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Caro'sacid-silicagel: An Efficient and Reusable Catalyst for the Synthesis of 2, 4, 5- Trisubstituted Imidazoles under Solvent-free Conditions

Khalil Pourshamsian, Naser Montazeri, Sadegh Asadyan*

Department of Chemistry, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran

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Abstract

Caro's acid-silicagel was found to be a mild and effective catalyst for the one –pot multi-component condensation of benzyl, aldehydes and ammonium acetate used for synthesis of 2, 4, 5-trisubstituted imidazole derivatives under solvent–free conditions. This catalyst has several advantages such as simple work-up, low cost and reusability.

Keywords: *Caro's acid-silicagel, 2, 4, 5 –Tri substituted imidazoles, Multicomponent reactions.*

Introduction

Multicomponent reactions (MCRs) forming heterocyclic compounds are powerful tools in the drug-discovery process as they can offer expedient synthesis of libraries of drug like compounds in a single operation [1]. Highly substituted imidazole derivatives are also the key intermediates in the synthesis of many therapeutic agents. Omeprazole, pimobendan, losarton, olmesartan, eprosartan and triphenagrel are some of the leading drugs in the market with diverse functionality [2]. Triarylimidazoles are used in photography as photosensitive compound [3]. In addition, they are of interest due to their herbicidal [4], analgesic [5], fungicidal [6], anti-inflammatory [6], and anti thrombotic activities [7]. Recent advances in green chemistry and organo metallic catalysis have extended the application of imidazole as ionic liquids [8] and n-heterocyclic carbenes [9]. There are numerous methods in the literature for the synthesis of highly substituted imidazoles. 2, 4, 5-Trisubstituted imidazoles

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***Corresponding author:** *Dr. Sadegh Asadyan, Department of Chemistry, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran. Tel: 00981924271105 , Email:sadegh.asadyan@gmail.com.*

are generally synthesized by three component cyclocondensation of a 1, 2-diketone, α-hydroxyketone or α-ketomonoxime with an aldehyde and ammonium acetate, which comprise the use of microwaves, ionic liquids. Refluxing in acetic acid, silica sulfuric acid, and $NiCl_2$. $6H_2O/Al_2O_3$ [10]. Moreover, they have also been prepared by the reaction of arylnitriles and α, α-dilithioarylnitromethanes or by multistep synthesis [11]. Although the reported methods are suffered by low yields, mixture of products, and lack of generality, harsh reaction conditions, excess of reagents. We report here simple and green approach for the synthesis of 2, 4, 5-trisubstituted-1H-imidazole derivatives by the condensation of benzyl, aldehydes, ammonium acetate using caro's acid-silicagel as catalyst. This catalyst is heterogeneous, mild, non-explosive, easy to handle and reusable. In view of emerging importance of heterogeneous catalyst, we wish to explore the use of caro's acid-silicagel under solvent-free conditions.

Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. Products were characterized by spectroscopic data (IR, NMR spectra) and melting points with authentic samples. All melting points are uncorrected and were measured by Electrothermal 9100s melting point apparatus. Progress of reactions was monitored by TLC.IR spectra were recorded (KBr disk) on a 4300 Shimadzu fourier transform spectrophotometer. ^{1}HNMR spectra were recorded on a Bruker AVANCE 300-MHz instrument.

Typical procedure

Caro's acid-silicagel was prepared with identical procdure [13]. Mixture of benzyl (5mmol), aromatic aldehyde (5mmol), and NH_4OAC (10mmol) in the precence of caro's acid (20 mol%) was heated in a test tube under 120◦C at solvent-free conditions. The progress of reaction was monitored by TLC using pet.ether and ethylacetate (7:3). After 40 min the reaction was completed, the chloroform was added and the solid caro's acid-silicagel was filtered and dried at 80◦C and used for reusability. The organic layer was removed under reduced pressure. Further, crude product was purified by 75% EtOH and gave 2, 4, 5-triphenyl-*1H*-imidazole in 93% yield. All products prepared with the same methods and the structures of them confirmed by 1HNMR, IR spectra and comparison with authentic samples prepared by reported methods (Scheme 1).

Selected IR and 1H-NMR data

3a: IR (KBr disk): 3340 (NH), 1670 (C=N), 1600, 1462 (C=C) cm^{-1}.

^{1}HNMR (DMSo-d_6): δ 9.30 (S, 1H, NH), 6086- 7.62 (m, 1SH, arom-H) ppm.

3b: IR (KBr disk): 3348 (NH), 1668 (C=N), 1605, 1456 (C=C) cm^{-1}.

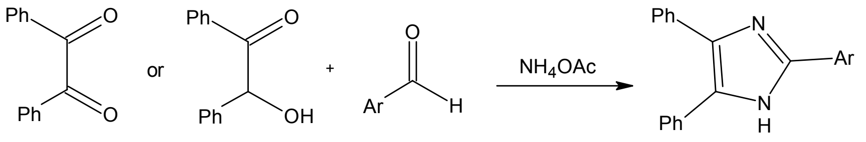
^{1}HNMR (DMSo-d_6):δ 9.28 (S, 1H, NH), 8.13 (d, 2H, ^3J=8.12 Hz, arom- H), 7.88 (d, 2H, 3J= 8.16 Hz, arom-H), 6.98- 7.66 (m, 1OH, arom-H) ppm.

3d: IR (KBr disk): 3335 (NH), 1677 (C=N), 1350, 1550 (NO_2)cm^{-1}.

^{1}HNMR (DMSo-d_6):δ 9.18 (S, 1H, NH), 8.58 (d, 2H, 3J=8.03Hz, arom-H) , 7.92 (d, 2H, ^3J=8.08Hz, arom-H), 6.92- 7.55 (m, 1OH, arom-H)ppm.

3h: IR (KBr disk): 3348 (NH), 1670 (C=N), 1180 (C-O)cm^{-1}.

^{1}HNMR (DMSo-d_6):δ 9.22 (s, 1H, NH), 6.66- 7.84 (m, 13H, arom-H), 4.01 (s, 3H, OCH3), 3.88 (s, 3H, OCH3)ppm

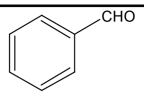
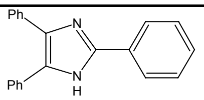
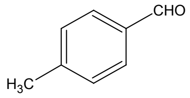
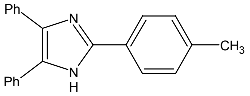
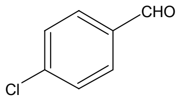
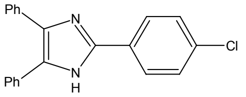
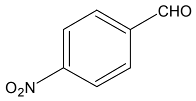
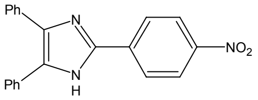
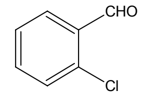
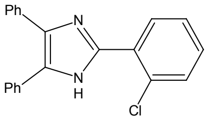
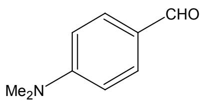
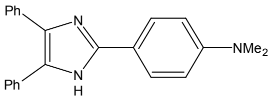
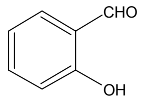
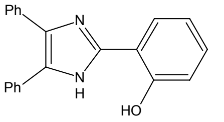
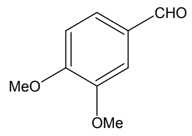
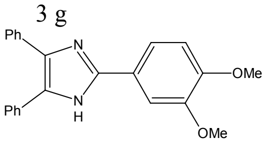


(1) (2) (3a-h)

Scheme 1. Preparation of 2, 4, 5-triphenyl-*1H*-imidazole.

The results were summarized in Table 1.

Table1. Condensation of benzyl, aldehydes and ammonium acetate using caro's acid-silicagel as solid acid catalyst under conventional heating (120°C).

Entry	Aldehyde	Products	Time (min)	Yields ^{ab}%	Mp (°C)^{c} foundreported
1		 3 a	40	93	271-272270-271[14]
2		 3 b	60	85	224-226222-223[14]
3		 3 c	40	92	253-254251-252[14]
4		 3 d	30	96	240-242239-240[14]
5		 3e	48	90	179-181180-181[14]
6		 3 f	80	76	252-253253-254[14]
7		 3 g	75	72	200-201202-203[14]
8		 3 h	95	71	185-187187-188[14]

[a] Isolated products.

[b] All products were characterized by IR. ^{1}HNMR and compared with authentic samples.

[c] Literature data of known compounds.

Table 2. Optimization of the reaction conditions in the synthesis of 2, 4, 5-triphenyl-*1H*-imidazole using caro's acid-silicagel as solid acid catalyst under solvent free-conditions.

Entry	Catalyst loading (mol%)	T°C	Time (min)	Yield (%)[a]
1	none	100	80	Trace
2	5	110	80	20
3	5	120	80	32
4	10	120	80	52
5	10	130	80	57
6	15	110	80	72
7	15	120	40	78
8	20	110	40	82
9	20	120	40	93
10	20	130	40	90
11	25	120	40	66
12	25	130	40	58

[a] Isolated products.

Results and discussion

As a part of our ongoing efforts towards the development of new procedure for the highly substituted heterocycles through multi component reaction. We have discovered an efficient and environmentally friendly procedure for the synthesis of trisubstituted imidazoles. In continuation of our effort to develop lewis and bronsted acid [12-14]. Catalyzed synthesis methodologies, we report herein, for the first time, a simple, mild and expeditious synthesis of 2, 4, 5-trisubstituted imidazoles in high yields using caro's acid-silicagel as a catalyst at 120◦C in solvent-free conditions.

Initially, we bought a mild and convenient method for the synthesis of trisubstituted imidazoles in solvent-free conditions. Our investigation began with the evaluation of caro's acid-silicagel as a catalyst in the reaction of benzyl (10mmol), benzaldehyde (10mmol) and ammonium acetate (20mmol) at 120◦C in solvent-free conditions. The use of 20 mol% of caro's acid-silicagel in this conditionaffordeda93% yield (Table 2, Entry 9) of the desired product. Optimization of the reaction conditions was undertaken to increase the yield employing different catalyst loadings in solvent-free conditions. The results were summarized in table 2. The yield was increased to using 10mol% of caro's acid (Table 2, Entry 4, 5). However, the addition of 25 mol% of the catalyst was found to have an inhibitory effects on the formation of 2, 4, 5-triphenylimidazole (Table2, Entry 11, 12). At the same time a reduction in yield was observed by decreasing the catalyst among to 5mol% (Table2, Entry 2, 3). In the absence of catalyst, the reaction proceeded sluggishly (Table2, Entry 1). The influence of other solvents was also examined. Changing the solvent from polar protic (methanol and ethanol) to polar aprotic (acetonitril, tetrahydtofurane) furnished poor yields. Other solvents, such as CH_2Cl_2, $CHCl_3$ and toluene were ineffective for this transformation. The results summarized in table 3.

The effects of temperature were also examined on model reaction. Increasing of temperature to the point of 120◦C causes increase the yield or reaction but in temperature higher than 120◦C, the results showed that the yield gradually decreased (Table 2, Entry 12), hence the conditions of entry, shown in Table 2 were the optimized reaction conditions.

The reusability of the catalyst is also investigated by the same model reaction under optimized conditions. After completion of the reaction, the catalyst was filtered, washed with acetone dried and reused for the same reaction process. As shown in table4, the catalyst could be reused at least seven times with only slight reduction in the catalytic activity of the catalyst. In all cases aromatic aldehydes containing electron with drawing groups (such as nitro) gave shorter time them that with electron-donating groups (such as methoxy). Though meta and para substituted aromatic aldehyde gave good results, or mono-substituted aromatic aldehyde (such as 2-chloro benzaldehyde) gave lower yields and longer reaction time because of the steric effects.

Table 3. The effects of different solvents on model reaction.

Entry	Solvent	Time (min)	Yield (%)
1	CH_3OH	130	64
2	CH_3CH_2OH	130	66
3	CH_3CN	130	46
4	THF	150	54
5	CH_2Cl_2	150	33
6	$CHCl_3$	150	30

Table 4. Reusability of catalyst for model reaction.

Entry cycle	1 (Fresh)	2	3	4	5	6	7	8
Yield (%)	91	91	90	90	89	89	88	80

Conclusion

In summary, we have developed a general and highly efficient one-pot multi-component reaction for the synthesis of 2, 4, 5-triaryl-*1H*-imidazole derivatives using heterogeneous and reusable catalysts caro's acid-silicagel in solvent free-conditions. Compared to previous reported methodologies, the present protocol features simple operation short reaction time, environmental friendliness, good yields, easy work-up and omits any volatile and hazardous organic solvents.

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