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A convenient one-pot synthesis of 1-aryl-substituted 2*H*-isoquinolin-3-ones

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ABSTRACT

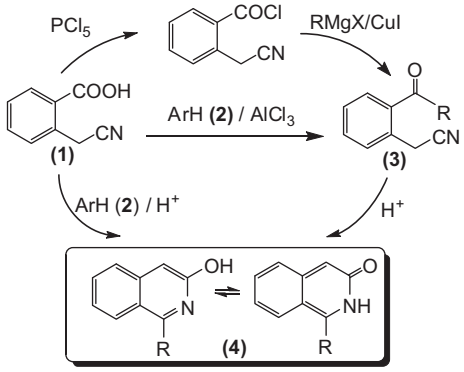
The synthesis of 1-aryl-substituted 2*H*-isoquinolin-3-ones is studied from 2-cyanomethylbenzoic acid and substituted benzenes via Friedel–Crafts acylation and intramolecular cyclization of 2-acylphenylacetonitriles formed in a one-pot method using sulfated zirconia as catalysts. Short reaction times, simplicity of operation, and easy work-up are some advantages of this method.

For many years isoquinolones have been an interesting structural class of compounds, which have been found to have many uses in the field of medicinal and synthetic chemistry. In particular, 2*H*-isoquinolin-3-ones 1-alkyl-4-substituted derivatives were investigated in connection with their cardiotonic and renal vasodilating effects[1,2] and antiplasmodial falcipain-2 inhibitors.[3]

A large number of methods exists in the literature for the synthesis of these compounds.[4,5] However, most of these multi-step procedures have significant drawbacks such as long reaction times, harsh reaction conditions, difficult work-up, and the use of expensive and toxic reagents. For these reasons new methods for the facile production of isoquinolinones continue to be of interest.

In a previous work, we have prepared 2*H*-isoquinolin-3-ones **4** with excellent yields by intramolecular cyclization of 2-acylphenylacetonitriles **3** under strongly acidic conditions using sulfuric and methanesulfonic acids as homogeneous catalysts and ion exchange resins Amberlyst 15 as heterogeneous catalysts.[6] The 2-acylphenylacetonitriles **3** used were previously obtained by reaction of 2-cyanomethylbenzoyl chloride and Grignard reagents in the presence of cuprous iodide (R = alkyl, aryl)[7] (Scheme 1).

Another method to prepare 2-acylphenylacetonitriles **3** for R = aryl is via Friedel–Crafts acylation of aromatic compounds with 2-methylbenzoic acid using $AlCl_3$, followed by bromination–cyanuration of 2-methylbenzophenone or, more directly, through Friedel–Crafts acylation of aromatic compounds with 2-cyanomethylbenzoic acid **1**, but this method possesses low performance with a large amount of toxic waste generated. Another disadvantage for the mentioned methods is long reaction periods (e.g., 7–10 days) to carry out all the synthetics steps (Scheme 1).



Scheme 1. Synthetic method for the preparation of 2*H*-isoquinolin-3-ones **4**.

As continuation of our work on the development of useful synthetic methodologies, we investigated the possibility of combining the Friedel–Crafts reactions of 2-cyanomethylbenzoic acid **1** and intramolecular cyclization of 2-acylphenylacetonitriles **3** formed in a one-pot method for the synthesis of 1-aryl-substituted 2*H*-isoquinolin-3-ones **4** using heterogeneous catalysts (Scheme 1).

The reaction between 2-cyanomethylbenzoic acid **1** (1 mmol) and benzene was selected as a model to optimize the experimental conditions testing various catalysts in different amounts using benzene as solvent at refluxing temperature. The results, summarized

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Table 1
Comparative study of catalysts for one pot synthesis of 1-phenyl-2*H*-isoquinolin-3-one **4a**

Entry	Catalyst	Temp./time (°C/h)	Acid **1** recovered (%)	Intermediate **3a** yield (%)	Product **4a** yield (%)
1	Amberlyst 15	80/24	90	—	—
2	P_2O_5/SiO_2	80/12	60	35	—
3	SO_4^{2-}/ZrO_2	80/5	16	—	70[a]
4	ZrO_2	80/8	50	—	34[a]
5	ZnO	80/24	60	—	10

[a] Extension of the reaction time (24 h) did not improve the yield.

Table 2
Synthesis de 2*H*-isoquinolin-3-ones **4** using sulfated zirconia[a]

Entry	Substrate 2	Solvent	Time (h)	Temperature (°C)	Product yield (%)		Mp (°C) Found/Lit.[6]
1	C_6H_6	C_6H_6	5	Reflux	**4a**	70	205–206 204–205
2	MeC_6H_5	MeC_6H_5	5	Reflux	**4b**	78	203–204 205–206
3	EtC_6H_5	1,2-$C_2H_4Cl_2$	5	Reflux	**4c**	75	200–200.5
4	ClC_6H_5	1,2-$C_2H_4Cl_2$	6	Reflux	**4d**	52	235–237 236–237
5	3-Br-$C_6H_4CH_3$	1,2-$C_2H_4Cl_2$	5	Reflux	**4e**	10	245–246
6	$MeOC_6H_5$	1,2-$C_2H_4Cl_2$	4	Reflux	**4f**	<5	229–230
7	1,3-$(MeO)_2C_6H_4$	1,2-$C_2H_4Cl_2$	6	Reflux	**4g**	30	190–191 (d)

[a] Commercial SO_4^{2-}/ZrO_2 from Mel Chemical Co was dried at 110 °C for 2 h in air atmosphere and was subsequently calcined for 5 h in air atmosphere at 550 °C.[15]

in Table 1, clearly indicate that among the various catalysts studied, sulfated zirconia was found to be the most efficient for the process.

We found that the reaction proceeded with the best yields when performed using SO_4^{2-}/ZrO_2 (100 wt %). Other catalysts used have not been effective in the generation of isoquinolinone **4a** in this one pot sequence, with the formation in some cases of 2-cyanomethybenzophenone **3a** (Table 1, entry 2).

On the other hand, sulfated zirconia has attracted much attention in the recent years because of its good catalytic activity, super-acidity, non-toxicity, and offer several advantages such as short reaction times, high selectivity and the easiness of work-up procedure.[8–10] Some of these interesting methodologies studied include Friedel–Crafts acylation,[11] stereo controlled glycosidation,[12] synthesis of coumarins by Pechmann reaction,[13] 1,5-benzodiazepines,[14] 3,2-benzothiazepine 3,3-dioxides, and 2,3-benzothiazine 2,2-dioxides[15] among others.

With the selected catalyst, we expanded the scope of the reaction to various substituted benzenes. The solvent reaction was the benzene derivative **2** or 1,2-dichloroethane according to the properties of aromatic derivative used for the acylation, especially having in mind a boiling temperature and availability.[16] The results of the reaction are summarized in Table 2.

As seen in Table 2, the reactions proceeded smoothly with various aromatic substrates **2** in moderate to good yields. However, 1,3-$(MeO)_2C_6H_4$, 3-Br-$C_6H_4CH_3$, and $MeOC_6H_5$ were not good substrates. As shown in entries 5, 6, and 7 we have observed the formation of the products **4** in low to very low yield, with a complex mixture of compounds formed by using different reactions conditions such as temperature, catalyst ratio, and reactive relations. Intermediates ketones **3** could be detected in low yield in the reaction mixtures. Different results about the acylation of methoxybenzene using sulfated zirconia have been found in the literature.[13,14]

Moreover, it is noteworthy that the acylation reaction occurred with high regioselectivity in *para* position to aromatic substrate, with the exception of 3-Br-$C_6H_4CH_3$ (entry 5), where the substitution occurs in *ortho* position at methyl group possibly due to a steric effect on the bromine substituent.

The products **4a**, **4b,** and **4d** are known compounds and were characterized by comparison of their physical and spectroscopic data with those of the reported ones. Physical properties of ^1H NMR and ^{13}C NMR spectral data and elemental analysis of new compounds **4c, 4e, 4f,** and **4g** are reported in the experimental section.[16]

In conclusion, a series of 2*H*-isoquinolin-3-ones 1-aryl-substituted were synthesized in good yields via the sequential Friedel–Crafts acylation of 2-cyanometylbenzoic acid **1** and benzene derivatives **2** followed by intramolecular cyclization of ketones formed **3**, catalyzed by sulfated zirconia. The current route is a practical and convenient method for the synthesis of 2*H*-isoquinolin-3-ones **4** derivatives in a one-pot reaction. Short reaction times, simplicity of operation, and easy work-up are some advantages of this method. It is important to take into account that the waste disposal of the process was greatly diminished compared with the alternative methods.

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16. *General procedure for the preparation of 2H-isoquinolin-3-one* ***4***: A flask equipped with a reflux condenser and magnetic bar was charged with a solution of 2-cyanomethylbenzoic acid **1** (1.0 mmol), benzenes derivatives **2** (2–2.5 mol), and the catalyst in 4 mL of dried solvent. The mixture was stirred at reflux for the specified time. The reaction was monitored by TLC. After cooling, the catalyst was filtered off, washed with fresh solvent, and the organic solution was concentrated under reduced pressure to give the crude products. They were purified by crystallization or by flash chromatography on silica gel 60 (70–230 mesh, Merck) with CH_2Cl_2/MeOH (9:1) as eluent in most cases. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 200 spectrometer using TMS as the internal standard.

*Characterization data of 1-(4-ethylphenyl)-2H-isoquinolin-3-one (**4c**)*: Oranges prisms (ethanol), mp: 200–200.5 °C.^{1}H NMR (200 MHz, DMSO): δ = 1.15 (t, J = 7.01 Hz, 3H, CH_2-$C\underline{H}_3$), 4.03 (q, J = 7.01 Hz, 2H, $C\underline{H}_2$–CH_3), 6.57 (s, 1H, H-4), 7.28–7.41 (m, 4H), 7.61–7.79 (m, 2H), 7.68 (d, J = 7.52 Hz, 1H, H-5), 8.00–8.22 (m, 2H) ^{13}C NMR (62.9 MHz): δ = 14.81, 55.58, 100.41, 122.77, 126.05, 127.44, 127.55, 127.90, 128.82, 131.38, 132.51, 133.05, 136.61, 143.07, 162.95. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H 6.06; N, 5.62. Found: C, 81.78; H, 6,15; N, 5.22.

*Characterization data of 1-(4-bromo-2-methylphenyl)-2H-isoquinolin-3-one (**4e**)*: Yellows needles (ethanol), mp: 244–246 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.99 (s, 3H, CH_3), 6.67 (s, 1H, H-4), 7.22–7.30 (m, 2H), 7.37 (td, J = 7.6, 1.4 Hz, 2H), 7.45–7.57 (m, 3H) 8.11 (dd, J = 7.81, 1.0 Hz, 1H) ^{13}C NMR (62.9 MHz): δ = 41.23, 100.51, 122.52, 127.70, 129.14, 131.05, 131.99, 132.56, 133.23, 134.31, 134.78, 136.90, 138.24, 140.87, 143.87, 163.66. Anal. Calcd for $C_{16}H_{12}BrNO$: C, 61.17; H 3.85; Br, 15.43, N, 4.46. Found: C, 61.22; H, 3.79; N, 4.38.

*Characterization data of 1-(4-methoxyphenyl)-2H-isoquinolin-3-one (**4f**)*: Yellows needles (ethanol), mp: 229–230 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.87 (s, 3H, OCH_3), 6.55 (s, 1H, H-4), 7.15 (m, 2H), 7.21–7.32 (m, 3H), 7.36–7.53 (m, 2H), 7.58 (d, J = 7.1 Hz, 1H), 7.98 (d, J = 7.9 Hz, 1H). ^{13}C NMR (62.9 MHz): δ = 54.66, 101.39, 114.89, 120.40, 121.0, 123.3, 127.45, 128.04, 131.5, 132.13, 133.06, 143.51, 158.46, 162.57. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.36 H, 5.20 N, 5.45.

*Characterization data of 1-(2,4-dimethoxyphenyl)-2H-isoquinolin-3-one (**4g**)*: Yellows prisms (ethanol), mp: 190–191 °C (d). ^{1}H NMR (200 MHz, DMSO): δ = 3.75 (s, 6H, $-OCH_3$), 6.29 (s, 1H, H-4), 6.48–6.58 (m, 2H), 6.82 (s, 1H, NH), 7.18 (t, J = 7.8 Hz, 1H, H-7), 7.44–7.52 (m, 1H, H-6), 7.59 (d, J = 8.4 Hz, 1H, H-5), 7.63 (d, J = 7.8 Hz, 1H, H-8), 7.67 (d, J = 8.5 Hz, 1H, H-6) ^{13}C NMR (62.9 MHz): δ = 55.74, 55.48, 100.19, 102.03, 105.47, 108. 48, 118.43, 122.85, 123.77, 126.11, 128.47, 130.65, 132.60, 140.95, 157.06, 159.97, 161.63. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.35 H, 5.21 N, 4.87.