3. The reaction is compatible for various substituents such as electron donating and withdrawing. This method is also effective for the heteroaromatic aldehydes which form their corresponding 2,4,5-triarylimidazole derivatives in 82~94% of yields. The formation of the desired products was confirmed by 1H-NMR, FT-IR and mass spectroscopic analysis techniques.

Table 3: Silicotungstic acid catalyzed synthesis of 2,4, 5, triaryl substituted imidazoles

Entry	Product	Ar-	Time (h)		Yield (%)		M.P. (°C)
			Benzil	Benzoin	Benzil	Benzoin	
1	4a	4-ClC_6H_4	5.5	6.5	94	90	257-259
2	4b	C_6H_5	4.5	6	92	89	273-275
3	4c	4-$OCH_3C_6H_4$	4	5.5	89	85	228-229
4	4d	4-$NO_2C_6H_4$	6.5	7	85	82	233-234
5	4e	4-$CH_3C_6H_4$	4	5	87	85	230-232
6	4f	2-ClC_6H_4	5	6.5	91	90	195-197
7	4g	4$(CH_3)_2NC_6H_4$	4.5	6	92	89	257-259
8	4h	4-OHC_6H_4	5.5	6.5	91	88	270-271
9	4i	4-FC_6H_4	3.5	4.5	93	90	192-193
10	4j	4-OH,3-OCH_3C_6H	5	6.5	90	88	220-222
11	4k	C_4H_3O	4.5	6	92	89	199-201
12	4l	C_4H_3S	5	6.5	91	88	259-261

CONCLUSION

In this report we have demonstrated the application of silicotungstic acid (STA) as a very effective, eco-friendly and inexpensive commercial-available catalyst in the synthesis of 2,4,5-triaryl-1*H*-imidazole at reflux temperature. Simple experimental procedure associated with high yield, less reaction time makes this protocol interesting for organic chemists.

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2-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (4a): IR (KBr, cm-1): 3442 (N-H), 1602 (C = C), 1577 (C = N). 1H NMR ($CDCl_3$/ DMSO-*d*6, 500 MHz, δ ppm): 7.25 (d, 2 H, *J* = 8.4 Hz, Ar-H), 7.75 (d, 2 H, *J* = 8.4 Hz, Ar-H) 7.25-7.70 (m, 10 H, Ar-H) 12.10 (1 H, brs, NH). ES-MS (m/z): 331 (M + 1), 332 (M + 3).
2,4,5-Triphenyl-1*H*-imidazole (4b): IR (KBr, cm-1): 3415 (N-H), 3045 (C-H), 1610 (C = C), 1585 (C = N). 1H NMR ($CDCl_3$/DMSO-*d*6, 500 MHz, δ ppm): 7.5-8.2 (m, 15 H, Ar-H), 12.51 (1 H, brs, NH). ES-MS (m/z): 297 (M + 1).
2-(4-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (4c): IR (KBr, cm-1): 3444 (N-H), 2951 (C-H), 1620 (C = C), 1565 (C = N), 1360 (C-O). 1H NMR ($CDCl_3$/DMSO-*d*6, 500 MHz, δ ppm): 3.81 (s, 3 H), 7.03 (d, 2 H, *J* = 8.4 Hz, Ar-H), 7.89 (d, 2 H, *J* = 8.4 Hz, Ar-H). 7.27-7.77 (m, 10 H, Ar-H), 12.22 (1 H, brs, NH). ES-MS (m/z): 327 (M + 1).