Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 9257–9259
Tetrahedron Letters

A versatile and efficient synthesis of 3-aroyl-1,4-dihydroquinolin-4-ones

Eric Stern, Régis Millet, Patrick Depreux* and Jean-Pierre Hénichart

Institut de Chimie Pharmaceutique Albert Lespagnol, Université de Lille 2, EA 2692, 3, rue du Professeur Laguesse, BP83, F-59006, France

Received 13 September 2004; revised 12 October 2004; accepted 12 October 2004
Available online 28 October 2004

Abstract—A versatile and efficient method for preparation of 3-aroyl-4-quinolones is described. The procedure involved a Michael-type addition of methyl anthranylate with various β-ketonic enol ethers followed by based promoted cyclisation. Different quinolones have been obtained. The ring closure is facilitated by heating at reflux in diphenyl ether leading to increase the rate of the cyclisation.

Quinolone derivatives represent an important class of organic compounds regarding their various biological and pharmacological activity. Many drugs with antibacterial properties[1–3] (norfloxacin or ciprofloxacin) have a 3-substituted-4-quinolone ring. The target enzymes of quinolones are bacterial DNA gyrase and topoisomerase IV, which are needed for the replication and transcription of bacterial DNA. Theses compounds have an excellent oral bioavailability, with good tissue penetration. They are widely used for infection of urinary tract, respiratory tract, skin and soft tissue infections. They did not reveal particular toxicity or side effects and then their structure constitutes an interesting pattern in building of enlarged chemical derivatives with various biological and pharmacological properties.

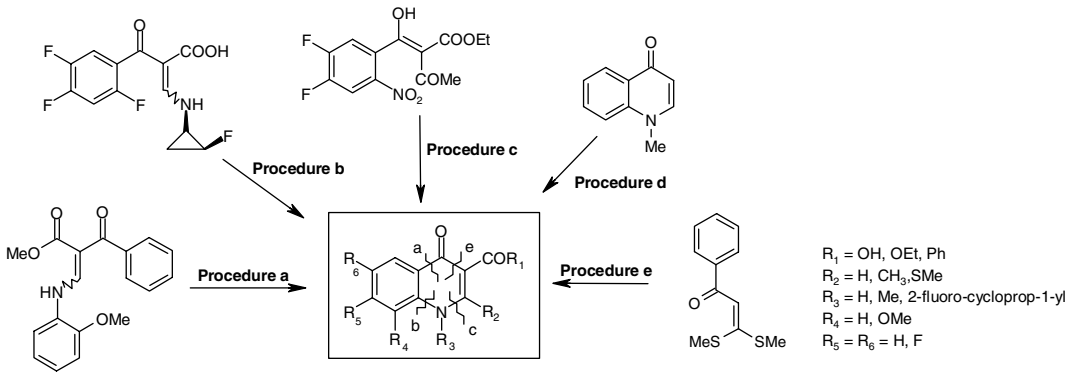
In the course of our investigation on quinolone series we wished to consider an efficient approach leading different 3-aroyl-1,4-dihydroquinolin-4-ones (**1a**–**g**). The 3-acyl-1,4-dihydroquinolin-4-ones and the 3-benzoyl derivatives have been prepared by a modified Gould–Jacobs reaction[4–6] (Scheme 1, procedure a) involving thermal cyclisation of ethyl β-anilinoacrylate derivatives.

Alternative methods of cyclisation involve intramolecular aromatic substitution such as in the preparation of sitafloxacin[7,8] (procedure b) or reductive cyclisation[9,10] (procedure c) for the preparation of 3-carboxylic-1,4-dihydroquinolin-4-ones acid derivatives. The direct addition of lithiated 1,3-dithianes to 1-methyl-4-quinolone (procedure d) also lead to such derivatives.[11] Nevertheless the *N*-1 position of the quinolone ring should be alkylated and the quinolone ring should be temporally protected by 1,3-dithianes to avoid the C-2 acylation. Other methodologies ultimately proved to be ineffective for our target molecules. For example, procedure a did not allow to prepare rapidly a broad series of compounds. In the procedures b and c, the conversion of carboxylic acid function into aryl ketone by classical methodologies such as Friedel and Craft,[12] Vilsmeier–Haack,[13] or methodology using PPA[14] failed.

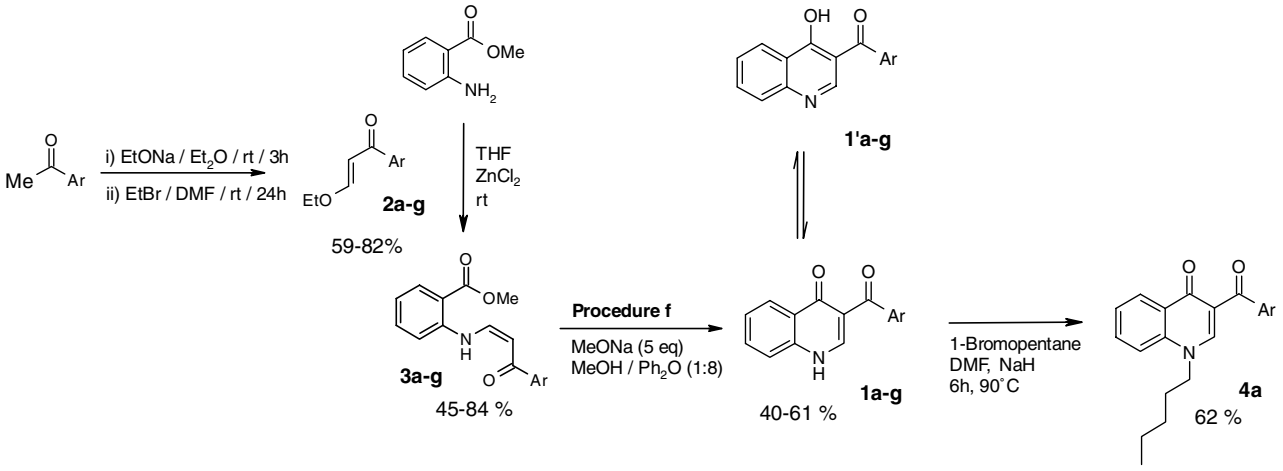
To continue our investigation on the rapid and facile synthesis of 3-aroyl-4-quinolone derivatives, we engaged in a new approach (Scheme 2). Recently, Wang et al.[15] described the synthesis of 3-aroyl-2-(methylsulfanyl)-1,4-dihydroquinolin-4-one, using methyl anthranylate as starting material (Scheme 1, procedure e). The reaction involved a tandem reaction comprising of the formation of ketene aminals between α-aroylketene dithioacetals and methyl anthranylate followed by an intramolecular enaminic cyclisation to furnish quinolone. In order to generalise this procedure and to obtain unsubstituted C-2 quinolone, we therefore envisaged modifying (Scheme 2) this methodology using various β-ketonic enol ethers (**2a**–**g**) as carbon nucleophilic agents (Table 1).

Keywords: Quinolone; Enaminoester; Methyl anthranylate.
* Corresponding author. Tel.: +33 320964379; fax: +33 320964906; e-mail: pdepreux@phare.univ-lille2.fr

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.067



Scheme 1. Reagents and conditions: Procedure a: Ph_2O, reflux, 45 min, R_1 = Ph, $R_2 = R_3 = R_5 = R_6$ = H, R_4 = OMe. Procedure b: K_2CO_3, DMF, 100 °C. R_1 = OH, R_2 = H, R_3 = cyclopropyl, R_4 = H, $R_5 = R_6$ = F. Procedure c: (i) H_2, Pd–C, EtOH, 1 bar, (ii) 2 N NaOH, reflux, 3 h, 10% HCl. R_1 = OH, R_2 = Me, $R_3 = R_4$ = H, $R_5 = R_6$ = F. Procedure d: BuLi, 1,3-dithiane, THF, HMPA, PhCOCl, −80 °C, 1 h. R_1 = Ph, $R_2 = R_4 = R_5 = R_6$ = H, R_3 = Me. Procedure e: methyl anthranilate, $C_2H_5CO_2H$, reflux, 5 days. R_1 = Ph, R_2 = SMe, R_3 = H, $R_4 = R_5 = R_6$ = H.



Scheme 2. Reagents and conditions: Procedure f: synthesis of 3-aroyl-4-quinolones **1a**–**g** and their derivatives.

No reaction was observed when (*E*)-3-ethoxy-1-(4-methoxyphenyl)prop-2-en-1-one[16,17] prepared from 1-(4-methoxyphenyl)ethan-1-one (**2a**) was refluxed (1 → 6 days) with methyl anthranylate in propionic acid (1 → 5 equiv). When the reaction was carried out in acetic acid, DMF or diphenyl ether at room temperature or reflux, we observed the formation of traces of enamino ester (**3a**). The best result was obtained when we used a Lewis acid such as $ZnCl_2$.[18] In the presence of 2 equiv of anhydrous zinc chloride in tetrahydrofuran enaminoester (**3a**) was obtained in 83% yield. According to this procedure, the reaction of (*E*)-β-ketonic ester (**2b**–**g**) and methyl anthranylate was generalised and furnished corresponding (*Z*)-enaminoester (**3b**–**g**) in 40–84% yields.[19]

The cyclisation into 3-aroyl-4-quinolone was next investigated. Thus, we envisaged using strong bases to promote the intramolecular cyclisation since thermal and acid conditions failed.[15] Different bases were used such as sodium in MeOH, EtOH or *t*-BuOH reported to prepare 4-pyridinones,[20] NaH in DMF or *t*-BuOK/*t*-BuOH/DMSO.[21]

After many trials, we found that Na (5 equiv) in a mixture of dry MeOH[21] and diphenyl ether (1:8) at reflux (240 °C) is the best choice for the conversion of enaminoesters (**3a**–**g**) to quinolone (**1a**–**g**).[22] Combination of thermal and basic conditions allowed accelerating the cyclisation. In a general way, the yields obtained in a Ph_2O/methanol mixture at reflux (240 °C) were found to be better than in methanol at reflux, except for **1a**. We noted a decomposition of the compound into methyl anthranilate. When the reaction was made at 120 °C, the yield was improved at 37%.

4-Quinolones (**1a**–**g**) can also exist as the tautomeric 4-quinolinol (**1′a**–**g**) form.[23,24] The NMR studies[25,26] revealed that only the tautomers **1a**–**g** were present in DMSO-d_6. Alkylation of **1a** by 1-bromopentane with NaH lead also to the *N*-alkylated product rather than the O-alkylated and confirmed that the synthesis produced exclusively the 4-quinolones tautomers.

In conclusion, we describe a versatile and efficient method to prepare 3-aroyl-1,4-dihydroquinolin-4-ones from methyl anthranylate. Optimisation of the procedure

Table 1. Synthesised enamino ester **3a–g** and 1,4-dihydroquinolin-4-ones **1a–g**

Entry	R	Yield (%)
Condition A: THF/$ZnCl_2$/rt		
4a	–4-Methoxyphenyl	83
4b	–Phenyl	84
4c	–Naphth-1-yl	78
4d	–Naphth-2-yl	82
4e	–6-Methoxy-naphth-2-yl	62
4f	–Anthracen-9-yl	40
4g	–1,3-Benzodioxole-5-yl	50
Condition A: MeONa (5 equiv)/MeOH/reflux/4 h		
1a	–4-Methoxyphenyl	22
1b	–Phenyl	5
1c	–Naphth-1-yl	0
1d	–Naphth-2-yl	10
1e	–6-Methoxy-naphth-2-yl	0
1f	–Anthracen-9-yl	0
1g	–1,3-Benzodioxole-5-yl	33
Condition B: MeONa (5 equiv)/MeOH:Ph–O–Ph (1:8)/reflux/4 h		
1a	–4-Methoxyphenyl	0
1b	–Phenyl	40
1c	–Naphth-1-yl	39
1d	–Naphth-2-yl	60
1e	–6-Methoxy-naphth-2-yl	55
1f	–Anthracen-9-yl	43
1g	–1,3-Benzodioxole-5-yl	47

was explored. The purification of the products was found to be flexible enough to obtain appreciable quantities of compounds. This protocol opens a way for the synthesis of other 3-aroyl-1,4-dihydroquinol-4-ones derivatives with various biological and pharmacological properties.

References and notes

1. Srivastava, S. K.; Chauban, P. M. S.; Bhaduri, A. P.; Fatima, N.; Chatterjee, R. K. *J. Med. Chem.* **2000**, *43*, 2275–2279.
2. Appelbaum, P. C.; Hunter, P. A. *Int. J. Antimicrob. Ag.* **2000**, *16*, 5–15.
3. Sissi, C.; Palumbo, M. *Curr. Med. Chem. Anti-Cancer Ag.* **2003**, *6*, 439–450.
4. Ife, R. J.; Brown, T. H.; Keeling, D. J.; Leach, C. A.; Meeson, M. L.; Parsons, M. E.; Reavill, D. R.; Theobald, C. J.; Wiggall, K. J. *J. Med. Chem.* **1992**, *35*, 3413–3422.
5. Gould, R. G.; Jacobs, W. A. *J. Am. Chem. Soc.* **1939**, *61*, 2890–2895.
6. Price, C. C.; Roberts, R. M. *J. Am. Chem. Soc.* **1946**, *68*, 1204–1208.
7. Takemura, M.; Hayakawa, I. *Il Farmaco* **2001**, *56*, 37–40.
8. Anquetin, G.; Rouquayrol, M.; Mahmoudi, N.; Santillana-Hayat, M.; Gozalbes, R.; Greiner, J.; Farhati, K.; Derouin, F.; Guedj, R.; Vierling, P. *Bioorg. Med. Chem. Lett.* **2004**, *13*, 2773–2776.
9. Jung, J.-C.; Jung, Y.-J.; Park, O.-S. *J. Heterocycl. Chem.* **2001**, *38*, 61–67.
10. Jung, J.-C.; Baek, S.; Park, O.-S. *Il Farmaco* **2001**, *56*, 665–675.
11. Griera, R.; Rigat, L.; Alvarez, M.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1223–1227.
12. Jarret, R. M.; Kell, N.; Allen, S.; Cannon, L.; Coughlan, J.; Cusumano, L.; Nolan, B. *J. Chem. Ed.* **1989**, *66*, 1056–1057.
13. Augé, F.; Hornebeck, W.; Decarne, M.; Laronze, J.-Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1783–1786.
14. Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Nakanishi, Y.; Nampoothiri, P.; Hamel, E.; Brossi, A.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2891–2893.
15. Wang, M.-X.; Liu, Y.; Huang, Z.-T. *Tetrahedron Lett.* **2001**, *42*, 2553–2555.
16. Spassky-Pasteur, A.; Riviere, H. *Bull. Soc. Chim. Fr.* **1969**, 811–815.
17. Spassky, A. *Bull. Soc. Chim. Fr.* **1970**, 2954–2962.
18. Okumara, K.; Adachi, T.; Tomie, M.; Kondo, K.; Inoue, I. *J. Chem. Soc.* **1972**, *94*, 173–177.
19. General procedure for the synthesis of (*Z*) enaminoester **3a–g**. A mixture of the appropriate β-ketonic-enol ether (**2a–g**) (1 equiv), anhydrous zinc chloride (2 equiv) in dry THF was stirred at room temperature for 15 min. The methyl anthranilate (1.2 equiv) was added, and the resulting solution was stirred at room temperature for 24 h, evaporated and diluted with ethyl acetate. The solution was washed with water and sodium bicarbonate aqueous solution (5%), dried and evaporated. The residue was triturated in ether and the resulting solid was recrystallised from isopropyl ether. NMR analysis revealed the formation of (*Z*) isomers.
20. Leflemme, N.; Dallemagne, P.; Rault, S. *Synthesis* **2002**, *12*, 1740–1746.
21. Demir, A. S.; Akhmedov, I. M.; Sesenoglu, O. *Tetrahedron* **2002**, *58*, 9793–9799.
22. General procedure for the synthesis of 4-aroyl-quinolone **1a–g**: appropriate enaminoester **3a–g** (1 equiv) was added to a solution of sodium (5 equiv) in anhydrous methanol (5 mL) and diphenyl ether (40 mL). The mixture was refluxed for 4 h. After cooling, the pH was adjusted to 4 with 2 N HCl. The solid obtained was collected by filtration and recrystallised.
23. Staskun, B. *J. Org. Chem.* **1961**, *26*, 2791–2794.
24. Singh, G.; Nair, G. V. *J. Am. Chem. Soc.* **1956**, *78*, 6105–6109.
25. Tautomer form was determined by 2D NMR (COSY and ROESY). Cross-peaks between H_2 and NH for **1a** and N–CH_2 for **4a** were observed.
26. Zalibera, L.; Milata, V.; Llavsky, D. *Magn. Reson. Chem.* **1998**, *36*, 681–684.