Commercial ZrO_2 as a new, efficient, and reusable catalyst for the one-step synthesis of quinolines in solvent-free conditions

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Abstract: Commercially available zirconia (ZrO_2) is reported as an extremely efficient catalyst for the synthesis of quinolines. A one-step reaction of 2-aminoarylketones and a carbonyl compound (Friedlander reaction) took place under solvent-free conditions to afford the corresponding quinolines in good-to-high yields in the presence of ZrO_2. Furthermore, the catalyst is reused several times without any significant loss of its catalytic activity.

Key words: ZrO_2, Quinoline, Friedlander reaction, solvent-free, 2-aminoarylketones.

Résumé : On a observé que la zircone commercialement disponible est un catalyseur extrêmement efficace pour la synthèse des quinoléines. En présence de ZrO_2, la réaction de Friedlander, une réaction en une étape entre une 2-aminoarylcétones et un composé carbonylé, se produit dans des conditions sans solvant pour conduire aux quinoléines correspondantes avec des rendements allant de bons à excellents. De plus, on peut réutiliser le catalyseur à plusieurs reprises sans perte significative de son activité catalytique.

Mots-clés : ZrO_2, réaction de Friedlander, sans solvant, 2-aminoarylcétones.

[Traduit par la Rédaction]

Introduction

Quinolines are well-known for a wide range of medicinal properties and for being used as antimalarial, antiasthmatic, antihypertensive, antibacterial, and tyrosine-kinase-inhibiting agents.[1] They also undergo hierarchical self-assembly into a variety of nano- and meso-structures with enhanced electronic and photonic functions.[2] Thus, a great deal of effort has been drawn to develop new and efficient synthetic routes to quinoline derivatives. Among several routes to quinoline synthesis, an acid- or base-catalyzed condensation followed by a cyclodehydration between a 2-aminoarylketone and a carbonyl compound containing a reactive α-methylene group, namely the Friedlander reaction, is one of the simplest and straightforward methods.[3] This classical method is still not fully satisfactory with regard to the relatively low yield, harsh reaction conditions, side reactions, and also under base-catalyzed conditions. In addition, *o*-aminobenzophenone fails to react with simple ketones such as cyclohexanone and β-ketoesters.[4] Recently, modified methods employing $ZnCl_2$, $SnCl_2$, $Bi(OTf)_3$, $AuCl_3$, $CeCl_3$, and so forth[5,6] have been reported for the synthesis of quinolines. In these methods, the catalyst is destroyed during the work-up and cannot be recovered. However, development of a new catalyst, which can be reused, commercially available, new, and simplest for the synthesis of this important class of heterocyclic compounds is of demand.

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Today, active surfaces, such as metal oxides, play an ever growing role in organic synthesis and are widely employed not only for preparative organic reactions but also in the industry. Such reactions normally proceed under mild conditions, with high chemo-, regio-, and stereo-selectivities, securing simpler isolation procedures compared with similar reactions in solution.[7,8]

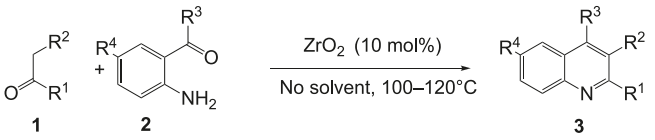
Results and discussion

Herein, I have studied the reaction of ethylacetoacetate with 2-aminoacetophenone in the presence of metal oxides as a model reaction in solvent-free conditions (Table 1). The progress of the reaction was monitored by TLC and ^1H NMR spectra from the reaction mixture.

For the first time, it is shown (Table 1) that certain metal oxides are active catalysts for the interaction studied, particularly ZrO_2, TiO_2, and both acidic and basic types of Al_2O_3. So, by considering the reaction time and yield, ZrO_2 was found to be the most effective in comparison with other metal oxides that were chosen. Subsequently, a series of substituted quinolines were synthesized following the same method using this catalyst (Scheme 1, Table 2). Interestingly, cyclic ketones, such as cyclohexanone and cyclopentanone, reacted with 2-arylketones to afford the respective tricyclic quinolines. The reaction is fairly general, clean, and efficient. The experimental procedure is very simple. The good-to-high yield transformation did not form any significant amounts of undesirable side products.

The condensation of 2-aminoarylketones (**2**) (R^3 = Me, Ph; R^4 = H, Cl) with unsymmetrical 1,3-diones (**1**) gave exclusively the regioisomer **3** if the two carbonyl groups present in **1** had dissimilar reactivity with regard to enamine

Scheme 1.



formation. However, the condensation of 2-aminoarylketones (**2**) with ethyl-4,4,4-trifluoro-3-oxobutanoate led to regioisomeric mixtures of quinolines **3** and **4**, respectively (Table 2, entries 3 and 12). This can be discussed by the similar activity of the two carbonyl groups present in ethyl-4,4,4-trifluoro-3-oxobutanoate, where the actual mechanism seems to be that the enamine formation may proceed in the condensation step; however, in this case, it is rather an iminoether (**4c**, **4l**).

From an environmental point of view, it is desirable to minimize the amount of waste for organic transformation. In this context, the catalyst was recycled for subsequent runs. The recyclability of the catalyst was investigated using a model reaction of the synthesis of quinoline **3a** in the presence of 10 mol% of the catalyst in solvent-free conditions. After the completion of the reaction (monitored by TLC), EtOAc was added to the reaction mixture and then filtered to separate the catalyst. The recycled catalyst was used for further runs, and it was found that its activity does not show any significant decrease even after six runs. It should be noted that although no solvents are used in the reaction itself, but to separate the catalyst and for the isolation and purification of the products, quantitative amounts of solvent are used.

In summary, the present protocol is the first example of ZrO_2-catalyzed synthesis of quinolines in benign conditions. The advantages of this method are the use of a cheap and commercially available catalyst. No toxic reagents, solvents, or byproducts were involved, and no laborious purifications were necessary. These conditions are also environment-friendly, cost-effective, and possess high generality to make our methodology industrialized as a valid contribution to the existing methodologies in the field of quinoline synthesis.

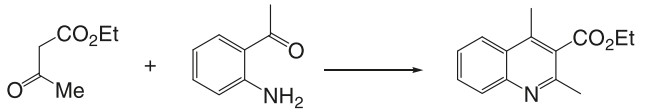
Experimental

Chemicals were purchased from Fluka, Merck, BDH, and Aldrich Chemical Companies. Progress of the reactions was followed by TLC using silica gel polygrams SIL G/UV 254 plates. NMR spectra were recorded on a Bruker DPX 250 MHz instrument. Microanalyses were performed on a PerkinElmer 240-B microanalyzer.

General procedure

To a mixture of 2-aminoaryl ketone (1 mmol) and a methylene carbonyl compound (1.5 mmol) ZrO_2 (0.12 g, 10 mol%) was added. The mixture was heated in an oil bath at 100–120 °C, and the reaction was monitored by TLC. After the reaction was complete, EtOAc was added to the reaction mixture, which was filtered to separate the catalyst. The organic solvent was removed under reduced pressure. After purification by chromatography on silica gel (*n*-hexane/ethyl acetate, 70:30), the product was obtained. The structures of the products were confirmed by ^{1}H NMR, IR, and comparison with authentic samples obtained commercially or prepared by reported methods. All products are known and were characterized by ^{1}H NMR, IR, and mass spectral data, which were found to be identical to those described in the literature, and for the new compounds, complete spectroscopic data are described below.

Table 1. ^{1}H NMR spectroscopic monitoring of the reaction of ethylacetoacetate (**1a**, 1.5 mmol) with 2-aminoacetophenone (**2a**, 1 mmol) at 100 °C under solvent-free condition.



Entry	Active surface[a]	Time (h)	Yield (%)
1	MgO	24	40
2	TiO_2	8	90
3	CaO	24	73
4	ZnO	11	90
5	Al_2O_3 (acidic type)	6	82
6	Al_2O_3 (basic type)	9	80
7	ZrO_2	4	98

[a]10 mol% of the metal oxide was used as catalyst.

Compound (3c)

Light yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ_H: 7.23–7.33 (4H, m, Ar*H*), 3.95–4.03 (2H, m, –OC*H*$_2$CH$_3$), 2.33 (3H, s, ArC*H*$_3$), 1.13 (3H, t, *J* =7.05 Hz, –OCH$_2$C*H*$_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C: 15.3, 17.2, 64.7, 108.1, 115.2, 122.3, 128.9 (–*C*F$_3$), 119.2, 124.5, 124.8, 128.8, 131.3, 134.6, 145.3, 147.6, 148.9, 171.3. MS (ESI) *m*/*z*: 283 (M^+ + H). HR-MS calcd. for $C_{14}H_{12}F_3NO_2$ (M^+ + H): 283.2490, found: 283.2489. Anal. calcd. for $C_{14}H_{12}F_3NO_2$: C, 59.37; H, 4.27%. Found: C, 59.12; H, 4.00.

Compound (4c)

Light yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ_H: 7.50–7.93 (4H, m, Ar*H*), 4.39 (2H, m, –OC*H*$_2$CH$_3$), 2.60 (3H, s, ArC*H*$_3$), 1.31 (3H, t, *J* = 7.05 Hz, –OCH$_2$C*H*$_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C: 15.4, 17.5, 65.1, 107.5, 115.1, 122.5, 129.2 (–*C*F$_3$), 100.2, 162.5, 124.8, 128.9, 130.4, 130.9, 132.7, 141.7, 151.4, 185.0. MS (ESI) *m*/*z*: 283 (M^+ + H). HR-MS calcd. for $C_{14}H_{12}F_3NO_2$ (M^+ + H): 283.2490, found: 283.2489. Anal. calcd. for $C_{14}H_{12}F_3NO_2$: C, 59.37; H, 4.27%. Found: C, 59.20; H, 4.03.

Compound (3l)

Light yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ_H: 7.40–8.50 (9H, m, Ar*H*), 5.25 (2H, m, –OC*H*$_2$CH$_3$), 1.96 (3H, t, *J* =7.06 Hz, –OCH$_2$C*H*$_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C: 31.2, 65.8, 107.1, 119.2, 122.3, 128.8 (–*C*F3), 116.0, 122.5, 126.4, 126.9, 127.7, 127.8, 128.1, 128.2, 128.5, 128.7, 130.9, 137.5, 148.0, 161.2. MS (ESI) *m*/*z*: 345 (M^+ + H). HR-MS calcd. for $C_{19}H_{14}F_3NO_2$ (M^+ + H): 345.3190, found: 345.3189. Anal. calcd. for $C_{19}H_{14}F_3NO_2$: C, 66.09; H, 4.09%. Found: C, 66.02; H, 4.00.

Compound (4l)

Light yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ_H: 7.13–7.28 (9H, m, Ar*H*), 4.00 (2H, m, –OC*H*$_2$CH$_3$), 1.08 (3H, t, *J* = 7.06 Hz, –OCH$_2$C*H*$_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$)

Table 2. Quinolines synthesis using ZrO_2 (10 mol%) as catalyst under solvent-free conditions.

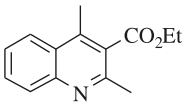
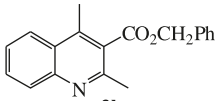
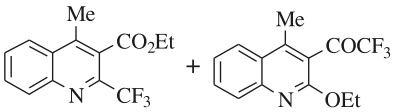
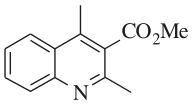
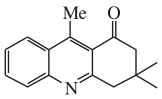
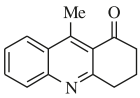
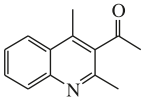
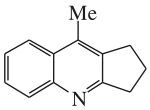
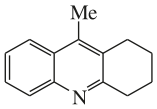
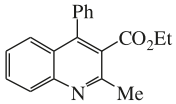
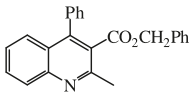
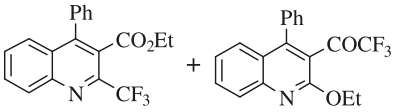
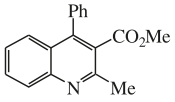
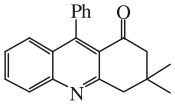
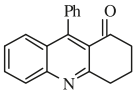
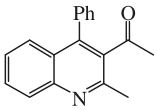
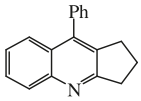
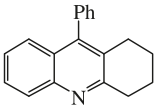
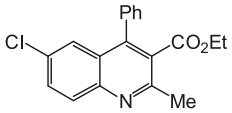
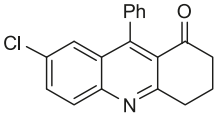
Entry	R^1	R^2	R^3	R^4	Product	Time (h)	Yields[a] (%)	Mp (°C)
1	Me	CO_2Et	Me	H	 **3a**	4	98	Oil (oil)[5h]
2	Me	CO_2CH_2Ph	Me	H	 **3b**	2.5	93	54–57
3	CF_3	CO_2Et	Me	H	 **3c** + **4c**	2	95 (70:30)[b]	**3c:** 86–88 **4c:** (97–100)
4	Me	CO_2Me	Me	H	 **3d**	3	98	Oil
5	$-COCH_2CMe_2CH_2-$		Me	H	 **3e**	4	90	103–105 (105–106)[5m]
6	$-CO(CH_2)_3-$		Me	H	 **3f**	4	86	78–79 (78)[5h]
7	Me	COMe	Me	H	 **3g**	6	65	Oil (oil)[5m]
8	$-(CH_2)_2-$		Me	H	 **3h**	6	60	54–56 (58–56)[5m]
9	$-(CH_2)_3-$		Me	H	 **3i**	6	65	75–78 (75–77)[5m]
10	Me	CO_2Et	Ph	H	 **3j**	3	95	95–97 (96)[5h]

Table 2. *Concluded.*

Entry	R^1	R^2	R^3	R^4	Product	Time (h)	Yields[a] (%)	Mp (°C)
11	Me	CO_2CH_2Ph	Ph	H	 **3k**	2.5	90	89–91 (90–93)[6c]
12	CF_3	CO_2Et	Ph		 **3l** **4l**	2.5	95 (70:30)[b]	**3l:** 165–167 **4l:**192–194
13	Me	CO_2Me	Ph	H	 **3m**	3	95	131–133 (132–134)[6d]
14	$-COCH_2CMe_2CH_2-$		Ph	H	 **3n**	3.5	92	189–191 (191)[5h]
15	$-CO(CH_2)_3-$		Ph	H	 **3o**	4	90	156–158 (158)[5h]
16	Me	COMe	Ph	H	 **3p**	5.5	70	110–112 (113)[5h]
17	$-(CH_2)_2-$		Ph	H	 **3q**	5	72	131–133 (132)[5h]
18	$-(CH_2)_3-$		Ph	H	 **3r**	5	68	137–139 (139)[5h]
19	Me	CO_2Et	Ph	Cl	 **3s**	2.5	95	105–107 (108)[4]
20	$-CO(CH_2)_3-$		Ph	Cl	 **3t**	3	90	160–162 (163)[4]

[a] Isolated yields.
[b] The ratios of regioisomers **3** and **4** were determined by ^1H NMR.

δ_C: 49.5, 66.9, 108.2, 121.1, 123.5, 129.0 (–*CF3*), 119.3, 126.0, 126.6, 127.1, 127.8, 127.9, 128.2, 128.4, 128.8, 129.1, 133.3, 137.8, 149.3, 201.5. MS (ESI) *m/z*: 345 (M^+ + H). HR-MS calcd. for $C_{19}H_{14}F_3NO_2$ (M^+ + H): 345.3190, found: 345.3189. Anal. calcd. for $C_{19}H_{14}F_3NO_2$: C, 66.09; H, 4.09%. Found: C, 66.00; H, 4.05.

Acknowledgement

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