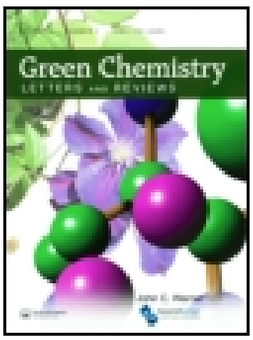

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RESEARCH LETTER

A convenient synthesis of 2,4,5-triarylimidazoles catalyzed by $Y(TFA)_3$

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Yttrium(III) trifluoroacetate is used as efficient catalyst for reaction of benzil, aldehydes, and ammonium acetate under mild and solvent-free conditions to afford the corresponding 2,4,5-triarylimidazoles in high yields and short reaction time. Furthermore, the catalyst can be recovered conveniently and reused several times in the reaction without a significant loss of catalytic activity.

Keywords: Yttrium(III) trifluoroacetate; catalyst; 2,4,5-triarylimidazoles; solvent-free; synthesis

Introduction

Triarylimidazole derivatives have many pharmaceutical activities and play important roles in biochemical processes (*1*). Some substituted triarylimidazoles are selective antagonists of the glucagon receptor (*2*) and inhibitors of IL-1 biosynthesis (*3*). There are several methods for the synthesis of substituted imidazoles (*4*). The reaction of aldehydes, benzil, and ammonium acetate with low yields after many hours refluxing in HOAc was the classical route to synthesize imidazoles (*5*). Later, the procedure of three components condensation of benzil, benzaldehyde derivatives, and ammonium acetate was frequently employed. In this procedure, $[HeMIM]BF_4$ (*6*), $Eu(OTf)_3$ (*7*), Keggin-type heteropolyacid (*8*), $HClO_4$–SiO_2 (*9*), iodine (*10*), zeolite HY and silica gel (*11*), silica sulfuric acid (*12*), $NiCl_2{\cdot}6H_2O$ (*13*), and $Yb(OTf)_3$ (*14*) were used as catalysts to synthesize triarylimidazoles. Moreover, the synthesis of these triarylimidazoles has been usually carried out in the presence of microwave irradiation (*15–18*). But some of the synthesis methods suffer from one or more disadvantages to a large extent, such as harsh reaction conditions, poor yields, longer reaction times, and the use of hazardous and often expensive acid catalysts. Thus, the development of a simple and efficient method for the preparation of 2,4,5-triarylimidazoles is an active area of research with a scope for further improvements toward milder reaction conditions and higher product yields.

In recent times, the use of trifluoroacetates has received considerable attention as inexpensive, nontoxic, and readily available Lewis acid catalysts for various organic transformations. Trifluoroacetates such as $Cu(TFA)_2$, $Ag(TFA)$, $Ni(TFA)_2$ (*19*), $Fe(TFA)_3$ (*20*), and $Bi(TFA)_3$ (*21*) were utilized as powerful catalysts to synthesize multifarious compounds. Our research group has successfully synthesized 3,4-dihydropyrimidin-2(1*H*)-ones and α,α′-bis(substituted benzylidene)cycloalkanones catalyzed by $Cu(TFA)_2$ in high yields and short reaction times under solvent-free conditions (*22,23*).

In this report, Yttrium(III) trifluoroacetate ($Y(TFA)_3$) was employed as Lewis acid catalysts for the synthesis of 2,4,5-triarylimidazoles via solvent-free conditions (Scheme 1).

Results and discussion

Firstly, the reaction of benzaldehyde, benzil, and ammonium acetate was chosen as the model reaction to detect the catalytic activity of $Y(TFA)_3$ and to investigate the optimized conditions. The reaction was carried out at different reaction temperatures (r.t., 70–100°C) and different reaction times (2–4 h). Furthermore, we changed the amount of catalyst from 1 to 5 mol%. Through thorough investigation, the best result in 97% yield was obtained by carrying out the reaction with 1:1:7 mole ratios of benzaldehyde, benzil, and ammonium acetate at 100°C and the dosage of 3 mol% catalysts for 3 h under solvent-free conditions.

Encouraged by these results, we have extended the methodology to a variety of aldehydes. Based on the optimum reaction conditions obtained above, the reactions of various aldehydes with benzil and

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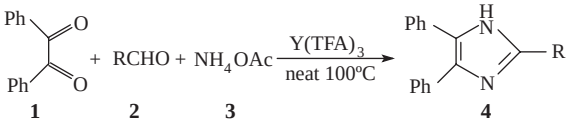


Scheme 1. Synthesis of 2,4,5-triarylimidazoles using benzil, aldehydes and $Y(TFA)_3$.

ammonium acetate were investigated. The results are summarized in Table 1.

In the course of the study, the reactions proceeded completely to afford the corresponding 2,4,5-triarylimidazoles. We found that for aldehydes bearing either electron-releasing or electron withdrawing substituents in the meta or para positions, the reaction proceeded very efficiently in all cases. It seems that the effect of substituted groups on the aromatic aldehydes is not very strong. As expected in the case of propionaldehyde, as an aliphatic aldehydes, the desired product was obtained in lower yield (Table 1, **4j**, 45%).

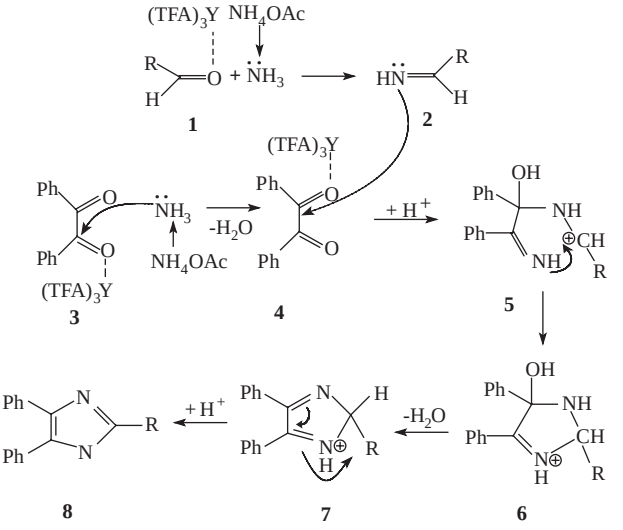
The recyclability of $Y(TFA)_3$ was also investigated (Table 1, **4a**). Of particular note was the fact that the $Y(TFA)_3$ was very easy recovered quantitatively from the aqueous layers of the reaction mixture. It was reused in subsequent reactions and the yields of 2,4,5-triphenylimidazoles were 90%, 88%, 85%, and 80% in consecutive runs, respectively. Accord to the results above, $Y(TFA)_3$ is efficient and reusable catalyst for the synthesis of 2,4,5-triarylimidazoles.

A probable mechanism for the synthesis of 2,4,5-triarylimidazoles may be presumed as shown below (Scheme 2). Ammonium acetate decomposes ammonia under the condition of heating which is the main source of nitrogen in the course of the reaction. Because of the strong withdrawing effect of trifluoroacetic group and the character of its metal cation, $Y(TFA)_3$ is a strong Lewis acid catalyst. The carbonyl

Table 1. Synthesis of 2,4,5-triarylimidazoles catalyzed by $Y(TFA)_3$ under solvent-free conditions at 100°C for 3 h.

			Mp (°C)	
Entry	*R*	Yield[a] (%)	Found	Reported
4a	C_6H_5	97	278	276–277 *(25)*
4b	p-ClC_6H_4	97	264–266	263–264 *(25)*
4c	2,4-$(Cl)_2$-C_6H_3	88	174–176	176–178 *(14)*
4d	p-HOC_6H_4	99	262–264	260–261 *(26)*
4e	p-$MeOC_6H_4$	96	230–232	228–231 *(12)*
4f	p-MeC_6H_4	90	232–234	232–235 *(18)*
4g	m-$NO_2C_6H_4$	93	315–318	313–315 *(13)*
4h	2-ClC_6H_4	90	194–196	196–197 *(18)*
4i	p-$NO_2C_6H_4$	93	225–227	227 *(27)*
4j	$CH_3CH_2CH_2$	45[b]	255–257	256–258 *(14)*

[a]Isolated yield.
[b]The reaction time is 5 h.



Scheme 2. A probable mechanism for the synthesis of 2,4,5-triarylimidazoles catalyzed by $Y(TFA)_3$.

group can be activated to decrease the energy of transition state. It is highly probable that when the carbonyl oxygen is coordinated by $Y(TFA)_3$, the carboxyl groups of benzyl 3 and aldehydes 1 can be activated. Then nucleophilic attack of the nitrogen of ammonia obtained from NH_4OAc on the activated carbonyl group, produced the formation of aryl aldimine 4 and a-imino ketone 2, and it followed by the nucleophilic attack of the in situ generated imine 2 to carbonyl of aryl aldimine 4, obtaining the intermediate 5. Their subsequent intramolecular interaction results in cyclizations and eventually creates the formation of intermediate 6, which through the process of dehydration and dehydrogenation to afford the trisubstituted imidazoles 8.

Experimental

General

Melting points were measured on X-6 microscope melting points apparatus and uncorrected. IR spectra were measured on Spectrum GX spectrometer (KBr). ^1H NMR spectra were recorded on Bruker AVANCE 600 spectrometer (600 MHz for ^1H NMR), using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference.

General procedure for preparation of Yttrium(III) trifluoroacetate ($Y(TFA)_3$)

$Y(TFA)_3$ was prepared according to the reported procedure (*24*). Excessive Y_2O_3 was reacted with the trifluoroacetic acid. After completion of the reaction, the mixture was filtered, and then the filtrate was evaporated to dryness on water bath. The obtained crude product was recrystallized twice from water.

General procedure for preparation of 2,4, 5-triarylimidazoles

Aldehyde (1 mmol), benzil (1 mmol), ammonium acetate (7 mmol), and $Y(TFA)_3$ (0.03 mmol) were mixed. The mixture was stirred at 100°C for 3 h in 100 mL conical flask in water bath. When thin layer chromatography (TLC) indicated completion of the reaction, ethanol (10 mL) and de-ionized water (15 mL), was dumped into the conical flask and stirred for 10 min. The solid was filtered under suction, washed with ice-cold water, and dried to afford pure product. All products are known compounds, which were satisfactorily characterized by physical and spectra data.

2,4,5-Triphenylimidazole ***(4a)***
Mp 278°C. IR (KBr): v = 3413 (N–H), 3038 (C–H), 1596 (C = C), 1488 (C = N) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, TMS): δ = 7.17–7.49 (m, $3C_6H_5$), 12.69 (s, NH) ppm.

2-(4-Chlorophenyl)-4,5-diphenylimidazole ***(4b)***
Mp 264–266°C. IR (KBr): v = 3204 (N–H), 1613 (C = C), 1492 (C = N) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, TMS): δ = 7.24–7.52 (m, 10H, Ph), 7.54 (d, 2H, J = 10 Hz, C_6H_4Cl), 8.09 (d, 2H, J = 10 Hz, C_6H_4), 12.77 (s, NH) ppm.

2-(2,4-Dichlorophenyl)-4,5-diphenylimidazole ***(4c)***
Mp 174–176°C. IR (KBr): v = 3439 (N–H), 3067 (C–H), 1594 (C = C), 1552 (C = N), 1101 (C–Cl) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, TMS): δ = 12.7 (s, 1H), 7.78 (d, 1H), 7.83 (s, 1H), 7.23–7.58 (m, 12H) ppm.

2-(4-Hydroxyphenyl)-4,5-diphenylimidazole ***(4d)***
Mp 262–264°C. IR (KBr): v = 3630 (O–H), 3411 (N–H), 3058 (C–H), 1602 (C = C), 1485 (C = N) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, TMS): δ = 7.51–7.86 (m, 10H), 6.99–7.04 (d, 2H), 7.87–7.90 (d, 2H), 12.61 (s, NH) ppm.

2-(4-Methoxyphenyl)-4,5-diphenylimidazole ***(4e)***
Mp 230–232°C. IR (KBr): v = 3409 (N–H), 3029 (C–H), 1613 (C = C), 1493 (C = N) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, TMS): δ = 3.79 (s, OCH_3), 7.03 (d, J = 8.7 Hz, 2H), 7.33–7.51 (m, 10H, Ph), 8.00 (d, J = 8.7Hz, 2H), 12.52 (s, NH) ppm.

Conclusion

In summary, we have developed a solvent-free procedure for the synthesis of 2,4,5-triarylimidazoles using $Y(TFA)_3$ as a reusable catalyst. The mild conditions, short reaction time, inexpensive, readily availability of the catalyst, and simpler experimental procedure are the great advantages of the method. Thus, $Y(TFA)_3$ could be an efficient, eco-friendly, and recyclable Lewis acid catalyst for the synthesis of 2,4,5-triarylimidazoles.

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