

Note

Fluorination of 2-chloro-3-formylquinolines using microwaves

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Fluorination on 2-chloro-3-formylquinolines has been carried out in sulfolane, acetonitrile and acetamide using potassium fluoride (KF) and tetramethylammonium chloride (TMAC) under microwave irradiation as well as conventional heating. The reaction time has been brought down from hours to minutes with improved yields using microwave irradiation. The rate of fluorination of 2-chloro-3-formylquinoline is more in acetamide followed by acetonitrile.

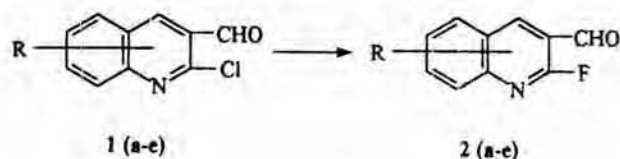
As fluorine in organic compounds leads to increase lipid solubility in membranes, because of higher solubility they are biologically active and can be used in the synthesis of drugs^{1,2}.

Recently, the use of microwave irradiation (MWI) in connection with the synthesis of heterocycles³, has become a field of interest in our laboratory^{4,6}. Keeping in view the substantial reduction in the reaction time with improved yield under MWI, it was thought worthwhile to synthesise new 2-fluoro-3-formylquinolines in different solvent systems under MWI using a domestic microwave oven as well as in a conventional way.

Fluorination of substituted 2-chloro-3-formylquinolines⁷ **1a-e** in sulfolane, acetonitrile and acetamide using KF and TMAC under MWI and also by conventional heating method furnished products **2a-e** (cf. Scheme 1). The reaction time has been brought down from hours to minutes with improved yields using microwave irradiation. The characterization data of the products **2a-e** are given in Tables I and II. The melting points of all the products were more than 300°C therefore could not be mentioned. The observed order of fluorination of 2-chloro-3-formylquinoline using KF and TMAC is: acetamide > acetonitrile > sulfolane.

Experimental

Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. ¹H NMR spectra were measured at 90



R

a 4-Me

b 4-H

c 6-Me

d 7-Me

e 8-Me

Scheme 1

MHz on a Perkin Elmer R-32 Spectrometer using TMS as internal standard (chemical shifts in δ , ppm). Elemental analyses were performed on a Heracus CHN Rapid Analyser. EI mass spectra were recorded on a JEOL-JHS-DX303 mass spectrometer. For microwave irradiation, Padmini essentia domestic microwave oven, model Brownie (2450 MHz) was used.

Fluorination of substituted 2-chloro-3-formylquinolines

Preparation using sulfolane

Method A—Sulfolane (0.07 mole) and spray dried KF (0.08 mole) were heated at 160°C and 4mL of sulfolane was distilled under reduced pressure. Substituted 2-chloro-3-formylquinoline (0.01 mole) and 0.005 mole of TMAC were added to the distillate. Reaction mixture was refluxed for 6 hr at 180°C. The completion of reaction was confirmed by TLC examination. The product was eluted by column chromatography using eluent: petroleum ether/EtOAc (1:1).

Method B—4 mL of distilled sulfolane was taken in an Erlenmeyer flask. To this 0.01 mole of substituted 2-chloro-3-formylquinoline (0.01 mole) and 0.005 mole of TMAC were introduced and zapped inside microwave oven for 3-4 min. The post

Table I—Reaction conditions used for the preparation of compounds 2a-e and their characterization data

Compd	Found (Calcd) (%)			Yield (%)			Reaction Period		
	C	H	N	Sulfolane A/B	Acetonitrile A/B	Acetamide A/B	Sulfolane A(hr)/B(min)	Acetonitrile A(hr)/B(min)	Acetamide A(hr)/B(min)
2a	69.75 (69.78)	4.21 (4.26)	7.38 (7.40)	45/70	72/80	82/93	6/3	36/7	4/1.5
2b	68.60 (68.58)	3.47 (3.45)	8.00 (7.99)	46/72	76/85	82/94	5/6.4	37/7.5	4.5/2
2c	69.76 (69.78)	4.21 (4.26)	7.39 (7.40)	48/75	75/84	83/96	6/3.5	36.5/6	4/2
2d	69.74 (69.78)	4.22 (4.26)	7.38 (7.40)	44/66	74/83	82/89	6/3.5	35/6.5	5/3
2e	69.75 (69.78)	4.21 (4.26)	7.38 (7.40)	45/67	68/79	81/91	5.5/3	36/8	5.2/5

Table II—Spectral data of compounds 2a-e

Compd	¹ H NMR (DMSO- <i>d</i> ₆ + CDCl ₃ δ, ppm)	M ⁺ observed/ (expected)
2a	2.8(s, 3H, 4-CH ₃), 7.25 – 8.35 (m, 4H, Ar-H), 10.40 (s, 1H, CHO)	188(189)
2b	7.25 – 8.35 (m, 5H, Ar-H), 10.35 (s, 1H, CHO)	175(175)
2c	2.56 (s, 3H, 6-CH ₃), 7.26 – 8.35 (m, 4H, Ar-H), 10.38 (s, 1H, CHO)	189(189)
2d	2.62 (s, 3H, 7-CH ₃), 7.25 – 8.35 (m, 4H, Ar-H), 10.40 (s, 1H, CHO)	188(189)
2e	2.72 (s, 3H, 8-CH ₃), 7.30 – 8.40 (m, 4H, Ar-H), 10.35 (s, 1H, CHO)	189(189)

reaction temperature was 172–75°C. Reaction was monitored by TLC after every half min. On completion of the reaction the product was worked-up similarly as described above.

Preparation using acetonitrile

Method A—The heterogeneous system of dry acetonitrile (0.36 mole), TMAC (0.07 mole) and dry KF (0.07 mole) was prepared by heating with stirring for 30 min. Then substituted 2-chloro-3-formylquinoline (0.01 mole) was added and the resulting mixture was refluxed for 36 hr at 80°C. The solution was poured over ice-cold water and the solid obtained was filtered, dried and recrystallised from DMF/ethanol mixture.

Method B—Heterogeneous system was prepared as described in method-A. To this solution substituted 2-chloro-3-formylquinoline (0.01 mole) was added and subjected to MWI for 6–8 min. The end reaction

temperature was 64–76°C. Product was worked-up as described above.

Preparation using acetamide

Method A—0.01 mole of substituted 2-chloro-3-formylquinoline and 0.15 mole of acetamide were taken in 100 mL round bottom flask and heated to 80°C until solution was affected. Then 0.7 mole of KF and 0.7 mole of TMAC were added to it. The resulting mixture was heated at 140°C with rapid stirring for 4–5 hr. It was allowed to cool upto 90°C and poured into 500 mL of ice-cold water. The solid separated was filtered, washed with water, dried and recrystallised from DMF/ethanol mixture.

Method B—A mixture of acetamide (0.15 mole) and substituted quinoline (0.01 mole) were taken in Erlenmeyer flask and heated under microwave irradiation for 0.5 min to get the clear solution. Then KF (0.7 mole) and TMAC (0.7 mole) were added and contents were subjected to MWI for a period of 1–3 min. The post reaction temperature was 131–34°C. Reaction mixture was worked-up as described in method A.

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