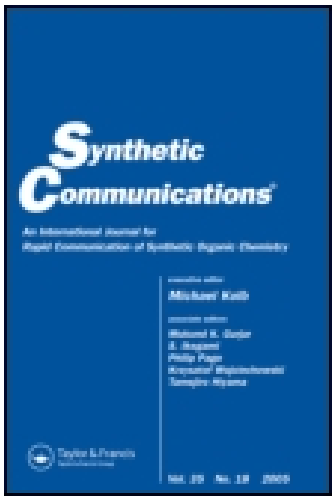

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A CONVENIENT SYNTHESIS OF 1-SUBSTITUTED 1,4-DIHYDROISOQUINOLIN-3-ONES

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ABSTRACT

A number of isoquinolin-3-ones have been obtained in fair to good yields by reaction of phenylacetonitrile with carbonyl compounds in PPA.

Key Words: Isoquinolinones; Phenylacetonitrile; PPA

The isoquinoline moiety occurs in a large number of alkaloids. Because of their application in chemotherapy, this heterocyclic system has generated much interest from synthetic chemists and biochemists. Very few methods have been developed to prepare isoquinolin-3-ones. They are generally obtained by condensation of amides with aromatic aldehydes with or without the assistance of the benzotriazole group[1,2] but cyclisations of chloroamides or diazoacetamides have also been described.[3,4] We here

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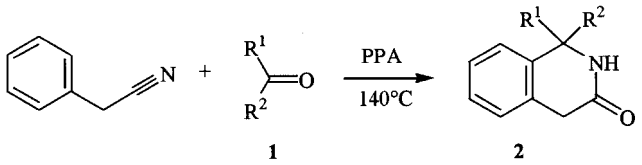

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Table 1. Synthesis of 1,4-Dihydroisoquinolin-3-ones

R^1	R^2	Compound	Yield (%)
C_6H_5	H	**2a**	90
Me	H	**2b**	68[a]
C_6H_5	Me	**2c**	40
Me	Me	**2d**	50
Et	Me	**2e**	45
$(CH_3)_2CHCH_2CH_2$	Me	**2f**	51[b]
$C_6H_5CH_2$	Me	**2g**	35
Cyclo hexyl		**2h**	40
Cyclo pentyl		**2i**	20

[a]With five equivalents of aldehyde.
[b]With one equivalents of ketone.

report (Table 1) an easily access to these compounds by reaction of phenylacetonitrile with all king of carbonyl compounds in polyphosphoric acid (PPA). Deak et al.[5] reported only the synthesis of 1-arylisoquinolin-3-ones in good yields from benzaldehydes and phenylacetonitrile.

The reaction is performed at 140°C in PPA in which the nitrile (10% w/w) is introduced and then an excess of carbonyl compound is added dropwise. A part of enolisable carbonyl compounds is consumed in aldol type condensations which lower the yield of isoquinolinone. The formation of the latter involves the initial attack of the nitrogen atom on the protonated carbonyl before aromatic electrophilic substitution. It is known that electrophilic attacks on phenylacetonitrile afford only 25% of ortho-substitution.[6] So the inverse order of the two steps would lead to smaller amounts of isoquinolones.

EXPERIMENTAL

Hundred gram of PPA were heated to 140°C. Ten gram (0.085 mol) of phenylacetonitrile were then added. After stirring for 5 min, the carbonyl

compound (0.17 mol, 2 equivalents) was added dropwise to the mixture which was stirred for one hour at 140°C and then poured into iced water. After extraction thrice with methylene chloride (200 ml), the combined organic layers were dried ($MgSO_4$) and the solvent removed. Diethyl ether (50 ml) was added. The precipitate was filtered and extracted (soxhlet) with petroleum ether. After removal of the solvent, the compound was dried under reduce pressure.

1,4-Dihydro-1-phenylisoquinolin-3-one[7] **2a:** $F = 138$°C; ^{1}H NMR: 3.65 (dd, 2H, $J = 18.8$), 5.2 (s, 1H), 7.0–7.5 (m, 9H), 7.8 (s, 1H); ^{13}C NMR: 36.5, 59.9, 126.7, 126.8, 127.2, 127.6, 127.9, 128.0, 128.9, 131.3, 134.7, 141.6, 171.6.

1,4-Dihydro-1-methylisoquinolin-3-one[8] **2b:** $F = 97$°C; ^{1}H NMR: 1.5 (d, 3H, $J = 6.8$), 3.6 (dd, 2H, $J = 18.1$), 4.65 (q, 1H), 7.1–7.3 (m, 4H), 8.1 (s, 1H); ^{13}C NMR: 23.6, 36.1, 51.3, 124.8, 126.8, 127.3, 127.8, 131.0, 136.2, 171.9. MS (EI): 118, 146 (100%), 161.

1,4-Dihydro-1-methy-1-phenylisoquinolin-3-one[9] **2c:** $F = 167$°C; ^{1}H NMR: 1.95 (s, 3H), 3.55 (dd, 2H, $J = 10.1$), 7.1–7.3 (m, 9H), 8.3 (s, 1H); ^{13}C NMR: 26.9, 37.4, 61.4, 124.9, 125.8, 126.8, 127.2, 127.7, 127.9, 128.5, 131.9, 139.9, 145.4, 171.9. MS (EI): 77, 105, 222 (100%), 237.

1,4-Dihydro-1,1-dimethylisoquinolin-3-one 2d: $F = 110$°C; ^{1}H NMR: 1.5 (s, 6H), 3.55 (s, 2H), 7.0–7.2 (m, 4H), 8.3 (s, 1H); ^{13}C NMR: 30.8, 35.8, 56.0, 123.5, 127.0, 127.2, 127.8, 130.2, 140.0, 171.3. MS (EI): 160 (100%), 175. Anal. calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99; O, 9.13; found C, 75.28; H, 7.51; N, 7.87.

1,4-Dihydro-1-ethyl-1-methylisoquinolin-3-one 2e: $F = 159$°C; ^{1}H NMR: 0.7 (t, 3H), 1.55 (s, 3H), 1.8 (m, 2H), 3.6 (dd, 2H, $J = 18.7$), 7.1–7.25 (m, 4H), 8.2 (s, 1H); ^{13}C NMR: 8.4, 29.7, 35.7, 36.9, 59.6, 124.3, 126.8, 127.0, 127.9, 130.9, 137.7, 171.3. MS (EI): 160 (100%), 189. Anal. calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40; O, 8.45; found C, 76.01; H, 8.08; N, 7.46.

1,4-Dihydro-1-ethyl-1-(3-methyl)butylisoquinolin-3-one 2f: $F = 109$°C; ^{1}H NMR: 0.7 (2d, 6H, $J = 6.6$), 0.9 (m, 1H), 1.1 (m, 1H), 1.4 (m, 1H), 1.65 (s, 3H), 1.7 (td, 1H, $J = 12.4/4.4$), 1.85 (td, 1H), 3.6 (dd, 2H, $J = 19.4$), 7.05–7.25 (m, 4H), 8.1 (s, 1H); ^{13}C NMR: 22.4, 22.5, 28.0, 30.4, 32.8, 35.5, 41.9, 59.3, 124.2, 126.8, 127.0, 127.9, 130.7, 138.2, 171.0. MS (EI): 160 (100%), 231. Anal. calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05; O, 6.92; found C, 77.90; H, 9.22; N, 6.11.

1-Benzyl-1,4-dihydro-1-methylisoquinolin-3-one 2g: $F = 165$°C; ^{1}H NMR: 1.7 (s, 3H), 2.3 (d, 1H, $J = 20.6$), 3.05 (dd, 2H, $J = 13.1$), 3.2 (d, 1H), 6.7 (d, 2H, $J = 7.8$), 6.85 (d, 1H, $J = 7.4$), 7.2–7.25 (m, 6H), 7.3 (s, 1H); ^{13}C NMR: 29.4, 34.9, 51.9, 60.1, 124.4, 126.7, 126.8, 127.4, 127.8, 128.9, 130.7, 131.8, 135.8, 137.1, 171.9. MS (EI): 160 (100%), 251. Anal. calcd

for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57; O, 6.37; found C, 80.81; H, 6.84; N, 5.56.

1′,4′-Dihydrospiro(cyclohexane-1,1′-isoquinolin-3-one)[1] **2h:** $F = 174°C$; ^1H NMR: 1.15 (m, 10H), 3.6 (s, 2H), 6.9 (s, 1H), 7.1–7.3 (m, 4H); ^{13}C NMR: 21.5, 24.9, 36.4, 37.5, 57.6, 123.4, 126.9, 127.2, 128.0, 131.2, 140.4, 170.7. MS (EI): 130, 144, 172 (100%), 215.

1′,4′-Dihydrospiro(cyclopentane-1,1′-isoquinolin-3-one) 2i: $F = 94°C$; ^1H NMR: 1.7–2.1 (m, 8H), 3.6 (s, 2H), 7.1–7.3 (m, 4H), 8.0 (s, 1H); ^{13}C NMR: 24.0, 36.7, 41.2, 66.4, 123.3, 126.9, 127.1, 127.8, 131.2, 139.4, 171.9. MS (EI): 172 (100%), 201. Anal. calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96; O, 7.95; found C, 76.81; H, 7.64; N, 6.65.

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