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Tetrahedron Letters 45 (2004) 5771-5773

Tetrahedron Letters

Microwave promoted solvent-free one-pot three-component reaction to 2-pentafluorophenylquinoline derivatives $\stackrel{\stackrel{}_{\leftrightarrow}}{}$

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> Received 25 February 2004; revised 16 April 2004; accepted 18 April 2004 Available online 15 June 2004

Abstract—A novel and efficient one-pot multi-component reaction of pentafluorobenzaldehyde, alkynes and anilines for the synthesis of 2-pentafluorophenyl substituted quinolines under microwave irradiation and a solvent-free condition is presented. © 2004 Elsevier Ltd. All rights reserved.

Quinoline derivatives are very important in medicinal chemistry because of their wide occurrence in natural products and drugs.¹ Also, quinolines are found to possess a wide spectrum of biological activities.² It is well known that replacement of hydrogen with fluorine frequently confers bioactivity to organic molecules.³ Therefore, the synthesis of fluorine-containing quinoline derivatives is of considerable importance due to the biological activities of the resulting products. Various methods have been reported for synthesis of fluorine-containing quinoline derivatives. For example, Gerus et al. have reported the synthesis of 2-trifluoromethyl-quinolines in 30% yield from the reaction of EtOCH=CHCOCF₃ with anilines followed by treatment with PPA (Eq. 1).⁴



Keywords: Microwave; Pentafluorobenzaldehyde; Aniline; Alkyne; Ouinoline.

- Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.04.179
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Billah et al.⁵ used anilines and ethyl 1,1,1-trifluoroacetate by three reaction steps to prepare 2-trifluoromethylquinolines in low yield (Eq. 2).

$$CF_{3}COCH_{2}CO_{2}Et + \underbrace{\overset{NH_{2}}{\overbrace{u}}_{u}R}_{u} \xrightarrow{} \underbrace{\underset{R}{\longrightarrow}}_{R} \underbrace{(2)}_{R}$$

Recently, we have reported the direct synthesis of 2-fluoroalkyl quinoline derivatives from the reaction of α -fluoroalkyl-aldehyde with anilines (Eq. 3).⁶



However, to the best of our knowledge, 2-perfluorophenylquinoline derivatives have not been reported.

In recent years, microwave-assisted reactions are of great interest because of simplicity in operation, enhanced reaction rates and greater selectivity. Thus, microwave irradiation, which has become a powerful synthetic tool for the rapid synthesis of a variety of biologically active compounds under solvent-free conditions, is used to enhance the rates of classical organic reactions.⁷ For example, Wang et al. have

reported the microwave-assisted amination from aryl triflates without base and catalyst.⁸ Furthermore, the one-pot multi-component synthetic procedure and the use of solid acid catalyst such as clay and zeolites have attracted considerable attention in different areas of organic synthesis, which can largely simplify the synthetic step and operation under environmentally benign conditions.⁹

In this paper, we wish to report a novel and efficient approach for the synthesis of 2-pentafluorophenylsubstituted quinolines by microwave promoted one-pot three-component reaction of pentafluorobenzaldehyde, anilines and alkynes on the surface of montmorillonite clay impregnated with catalytic amount of CuBr in solvent-free conditions (Scheme 1).

Firstly, the effect and the amount of the copper(I) salt, microwave irradiation time and irradiation power on the efficiency and yield were briefly investigated. Pentafluorobenzaldehyde, aniline and phenyl acetylene were used as starting materials in the presence of montmorillonite clay doped with copper(I) salt under microwave irradiation, the results are summarized in Table 1. It was noteworthy that the copper(I) bromide played an important role in the reaction system, in the absence of copper(I) bromide, no reaction occurred under the same condition (entry 14, Table 1). However, increasing the ratio of copper(I) bromide did not improve the yields obviously, whereas decreasing the ratio of copper(I) bromide affected the yield drastically (entries 10, 11, Table 1). It was found that the other catalysts such as CuCl and CuI had similar catalytic activity in terms of conversion and reaction time (entries 12, 13, Table 1). The reaction rates and yields were dramatically enhanced by microwave. By comparison, the same reaction took around 4h under the traditional thermal conditions (80 °C, oil bath) to afford expected quinoline derivatives in moderate yield (64%). Optimal reaction condition was obtained with 30% copper(I) bromide under 450 W irradiation power over 3.5 min (entry 4, Table 1). Prolonged irradiation time could not give higher yield of 4aa (entry 9, Table 1).

Both electron donating and electron withdrawing substituents on the aromatic amine afforded the corresponding quinoline derivatives in good to excellent yields (Table 2). However, it should be indicated that electron effect of substituent on aromatic amine might affect the



Scheme 1.

Table 1. One-pot three-component reactions of C_6F_3 CHO, PhNH₂ and PhC=CH give 4aa¹⁰ under the different reaction conditions^a

Entry	Copper(I) salt (equiv)	Microwave irradiation ^a		Yield ^b
		Irradiation time (min)	Irradiation power (W)	_
1	CuBr (0.3)	3.5	80	53
2	CuBr (0.3)	3.5	150	75
3	CuBr (0.3)	3.5	300	82
4	CuBr (0.3)	3.5	450	84
5	CuBr (0.3)	3.5	700	64
6	CuBr (0.3)	1.0	450	59
7	CuBr (0.3)	2.5	450	80
8	CuBr (0.3)	3.0	450	82
9	CuBr (0.3)	5.0	450	83
10	CuBr (0.1)	3.5	450	45
11	CuBr (1)	3.5	450	85
12	CuCl (0.3)	3.5	450	77
13	CuI (0.3)	3.5	450	68
14		3.5	450	

^a Microwave irradiations were carried out using a Sanyo, EM-551S/550S, domestic microwave oven with adjustable irradiation power, $C_6F_5CHO/PhNH_2/PhC\equiv CH = 1:1:2$.

^b Isolated yield based on pentafluorobenzaldehyde.

 Table 2. Microwave promoted synthesis of 2-pentafluorophenylquinoline derivatives^a

Entry	Arylamine	Alkyne	Product (Yield) ^b
1	2a	3a	4aa (84)
2	2b	3a	4ba (92)
3	2c	3a	4ca (81)
4	2d	3a	4da (86)
5	2a	3b	4ab (70)
6	2b	3b	4bb (86)
6	2c	3b	c
7	2d	3b	4db (76)
8	2b	3c	c

^a Microwave irradiation power: 450 W, time: 3.5–4.0 min.

^b Isolated yield based on pentafluorobenzaldehyde.

^cOnly the corresponding imines were formed.

yields. This may be attributed to the nature of nucleophilicity of amine, which is critical effect in the rapid formation of imine from pentafluorobenzaldehyde and amine on the clay surface.

Furthermore, other terminal alkynes such as propargyl alcohol and propargyl acetate were also studied (Table 2). However, under the same reaction condition, treatment of pentafluorobenzaldehyde with equimolar of aniline and 2 equivalent propargyl alcohol in the presence of 30% catalytic amount of copper(I) bromide gave the expected product in quite lower yield, only 20% yield of quinoline derivative was isolated, along with the N-phenyl pentafluorophenyl aldimine (derived in situ from pentafluorobenzaldehyde and aniline on the clay surface) as by-product in 60% yield. The better yields were obtained from increasing the amount of starting material propargyl alcohol up to 4 equivalent based on the pentafluorobenzaldehyde, and expected quinoline derivative was isolated in 86% yield. It should be indicated that treatment of 1 with equimolar of 2c and 4 equiv of **3b** gave *N*-(4-nitrophenyl)pentafluorophenyl aldimine only, without the formation of the corresponding quinoline. Neither increasing the irradiation power nor prolonged the irradiation time could change the result. Furthermore, when the more reactive 2b and propargyl acetate (3c) were used as starting materials to carry out this reaction, no desired products were obtained, although the reaction was carried out under more drastic reaction conditions. Reactions of 3c with other anilines such as 2a,c,d were also studied. None of them gave the satisfied results.

Acknowledgements

The authors thank the National Natural Science Foundation of China (NNSFC) (Nos. 20032010, 20372077) and Innovation Foundation of Chinese Academy of Sciences for financial support.

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- 10. Data for **4aa**: mp 118–119 °C. IR (KBr): v 3127, 1523, 1496, 1400 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 8.23 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.80 (t, J = 8.4 Hz, 1H), 7.62–7.53 (m, 7H); ¹⁹F NMR (282 MHz, CDCl₃ with CFCl₃): δ –142.8 (d, J = 15.7 Hz, 2F), –153.7 (t, J = 15.7 Hz, 1F), –161.7 (m, 2F). EIMS (70 eV), m/z (rel. int.): 371 (M⁺, 100.00), 204 (M⁺–C₆F₅, 7.45), 178 (M⁺–C₆F₅–CN, 12.30). Anal. Calcd for C₂₁H₁₀F₅N: C, 67.93; H, 2.71; N, 3.77. Found: C, 67.80; H, 2.82; N, 3.61.