A Novel Synthesis of 1-Substituted 2*H*-Isoquinolin-3-ones

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The intramolecular cyclization of 2-acylphenylacetonitriles **1** under strongly acidic conditions easily affords 1-substituted 2*H*-isoquinolin-3-ones **2** in excellent yields.

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2*H*-Isoquinolin-3-ones are substances with interest due to their pharmacological properties. For example 1-alkyl-4-substituted derivatives were investigated and discussed in connection with their cardiotonic and renal vasodilating effects [1-3].

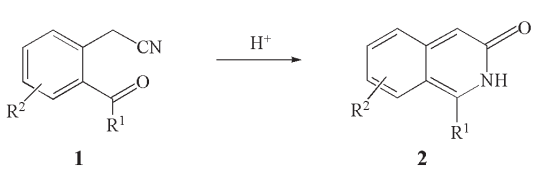
Numerous methods are available for the synthesis of 2*H*-isoquinolin-3-ones [4]. The important ones include: the cyclization of esters of *o*-acylphenylacetic acids with ammonia, alkylamines or formamides [5-7], the Pomeranz-Fritsch type cyclization of *N*-benzyl-diethoxyacetamides in sulfuric or polyphosphoric acid [8] and the reaction of carboxylic acid or their derivatives with 2-phenylethylamines, phenylacetamides, phenylacetonitriles and *N*-acylphenylethylamines in polyphosphoric acid [9-10]. Most of these methods, however, suffer from drawbacks namely long reaction periods and are limited to the presence of electron donating groups in the aromatic ring. Alternatively, these products can be obtained by aromatization of 1,4-dihydro-2*H*-isoquinolin-3-ones [11] Recently, Hussain *et al* reported the synthesis of 2*H*-isoquinolin-3ones by reaction of azaallyllithiums derived from imines of α-aminoesters with benzynes *via* 3+2 cycloaditions with moderate yields [12].

As far as we know, very few examples of 1-substituted 2*H*-isoquinolin-3-ones were reported [5,13-15].

Herein we describe a new effective method for the synthesis of 1-substituted-2*H*-isoquinolin-3-ones (**2**) by intramolecular cyclization of 2-acylphenylacetonitriles (**1**) under strongly acidic conditions (Scheme 1).

This cyclization methodology for analogous transformations was previously reported in the literature [16,17]. For example treatment of 1-cyanomethyl-anthraquinones under strongly acidic conditions gave 3*H*-1-azabenzo[*de*]-anthracene-2,7-diones in good yields [16].

Scheme 1



1 **2**

1a R^1= CH_2CH_3; R^2= H
1b R^1= i-$CH(CH_3)_2$; R^2= H
1c R^1= $CH_2C_6H_5$; R^2= H
1d R^1= C_6H_5; R^2= H
1e R^1= 4-ClC_6H_4; R^2= H
1f R^1= 4-$CH_3C_6H_4$; R^2= H
1g R^1= C_6H_5; R^2= 5-Cl

The starting 2-acylphenylacetonitriles (**1a-1f**) were obtained by reaction of 2-cyanomethylbenzoyl chloride and Grignard reagents in the presence of cuprous iodide at –5 ºC as previously described by us [18]. Compound **1g** was prepared from 4-chloro-2-methylbenzoic acid [19] *via* formation of 4-chloro-2-methylbenzophenone (**3**) by Friedel Crafts direct acylation with benzene [20]. Subsequent benzylic bromination with 1,3-dibromo-5,5-dimethylhydantoin (DBH) and cyanation of the haloderivative afforded 2-benzoyl-5-chloro-phenylacetonitrile (**1g**).

For the preparation of 2*H*-isoquinolin-3-ones (**2**), the keto nitrile **1** was stirred with the catalyst in 1,2-dichloroethane for 3-6 h to give the product **2**. We investigated the synthesis of **2** using conventional strong acids such as methanesulfonic and sulfuric acid and macroreticular ion exchange resins Amberlyst 15 and Amberlyst XN 1010. Different reaction temperatures and workup procedures were necessary depending on the catalyst employed. The yields of **2a-2g** are summarized in Table 1. The products were identified using ir, ^{1}H-nmr, ^{13}C-nmr and elemental analysis.

Very good yields were obtained when resins Amberlyst 15 and XN 1010 were used. The isoquinolinones **2** prepared with these catalysts also have high purity because the resins give a solid support to products **2** and make the workup and isolation procedure quite simple. In this case, when the reaction was complete, the resin was collected by filtration, treated with aqueous sodium hydrogen carbonate solution, water and then extracted with dichloromethane. The organic layer was dried, and the solvent evaporated to give the isoquinolinones **2** with high purity. There is no need to recrystallize the isolated products. In the case of a reaction brought about in conventional strong acid the yields were lower and the crude products were obtained with less purity.

Substrates **1** with aryl groups required a longer reaction time with the use of Amberlyst resins. On the contrary, the reaction time for substrates **1** with alkyl or aryl groups remain unaltered with the use of mineral acids. On the other hand, high yields using Amberlyst resins were only found if higher temperatures than in the case of mineral acids, were used. The resins can be easily regenerated and reused without affecting the yields.

Table 1

Cyclization of **1** with Amberlyst Resins, Sulfuric Acid and Methanesulfonic Acid

Compound	R^1	R^2	A-15 [a] Yield (%)/ Time (h)/ Temp (ºC)	A-XN 1010 [b] Yield (%)/ Time (h)/ Temp (ºC)	H_2SO_4 Yield (%)/ Time (h)/ Temp (ºC)	$HMeSO_3$ Yield (%)/ Time (h)/ Temp (ºC)
1a	CH_2CH_3	H	95 / 3/ 80	95 / 3/ 80	85 / 3/ 45	88 / 3/ 45
1b	i-$CH(CH_3)_2$	H	95 / 3/ 80	95 / 3/ 80	80 / 3/ 45	86 / 3/ 45
1c	$CH_2C_6H_5$	H	90 / 3/ 80	90 / 3/ 80	83 / 3/ 45	85 / 3/ 45
1d	C_6H_5	H	82 / 6/ 80	83 / 6/ 80	73 / 3 / 45	76 / 3/ 45
1e	4-ClC_6H_4	H	86 / 6/ 80	92 / 6/ 80	80 / 3/ 45	84 / 3/ 45
1f	4-$CH_3C_6H_4$	H	89 / 6/ 80	90 / 6/ 80	78 / 3/ 45	83 / 3/ 45
1g	C_6H_5	5-Cl	86 / 6/ 80	90 / 6/ 80	75 / 3/ 45	81 / 3/ 45

[a] Amberlyst 15; [b] Amberlyst XN 1010.

In conclusion, we have found a short and high yield route to 1-substituted 2*H*-isoquinolin-3-ones (**2**) by means of intramolecular ciclyzation of 2-acylphenylacetonitriles (**1**) under strongly acidic conditions, in particular with the use of ion exchange resins Amberlyst 15 and Amberlyst XN 1010.

EXPERIMENTAL

Mps were determined with a Buchi apparatus. Infrared spectra were recorded with a Perkin Elmer FT-IR 1600 spectrophotometer in potassium bromide. All nmr spectra were recorded on a Brucker AC 250 MHz in deuteriochloroform and are reported in ppm downfield from tetramethylsilane employed as an internal standard (δ). The mass spectra were recorded in a Finnigan Model 4500 Mass Spectrometer. Elemental analysis was carried out at the Institut für Organische Chemie of the Stuttgart University. Thin layer chromatography was performed on silica gel sheets 60 F_{254} (Merck) with chloroform-methanol (90:10). Reagent grade solvents were used. Amberlyst 15 (Aldrich) was dried at 60 °C under reduced pressure (5 mbar) for 15 minutes and Amberlyst XN 1010 (Aldrich) was dried at 80 °C (5 mbar) during 4 h.

The 2-acylphenilacetonitriles (**1a-1f)** were prepared applying a known method from 2-cyanomethylphenylchloride by reaction with Grignard reagents [18]. Compound **1g** was prepared from 4-chloro-2-methylbenzophenone (**3**) with benzylic bromination and cyanation of the haloderivative.

4-Chloro-2-methylbenzophenone (**3**).

This compound was prepared from 4-chloro-2-methylbenzoic acid [19] by Friedel Crafts direct acylation with benzene according to the literature procedure [20] in 62 % yield ; bp 140-142 ºC ,0.1 mm (lit [21] bp 143-144 ºC, 0.1 mm).

2-Benzoyl-5-chloro-phenylacetonitrile (**1g**).

A stirred mixture of **3** (13.8 g, 60 mmol) and DBH (10.2 g, 35 mmol) in carbon tetrachloride (120 mL) was heated under reflux for 4 h while a 150-W bulb situated 2 cm away was shining on the reaction flask. The cooled reaction mixture was filtered and the solution evaporated to give a yellow oil (17.2 g), which was dissolved in ethanol (60 mL) and an aqueous solution of potassium cyanide (3.6 g, 56 mmol in 8 mL) was added. The reaction mixture was stirred and boiled under reflux for 6 h, cooled to r.t. and the solid removed by filtration. The resulting solution was evaporated and the residue was poured onto water (26 mL). The organic layer was separated, the aqueous layer was extracted with chloroform (3 x 10 mL), and the combined organic layers were washed with water (3 x 10 mL), 5 % aqueous sodium hydrogen carbonate solution (10 mL) and water (10 mL). The extracts were dried with sodium sulfate, concentrated *in vacuo* and the residue purified by column chromatography in toluene/dichloromethane (80/20) to afford **1g**; yield: 12.5 g (49%); mp: 78-79 ºC; ir: 2238, 1658 cm^{-1}; ^1H nmr: δ 4.00 (s, 2H, CH_2CN), 7.39-7.44 (m, 2H, H-3', H-5'), 7.48-7.51 (m, 2H, H-4, H-4'), 7.62-7.67 (m, 2H, H-3, H-6), 7.66 (dd, 1H J_{3-4}= 9.5, J_{3-6}= 1.0, H-3); 7.76(dd, 2H, $J_{2'-3'}$= $J_{6'-5'}$= 8.3, $J_{2'-4'}$= $_{6'-4'}$= 1.26, H-2', H-6'); ^{13}C nmr (62.9 MHz) δ 21.7 (CH_2-), 117.1 (CN), 127.7 (C-4), 128.7 (C-3', C-5'). 130.1 (C-6), 132.0 (C-3), 130,2 (C-2'-C-6'),132.4 (C-1), 133.7 (C-4'), 134.9 (C-5), 136.9 (C-2), 138.0 (C-1'), 196.0 (CO); ms: *m/z* 255,5 (M+, 44 %), 230 (32), 228 (100), 220, (32), 139 (27), 89 (11).

Anal. Calcd. for $C_{15}H_{10}NOCl$ (255.69): C, 70.48; H, 3.91; N, 5.48. Found: C, 70.46; H, 4.02; N, 5.30.

Cyclization of 2-acylphenylacetonitriles (**1**) to 2*H*-Isoquinolin-3-ones (**2**).

General Procedure Using Amberlyst Resins.

A reaction flask equipped with a reflux condenser and magnetic bar, was charged with a solution of 2-acylphenylacetonitriles (**1**) (1 mmol) in 1,2-dichloroethane (4 mL) and the resin (6.0 meq) [22]. Stirring was continued at 80 °C for the time indicated (Table 1). The progress of the reaction was monitored by thin layer chromatography. When the reaction was complete, the resin was collected by filtration, washed with fresh 1,2-dichloroethane and then was treated with 10% aqueous sodium hydrogen carbonate solution and water. The resin was then extracted three times with dichloromethane (2 mL). The combined extracted was dried with sodium sulfate and concentrated *in vacuo* to give the final products.

General Procedure Using Sulfuric and Methanesulfonic Acid.

A reaction flask equipped with a magnetic bar and a Teflon cap, was charged with a solution of 2-acylphenylacetonitriles (**1**) (1 mmol) in 1,2-dichloroethane (4 mL) and the acid (1 mL). After

3 h stirring at 45 ºC the mixture was quenched with water, neutralized with 10% aqueous ammonium chloride solution and extracted three times with dichloromethane (2 mL). The organic layer was dried with sodium sulfate and concentrated *in vacuo* to give a yellow solid that was recrystallized from ethanol.

1-Ethyl-2*H*-isoquinolin-3-one (**2a**).

This compound was obtained as yellows prisms (ethanol), mp 209-210 ºC; ir: 1557, 1651cm^{-1}; ^{1}H nmr: δ 1.45(t, 3H, J= 7.5, CH_2-C*H*$_3$); 3.28 (q, 2H, J= 7.5, C*H*$_2$-CH_3); 6.76 (H-4); 7.12 (ddd, 1H, J_{7-6}= 6.8, J_{7-8}= 8.8, J_{7-5}= 1.4, H-7); 7.41 (ddd, 1H, J_{6-7}= 6.8, J_{6-5}= 8.8, J_{6-8}= 1.2 , H-6); 7.47 (dd, J_{5-6}= 8.8, J_{5-7}= 1.4, H-5), 7.83 (dd, J_{7-8}= 8.8, J_{8-6}= 1.0, H-8); ^{13}C nmr (62.9 MHz): δ 14.7(CH_2-*C*H$_3$); 25.0 (-*C*H$_2$-CH_3); 104.4 (C-4); 117.7 (C-9); 122.5 (C-7); 125.5 (C-8); 126.0 (C-5); 131.2 (C-6); 143.2 (C-10); 157.5 (C-1); 161.5 (C-3); ms: m/z 173(M, 100%); 172 (34);130 (90).

Anal. Calcd. for $C_{11}H_{11}N$ (173.21): C,76.32; H, 6.35; N, 8.08. Found: C, 76.32; H, 6.36; N, 8.00.

1-(*i*-Propyl)-2*H*-isoquinolin-3-one (**2b**).

This compound was obtained as yellows prisms (ethanol), mp 151-152 ºC (Lit [13] mp: 151-152 ºC); ir: 1557, 1651 cm^{-1}; ^{1}H nmr: δ 1.53 (d, 6H J= 7.0, CH(C*H*$_3$)$_2$); 3.85 (sept., 1 H J= 7.0 , C*H*(CH_3)$_2$; 6.77 (s, 1H, H-4) 7.09 (ddd, 1 H, J_{7-6}= 7.9, J_{7-8}= 8.7, J_{7-5}= 1.4, H-7); 7.36(td, 1H, J_{6-7}= 7.9, J_{6-8}= 1.0, H-6), 7.45(d, 1H, J_{5-6}= 7.8, H-5); 7.89 (dd, 1H, J_{8-7} = 8.7, J_{8-6}= 1.0, H-8); ^{13}C nmr (62.9 MHz) δ 21.3 ((*C*H$_3$)$_2$-CH); 29.4 (-*C*H-(CH_3)$_2$); 104.6 (C-4); 117.1 (C-9); 122.3 (C-7); 125.0 (C-8); 126.1 (C-5); 130.9 (C-6); 143.2 (C-10); 160.5 (C-1); 161.0 (C-3); ms: m/z 187 (M, 100%); 186 (36); 172 (41); 159 (13); 144 (40).

1-Benzyl-2*H*-isoquinolin-3-one (**2c**).

This compound was obtained as yellows needles (ethanol), mp 194-195 ºC; ir: 1556, 1648 cm^{-1}; ^{1}H nmr: δ 4.66 (s, 2H, C*H*$_2$Ph); 6.85 (s, 1H, H-4); 7.11-7.48 (m, 7H , H-6, H-7, H-2', H-3', H-4', H-5', H-6'); 7.51(d, 1H, J_{5-6}= 8.2, H-5); 7.92 (d, 1H, J_{7-8}= 8.8, H-8); ^{13}C nmr (62.9 MHz): δ 38.3 (-*C*H$_2$-Ph); 104.6 (C-4); 119.7 (C-9); 123.8 (C-7); 126.1 (C-8); 127.3 (C-5); 127.4 (C-2', C-6'); 128.9 (C-4'); 129.0 (C-3', C-5'); 131.3 (C-6); 137.8 (C-1'); 143.6 (C-9); 154.6 (C-1); 161.6 (C-3); ms: m/z 235 (M, 100%); 234 (95); 216 (10); 207 (8).

Anal. Calcd. for $C_{16}H_{13}NO$ (235.27) : C, 81.72; H,5.53; N,5.95. Found: C, 81.65; H, 5.51; N, 5.89.

1-Phenyl-2*H*-isoquinolin-3-one (**2d**).

This compound was obtained as yellows prisms (ethanol), mp 204-205 ºC (Lit. [5] m.p. 205-206 ºC. Spectral Data (ir, ms, ^{1}H nmr) are identical with those reported [5]; ^{13}C nmr (62.9 MHz): δ 103.1 (C-4); 121.0 (C-9); 123.6 (C-7); 125.8 (C-8); 127.5 (C-5); 128.4 (C-2', C-6'); 129.2 (C-4'); 129.9 (C-3', C-5'); 130.7 (C-6); 136.3 (C-1'); 142.0 (C-10); 156.9 (C-1); 160.3 (C-3).

1-(*p*-Chlorophenyl)-2*H*-isoquinolin-3-one (**2e**).

This compound was obtained as yellows prisms (ethanol), mp 236-237 ºC; ir: 1550, 1630 cm^{-1}; ^{1}H nmr: δ 6.96 (s, 1H, H-4); 7.21 (ddd, 1H, J $_{7-8}$= 8.5, J_{7-6}= 6.7, J_{7-5}= 1.4, H-7); 7.44-7.57 (m, 5H, H-6, H-2', H-3', H-5', H-6'); 7.65 (d, 1H, J_{5-6}= 8.5, H-5); 7.76 (dd, 1H, J_{8-7}= 8.5, J_{8-6}= 1.2, H-8); ^{13}C nmr (62.9 MHz): δ 103.2 (C-4); 122.0 (C-9); 124.2 (C-7); 126.3 (C-8); 127.5 (C-5); 128.9 (C-3', C-5'); 131.0 (C-6); 131.6 (C-2', C-6'); 135.5 (C-4'); 135.7 (C-1'); 142.0 (C-10); 156.7 (C-1); 160.6 (C-3); ms: m/z 255.5 (M,100%); 254 (6); 236 (4); 227 (53) ; 192 (8); 165 (11).

Anal. Calcd. for $C_{15}H_{10}NOCl$ (255.69): C, 70.48; H, 3.91; N, 5.48. Found: C, 70.59; H, 3.98; N, 5.41.

1-(*p*-Methylphenyl)-2*H*-isoquinolin-3-one (**2f**).

This compound was obtained as yellows prisms (ethanol), mp 205-206 ºC; ir: 1536, 1642 cm^{-1}; ^{1}H nmr: δ 2.45 (s, 3H, Ph-C*H*$_3$); 6.89 (s, 1H, H-4); 7.11 (td, 1H, H-6'); 7.55 (d, 1H, J_{5-6} = 6.3, H-5); 7.77 (d, 1 H, J_{7-8}= 8.6, H-8); ^{13}C nmr (62.9 MHz): δ 21.4 (CH_3); 103.7 (C-4); 120.4 (C-9); 123.2 (C-7); 125.7 (C-8); 127.8 (C-5); 129.0 (C-3', C-5'); 129.9 (C-2', C-6'); 130.7 (C-6); 132.7 (C-1'); 139.2 (C-4'); 142.2 (C-10); 156.3 (C-1); 160.5 (C-3); ms: m/z 235(M, 100%), 234 (9), 207 (54), 191 (4).

Anal. Calcd. for $C_{16}N_{13}NO$ (235.28): C, 81.48; H, 5.66; N,5.89. Found: C, 81.68; H, 5.57; N, 5.95.

7-Chloro-1-phenyl-2*H*-isoquinolin-3-one (**2g**).

This compound was obtained as yellows prisms (ethanol), mp 235-237 ºC; ir: 1538, 1665 cm^{-1}; ^{1}H nmr: δ 6.78 (s, 1H, H-4), 7.06 (dd, 1H, J_{7-8}= 9.1, J_{7-5}= 1.4, H-7); 7.54 (br, 6H, H-5, H-2', H-3', H-4', H-5', H-6'), 7.72 (d, 1H, J_{8-7} = 9.1, H-8); ^{13}C nmr (62.9 MHz): δ 102.9 (C-4); 120.0 (C-9); 124.5 (C-7); 125.0 (C-8); 128.9 (C-3', C-5'); 130.0 (C-5), 130.2 (C-4'), 130.4 (C-2', C-6'), 136.2 (C-1'); 137.9 (C-6); 142.9 (C-10); 157.9 (C-1); 161.1 (C-3); ms: m/z 255 (M, 100%), 236 (10), 227 (8), 150 (18).

Anal. Calcd. for $C_{15}H_{10}NOCl$ (255.69): C, 70.48; H, 3.91; N, 5.48. Found: C, 70.51; H, 3.94; N, 5.52.

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