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Robust synthesis of linear and angular furoquinolines using Rap–Stoermer reaction

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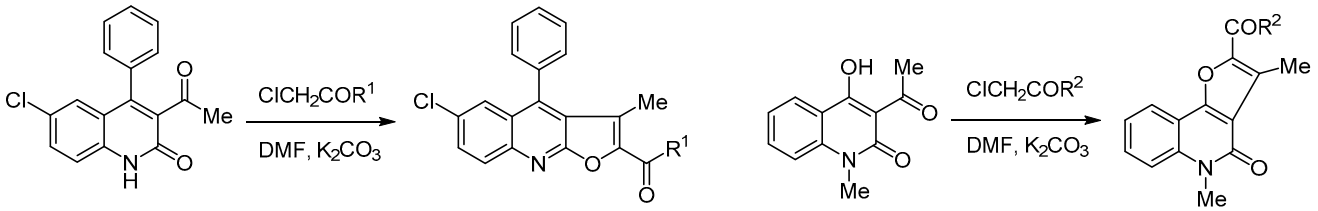

We have synthesized novel linear and angular furoquinolines *via* the Rap–Stoermer reaction by conventional as well as microwave method that furnished an enhanced yield. Initially, we synthesized linear furo[2,3-*b*]quinolines from 3-acetyl-6-chloro-4-phenyl-1*H*-quinolin-2-one and three different α-halocarbonyl compounds: chloroacetophenone, ethyl chloroacetate, and chloroacetamide. The scope of the methodology was further extended to the synthesis of angular furo[3,2-*c*]quinolines by utilizing 3-acetyl-4-hydroxy-1-methyl-1*H*-quinolin-2-one and α-halocarbonyl compounds.

Keywords: 3-acetyl-6-chloro-4-phenyl-1*H*-quinolin-2-one, 3-acetyl-4-hydroxy-1-methyl-1*H*-quinolin-2-one, angular furo[3,2-*c*]quinolines, linear furo[2,3-*b*]quinolines, Rap–Stoermer reaction.

Several naturally occurring compounds and their synthetic analogs containing the quinoline scaffold are known to possess promising pharmacological properties.[1] Primarily, various substituted linear furo[2,3-*b*]quinolines and angular furo[3,2-*c*]quinolines have attracted considerable attention as a result of their significant role in medicinal chemistry and their presence in a variety of alkaloids.[2,3] This class of compounds mainly isolated from *Rutaceae* plant family exhibit antiallergic,[4] anti-inflammatory,[4] cytotoxic,[5] platelet aggregation inhibiting,[5] antimicrobial,[6] voltage-gated potassium channel blocking,[7] spasmolytic,[8] antimalarial,[8] and mutagenic[8] activity. In addition, furoquinolines have a long and successful history in the treatment of Alzheimer's disease.[9] Such diverse types of biological activity have encouraged us to synthesize new linear and angular furoquinolines with different substituents at position 2.

Some reports are available in the literature regarding the construction of angular furo[3,2-*c*]quinolines, such as the synthesis of 5-methylfuro[3,2-*c*]quinolin-4(5*H*)-one *via* Perkin rearrangement of 3-bromo-6-methyl-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-2,5-dione,[10] synthesis of 2-alkyl/aryl-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-3-carboxylic acids by treating 3-acyl-4-hydroxy-1*H*-quinolin-2-ones with ethyl (triphenylphosphoranylidene)acetate,[11] synthesis of 2-alkylfuro[3,2-*c*]quinolin-4(5*H*)-ones by reacting 1-alkyl-4-hydroxyquinolin-2(1*H*)-ones with a number of alkynyl halides,[12] and the synthesis of furo[2,3-*c*]-condensed 1,2,3,4-tetrahydro-1,10-phenanthrolines from 8-aminoquinolines.[13] These methods required multiple steps and gave low yields. Previously we also reported the synthesis of 2-benzoylfuro[2,3-*b*]quinolines[14] and 2-acetylfuro[2,3-*b*]-quinolines.[15] In a continuation of our attempts to access this class of compounds, we herein report an efficient methodology for the synthesis of linear 4-phenylfuro[2,3-*b*]-quinolines and angular *N*-methylfuro[3,2-*c*]quinolines with amide, ester, and ketone groups as substituents at position 2 *via* the Rap–Stoermer reaction.[16]

The Rap–Stoermer reaction has been already applied in the synthesis of linear 2-substituted furo[2,3-*b*]quinolines by utilizing 3-formyl-2-hydroxyquinolines and α-halocarbonyl compounds.[17] There are no reports available in the literature regarding the reaction of 2- and 4-hydroxy-3-acetylquinolines with α-halocarbonyl compounds to obtain linear and angular furoquinolines in the Rap–Stoermer reaction.

We performed the Rap–Stoermer reaction with 3-acetyl-6-chloro-4-phenyl-1*H*-quinolin-2-one[18] (**1**) and three different

Scheme 1

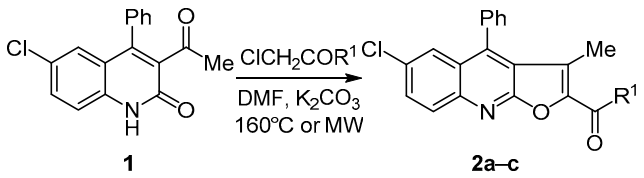

Table 1. Conditions* and yields for the synthesis of linear furo[2,3-*b*]quinolines **2a**–**c**

Compound	R^1	Method I		Method II	
		Time, h	Yield, %	Time, min	Yield, %
2a	OEt	15	72	5	93
2b	Ph	19	70	4	91
2c	NH_2	24	64	7	88

*Method I – conventional heating at 160°C; method II – microwave irradiation.

α-halocarbonyl compounds, namely, ethyl chloroacetate, chloroacetophenone, and chloroacetamide to synthesize linear 2,3,4,6-tetrasubstituted furo[2,3-*b*]quinolines **2a**–**c** (Scheme 1). Initially we carried out these reactions by a conventional method (method I, Table 1) using DMF as solvent and K_2CO_3 as base, reaching yields of 64–72%. The yields of the reactions were further enhanced up to 88–93% by using microwave methodology (method II).

The structures of all the synthesized compounds were confirmed by spectral techniques. For instance, the disappearance of IR absorption frequency at 1645 cm^{-1}, corresponding to the NHCO group of compound **1** and the appearance of peaks at 1721 cm^{-1}, corresponding to the $COOC_2H_5$ carbonyl, at 1661 cm^{-1} corresponding to COC_6H_5 carbonyl, and at 1649 cm^{-1} corresponding to the NHCO carbonyl confirmed the formation of compounds **2a**, **2b**, and **2c**, respectively. In ^{1}H NMR spectrum, the appearance of a triplet at 1.35 ppm for CH_3 and a quartet at 4.26 ppm for OCH_2 confirmed the formation of compound **2a**. There was a multiplet for thirteen aromatic protons over the range of 7.53–8.12 ppm, apparently due to the formation of compound **2b**. ^{1}H NMR spectrum of compound **2c** showed a broad singlet at 5.15 ppm for the NH_2 group. The mass spectrum of compound **2a** contained a peak at the *m*/*z* value of 366.27 $[M+H]^+$, confirming the formation of compound **2a**. The appearance of the *m*/*z* value of 398.33 $[M+H]^+$ confirmed the formation of compound **2b**, while compound **2c** gave a peak at the expected *m*/*z* value of 338.07 $[M+H]^+$.

Further, we extended this methodology to the synthesis of angular furoquinolines by utilizing 3-acetyl-4-hydroxy-1-methyl-1*H*-quinolin-2-one (**4**). The precursor **4** has been prepared previously by a ring opening reaction of pyranoquinolone and direct acylation of 4-hydroxyquinolin-2-one. These two methodologies resulted in very low yields and gave mixtures of products.[19] In this context, we are reporting an elegant and convenient methodology for the synthesis of compound **4** by regioselective methylation of 3-acetyl-4-hydroxy-1*H*-quinolin-2-one (**3**). Compound **3** has the potential to undergo methylation either at the oxygen or nitrogen atoms due to amido-imido tautomerism. However, in the presence of K_2CO_3 in DMF the methylation occurred solely at the nitrogen atom, rather than the oxygen atoms (Scheme 2).

N-Methylation was confirmed by spectral studies, in particular the ^{13}C NMR spectrum of compound **4** clearly showed the NCH_3 group carbon signal at 31.5 ppm. In the case if methylation had occurred at an oxygen atom, the OCH_3 group carbon signal would be around 60 ppm.

Next, we synthesized angular *N*-methylfuro[3,2-*c*]-quinolin-4-ones **5a**–**c** *via* the Rap–Stoermer reaction by treating 3-acetyl-4-hydroxy-1-methyl-1*H*-quinolin-2-one (**4**) with α-chlorocarbonyl compounds (chloroacetamide, ethyl chloroacetate, and chloroacetophenone) in the presence of K_2CO_3 in DMF (Scheme 2). In the case of compound **4**, due to the presence of *N*-methyl group, the formation of linear furo[2,3-*b*]quinolines is impossible, thus we isolated only angular *N*-methylfuro[3,2-*c*]quinolinones **5a**–**c**. These reactions were initially carried out by a conventional procedure (method I), which provided only moderate yields (56–63%). We were able to increase the yield up to 84–94% by using microwave methodology (method II). The variations of yields obtained according to these two methods are presented in Table 2.

The synthesized angular furo[3,2-*c*]quinolinones **5** were characterized by spectral studies. For instance, the appearance of the IR absorption peaks at 1712 cm^{-1} for ester carbonyl, at 1666 cm^{-1} for phenone carbonyl, and at 1625 cm^{-1} for amide carbonyl confirmed the formation of compounds **5a**, **5b**, and **5c**, respectively. Furthermore, in ^{1}H NMR spectrum a triplet signal at 1.35 ppm for CH_3

Scheme 2

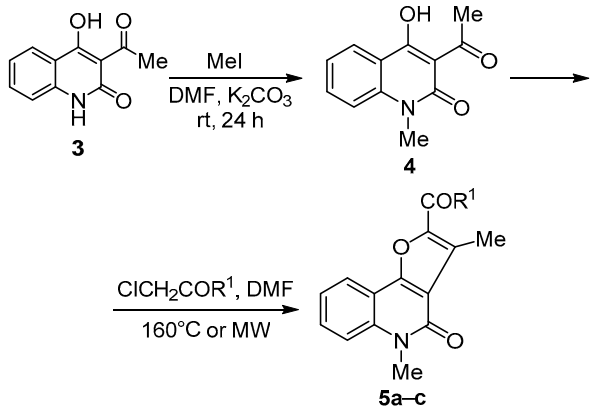

Table 2. Conditions* and yields for the synthesis of angular furo[3,2-*c*]quinolin-4-ones **5a**–**c**

Compound	R^1	Method I		Method II	
		Time, h	Yield, %	Time, min	Yield, %
5a	OEt	21	63	7	94
5b	Ph	18	58	6	86
5c	NH_2	24	56	9	84

*Method I – conventional heating at 160°C; method II – microwave irradiation.

group and a quartet at 4.36 ppm for OCH_2 group confirmed the formation of compound **5a**. There were multiplet signals in the aromatic region (7.40–8.06 ppm) corresponding to nine aromatic protons of compound **5b**. For compound **5c**, the NH_2 group signals were observed in the aromatic region as well. The elemental analysis data for compounds **5a**–**c** were in agreement with the molecular formulas.

Thus, we have synthesized novel linear and angular furoquinolines *via* the Rap–Stoermer reaction by conventional as well as microwave methods. The microwave method furnished an enhanced yield compared to the conventional method. We have chosen 3-acetyl-6-chloro-4-phenyl-1*H*-quinolin-2-one and 3-acetyl-4-hydroxy-1-methyl-1*H*-quinolin-2-one for synthesizing linear and angular furoquinolines, respectively. We have utilized three different α-halocarbonyl compounds, namely, chloroacetophenone, ethyl chloroacetate, and chloroacetamide for obtaining the title compounds.

Experimental

IR spectra in KBr pellets were recorded on a Shimadzu FT-IR 8201 PC spectrometer. ^{1}H and ^{13}C NMR spectra were acquired for DMSO-d_6 solutions on a Bruker AVIII spectrometer (500 and 125 MHz, respectively), using TMS as an internal standard. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage Max HRMS (ESI) ion trap mass spectrometer. Elemental analysis was performed on a Vario EL III CHNS Analyzer and a Perkin Elmer 2400 Series II CHNS analyzer. Melting points were determined by open capillary method using a Raga melting point apparatus and are uncorrected. The purity of the compounds was checked by TLC on silica gel plates using petroleum ether – ethyl acetate, 4:1, as the eluent. For microwave irradiation, a conventional (unmodified) domestic (LG) microwave oven was used at 360 W power setting.

Synthesis of 3-acetyl-4-hydroxy-1-methyl-1*H*-quinolin-2-one (4). Anhydrous K_2CO_3 (691 mg, 5 mmol) and methyl iodide (0.3 ml, 5 mmol) were added to a mixture of 3-acetyl-4-hydroxy-1*H*-quinolin-2-one (**3**) (1015.0 mg, 5 mmol) in DMF (40 ml) and the mixture was stirred for 24 h at room temperature. After completion of the reaction (control by TLC) the mixture was poured onto crushed ice. The precipitate was filtered off, dried, and separated by silica gel column chromatography using petroleum ether – ethyl acetate, 9:1, as eluent. Yield 984.5 mg (97%), colorless solid, mp 137–138°C (mp 138°C[19]).

Synthesis of linear 6-chloro-4-phenylfuro[2,3-*b*]-quinolines 2a–c and angular *N*-methylfuro[3,2-*c*]quinolinones 5a–c (General methods I and II). Anhydrous K_2CO_3 (345.5 mg, 2.5 mmol) was added to a solution of 3-acetyl-6-chloro-4-phenyl-1*H*-quinolin-2-one (**1**) (742 mg, 2.5 mmol) or 3-acetyl-4-hydroxy-1-methyl-1*H*-quinolin-2-one (**4**) (542.6 mg, 2.5 mmol) then the appropriate α-chlorocarbonyl compound (2.5 mol) in DMF (40 ml) was added dropwise. The resulting mixture was heated at 160°C (methods I) or irradiated with microwaves (methods II) for the time indicated in Table 1 and 2. After the reaction was complete (control by TLC) the mixture was poured onto crushed ice. The resulting precipitate was filtered off, dried, and then separated by silica gel column chromatography using 4:1 petroleum ether–ethyl acetate as eluent.

6-Chloro-3-methyl-4-phenylfuro[2,3-*b*]quinoline-2-carboxylic acid ethyl ester (2a). Yield 72% (method I), 93% (method II), colorless solid, mp 250–251°C. IR spectrum, ν, cm^{-1}: 1721 (C=OOC$_2$H$_5$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.35 (3H, t, *J* = 7.0, OCH_2CH_3); 2.31 (3H, s, 3-CH_3); 4.26 (2H, q, *J* = 7.0, OCH_2CH_3); 7.36–7.69 (8H, m, H Ar), ^{13}C NMR spectrum, δ, ppm: 11.6 (3-CH_3); 15.2 (OCH_2CH_3); 60.5 (OCH_2CH_3); 112.3; 114.2 (2C); 118.1; 123.8; 124.6; 129.3; 132.6; 135.3; 138.2; 139.6; 141.5; 146.5; 148.2; 153.4; 176.0 (CO). Mass spectrum, *m*/*z*: 366.27 [M+H]$^+$. Found, %: C 68.71; H 4.66; N 4.06. $C_{21}H_{16}ClNO_3$. Calculated, %: C 68.95; H 4.41; N 3.83.

6-Chloro-3-methyl-4-phenyl(furo[2,3-*b*]quinolin-2-yl)-phenylmethanone (2b). Yield 70% (method I), 91% (method II), colorless solid, mp 234–235°C. IR spectrum, ν, cm^{-1}: 1661 (COC$_6$H$_5$). ^{1}H NMR spectrum, δ, ppm: 2.29 (3H, s, 3-CH_3); 7.53–8.12 (13H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 11.5 (3-CH_3); 110.5; 112.3; 114.1; 115.8; 116.1; 120.6; 121.4; 122.5; 123.6; 125.8; 126.1; 128.5; 130.5; 131.6; 132.2; 134.8; 139.6; 140.7; 153.2; 165.5 (C=O). Mass spectrum, *m*/*z*: 398.33 [M+H]$^+$. Found, %: C 75.71; H 4.27; N 3.36. $C_{25}H_{16}ClNO_2$. Calculated, %: C 75.47; H 4.05; N 3.52.

6-Chloro-3-methyl-4-phenylfuro[2,3-*b*]quinoline-2-carboxylic acid amide (2c). Yield 64% (method I), 88% (method II), colorless solid, mp 265–266°C. IR spectrum, ν, cm^{-1}: 1649 (CONH$_2$). ^{1}H NMR spectrum, δ, ppm: 2.23 (3H, s, 3-CH_3); 5.15 (2H, s, NH_2); 7.20–7.65 (8H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 22.3 (3-CH_3); 108.6; 113.4; 114.8; 119.6; 120.6; 122.6; 123.4; 124.6; 125.2; 126.4; 132.1; 133.5; 135.5; 137.6; 138.2; 168.4 (CO). Mass spectrum, *m*/*z*: 338.07 [M+H]$^+$. Found, %: C 67.94; H 3.65; N 8.55. $C_{19}H_{13}ClN_2O_2$. Calculated, %: C 67.76; H 3.89; N 8.32.

3,5-Dimethyl-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2-carboxylic acid ethyl ester (5a). Yield 63% (method I), 94% (method II), colorless solid, mp 188–189°C (mp 182–189°C[11]).

2-Benzoyl-3,5-dimethyl-5*H*-furo[3,2-*c*]quinolin-4-one (5b). Yield 58% (method I), 86% (method II), colorless solid, mp 189–190°C. IR spectrum, ν, cm^{-1}: 1666 (C–CO), 1660 (N–CO). ^{1}H NMR spectrum, δ, ppm: 2.71 (3H, s, 3-CH_3); 3.69 (3H, s, NCH_3); 7.40–8.06 (9H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 11.2 (3-CH_3); 29.4 (NCH_3); 111.7; 115.1; 116.4; 118.2; 119.3; 120.4; 121.2; 122.2; 122.8; 123.2; 124.5; 130.1; 131.8; 139.5; 140.7; 155.5; 158.9 (C=O); 159.1 (NCO). Found, *m*/*z*: 340.0948 [M+Na]$^+$. $C_{20}H_{15}NO_3$. Calculated, *m*/*z*: 340.0950.

3,5-Dimethyl-4-oxo-4,5-dihydrofuro[3,2-*c*]quinoline-2-carboxylic acid amide (5c). Yield 56% (method I), 84% (Method II), colorless solid, mp 210–211°C. IR spectrum, ν, cm^{-1}: 3417 (NH_2), 1656 (N–CO), 1647 (CONH$_2$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.72 (3H, s, 3-CH_3); 3.55 (3H, s, NCH_3); 7.31–7.82 (4H, m, H-7,8, NH_2); 7.52

(1H, d, J = 8.5, H-6); 8.09 (1H, d, J = 7.5, H-9). ^{13}C NMR spectrum, δ, ppm: 20.2 (3-CH_3); 29.8 (NCH_3); 109.5; 114.6; 118.4; 122.4; 123.4; 124.5; 131.6; 132.4; 137.2; 138.9; 160.8 (NCO); 166.7 (CO). Mass spectrum, *m*/*z*: 257.09 $[M+H]^+$. Found, %: C 65.40; H 4.96; N 10.75. $C_{14}H_{12}N_2O_3$. Calculated, %: C 65.62; H 4.72; N 10.93.

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References

1. (a) Petit-pal, G.; Rideau, M.; Chenieux, J. C. *Planta Med. Phytother.* **1982**, *16*, 55. (b) Pirrung, M. C.; Blume, F. *J. Org. Chem.* **1999**, *64*, 3642. (c) Michael, Z. H.; Roger, L. X.; Richard, F. R.; Sylvia, M.; Alban, S.; Gregory, D. C.; James, R. H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 129.
2. Michael, J. P. *Nat. Prod. Rep*. **2008**, *25*, 166.
3. Michael, J. P. *Nat. Prod. Rep*. **2005**, *22*, 627.
4. Hoemann, M. Z.; Xie, R. L.; Rossi, R. F.; Meyer, S.; Sidhu, A.; Cuny, G. D.; Hauske, J. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 129.
5. Chen, Y. L.; Chen, I. L.; Wang, T. C.; Han, C. H.; Tzeng, C. C. *Eur. J. Med. Chem.* **2005**, *40*, 928.
6. Venkataraman, S.; Barange, D. K.; Pal, M. *Tetrahedron Lett.* **2006**, *47*, 7317.
7. Butenschon, I; Moller, K.; Hansel, W. *J. Med. Chem.* **2001**, *44*, 1249.
8. Nandini, D.; Asthana, M.; Mishra, K.; Singh, R. P.; Singh, R. M. *Tetrahedron Lett.* **2014**, *55*, 6257.
9. Cardoso-Lopes, E. M.; Maier, J. A.; Silva, M. R.; Regasini, L. O.; Simote, S. Y.; Lopes, N. P.; Pirani, J. R.; Bolzani, V. S.; Marx Young, M. C. *Molecules* **2010**, *15*, 9205.
10. Ohta, T.; Mori, Y. *Pharm. Bull.* **1957**, *5*, 80.
11. Klásek, A.; Kořistek, K.; Sedmera, P.; Halada, P. *Heterocycles* **2003**, *60*, 799.
12. Majumdar, K. C.; Choudhur, P. K. *Heterocycles* **1991**, *32*, 73.
13. Zaitsev, V. P.; Mikhailova, N. M.; Orlova, D. N.; Nikitina, E. V.; Boltukhina, E. V.; Zubkov, F. I. *Chem. Heterocycl. Compd.* **2009**, *45*, 308. [*Khim. Geterotsikl. Soedin.* **2009**, 383.]
14. Kumar, D. K.; Rajendran, S. P. *Synth. Commun.* **2012**, *42*, 2290.
15. Kumar, D. K.; Shankar, R.; Rajendran, S. P. *J. Chem. Sci*. **2012**, *124*, 1071.
16. (a) Rap, E. *Gazz. Chim. Ital*. **1895**, *285*, 2511. (b) Stoermer, R. *Liebigs Ann. Chem*. **1900**, *312*, 331.
17. Raghavendra, V.; Halehatty, S.; Bhojya, N.; Sherigara, B. S. *Can. J. Chem*. **2007**, *85*, 1041.
18. Kalyana Sundar, J.; Natarajan, S.; Sarveswari, S.; Vijayakumar, V.; Nilantha Lakshman, P. L. *Acta Crystallogr*., *Sect. E: Crystallogr. Commun.* **2010**, *E66*, o228.
19. Stadlbauers, W.; Hoias. G. *J. Heterocycl. Chem*. **2004**, *41*, 681.