Tetrahedron 72 (2016) 2006–2011

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Reinvestigation of *ortho*-amidoacetophenones' cyclization mediated by trimethylsilyl trifluoromethanesulfonate. The Lewis-acid-assisted and Brønsted-acid-catalyzed reaction

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ARTICLE INFO

Article history:
Received 3 November 2015
Received in revised form 22 February 2016
Accepted 29 February 2016
Available online 2 March 2016

Keywords:
Methylquinoline
Quinolone
Trifluoromethanesulfonic acid
Trimethylsilyl trifluoromethanesulfonate
Lewis-acid-assisted and Brønsted-acid-catalyzed reaction

ABSTRACT

Reinvestigation the synthesis of quinolones from *ortho*-amidoacetophenones by trimethylsilyl trifluoromethanesulfonate (TMSOTf) mediated reaction is reported. In addition to receiving the expected quinolones, an unexpected intermolecular self-condensation adduct was also isolated. The detailed mechanism of its formation is discussed.

1. Introduction

The quinolone derivatives are an important class of nitrogen-containing heterocycles because of the wide spectrum of biological activities, such as *anti*-malarial,[1] *anti*-cancer,[2] *anti*-viral[3] and *anti*-bacterial properties.[4] Owing to their pharmaceutical importance, many synthetic strategies have been demonstrated, such as by Camps,[5] Conrad–Limpach,[6] Gould–Jacobs,[7] and Niementowski,[8] respectively. Among these strategies, the Camps cyclization was most widely employed. However, all the above-mentioned methods were required the strong basic and harsh conditions and the less functional groups compatibility limited their applications. Therefore, several improved methods have been reported in the synthesis of 4-quinolones.[9]

We have noticed the condition of a Lewis acid, trimethylsilyl trifluoromethanesulfonate (TMSOTf) mediated *ortho*-amidoacetophenones' cyclization to synthesize 4-quinolone **2** and derivatives[10] (Scheme 1). The mechanism in formation of **2** has been addressed in that article. The authors claimed this strategy was a modified method of Camps cyclization to avoid a harsh condition. When we repeated this procedure recently, beside the desired product **2**, we observed a certain amount of a red pot on TLC. This red spot was isolated as a white solid by column chromatography. Its X-ray crystallography and HRMS data confirmed the structure **3** (vide infra). However, compound **3** was not discussed in that report and its formation arose our interests.

2. Results and discussion

To a flame-dried under vacuum, two-necked round-bottomed glassware equipped with a condenser was charged with **1**, 1,2-dichloroethane (1,2-DCE), Et_3N (3 equiv) and 'TMSOTf'[11] (6 equiv). This mixture was heated at 95 °C for 6 h (Table 1, Entry 1). The desired compound **2** was received as the major component (48%) along with a red spot observed on TLC, which was then isolated as **3** (38%). The structure of compound **3**, a methylquinoline framework, was confirmed by X-ray crystallography (Fig. 1). Compound **3** was most likely derived from the intermolecular self condensation of **1**. The earliest and recent reports regarding to the synthesis of **3** were by Camps[12] and Molina,[13] respectively. Especially, the later applied *ortho*-substituted arylazide by the Staudinger reduction and followed by condensation with *ortho*-azido acetophenone. When compound **1** was then treated with various equivalents of 'TMSOTf' by the same condition, respectively, the yields of both **2** and **3** were gradually declined till 3 equiv of 'TMSOTf' were used. The reaction was not complete by treating with 2 equiv of 'TMSOTf'. No compound **2** was isolated but trace of **3** was obtained when the

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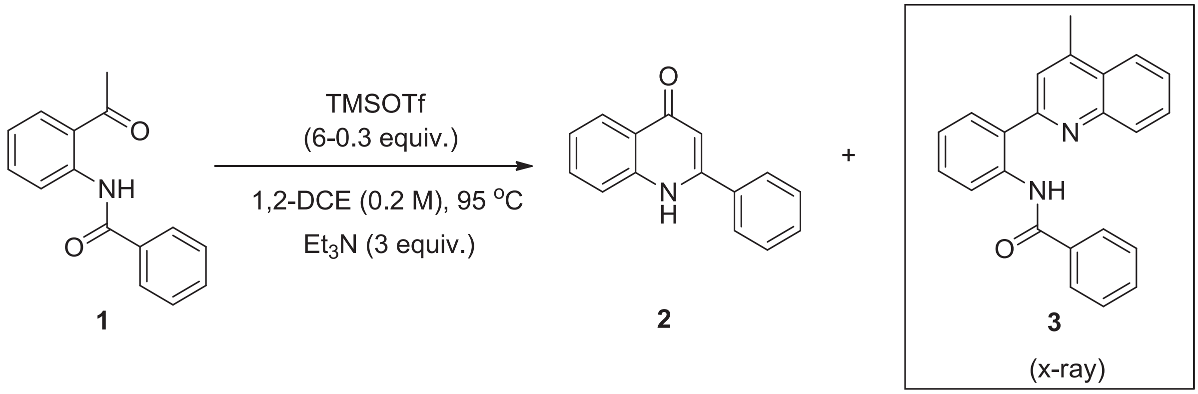
http://dx.doi.org/10.1016/j.tet.2016.02.068



Scheme 1. The TMSOTf mediated cyclization of **1**. Intramolecular cyclization versus intermolecular self condensation.

Table 1
Optimized conditions of cyclization reaction of **1** by 'TMSOTf'

Entry	'TMSOT' (equiv)	Time (h)	**2** (Yield%)	**3** (Yield%)
1	6	6	48	38
2	5	6	32	18
3	4	6	28	19
4	3	6	25	21
5	2	26	20 (22)[a]	24 (27)[a]
6	1	26	0	3 (4)[a]
7	0.3	30	0	2 (3)[a]

Condition: Et_3N (3 equiv), 'TMSOTf' (6–0.3 equiv), 1,2-DCE (0.20 M), 95 °C and flame-dried glassware.

[a] Yields based on the recovery of starting material **1**.

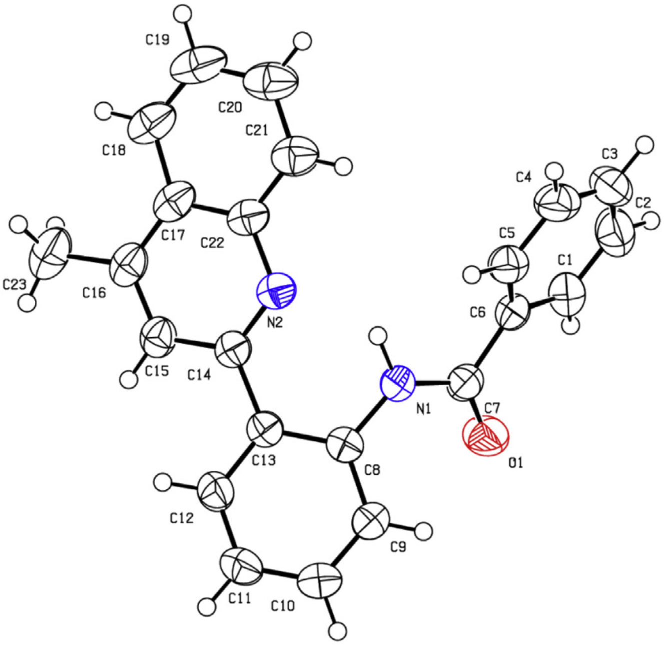


Fig. 1. Single crystal X-ray structure of **3**.

reactions were used one and 0.3 equiv of 'TMSOTf', respectively. Most of compound **1** was recovered.

We were aware that our results in Table 1 were different from literature (Et_3N, 3 equiv; TMSOTf, 6 equiv; 83% of **2**).[10] We assumed that the 'TMSOTf' used in reaction might contain certain amount of moisture. It has been reported that TfOH served as a super proton (H^+) donor to facilitate the ring cyclization.[14] The reaction mixture containing TMSOTf and moist TfOH might cause a different mechanism from the literature proposed.[10] In order to prove our assumption, a new bottle of anhydrous TMSOTf[15] was used and the glassware system was flame-dried under vacuum. A dramatically improved yield of **2** was obtained by using 6 equiv of TMSOTf (Table 2, Entry 1). The yield of **2** (91%) was comparable with the literature results.[10] However, a small quantity of compound **3** (2%) was also received. Compound **2** was isolated as major instead of compound **3** when compound **1** was treated with anhydrous TMSOTf (5–2 equiv). However, the longer reaction time was required (48 h) to compare with in Table 1. When the reaction was separately treated with one or 0.3 equiv of TMSOTf, no compound **2** was obtained and far low yields of compound **3** was received. In light of the results from Tables 1 and 2, we might conclude that not only TMS group but also moist TfOH were essential in affording **3**.

Conditions were used the non-flame-dried glassware and 'TMSOTf' (6–0.3 equiv) system to compare with the results of Tables 1–3. However, the data were in contrast to the results in Tables 1 and 2. The yields of compound **3** was slightly dominant over than **2**. This confirmed that the resulting moist TfOH from decomposition of TMSOTf by moisture was pertaining to the formation of **3**. The yields of **3** decreased gradually with reducing amounts of 'TMSOTf'. We also found two or less equivalents of TMSOTf would not drive the reaction in completion. Since we had no clue how much amount of moist content in TMSOTf was necessary to obtain **3**, therefore, the reaction mixture was added TMSOTf (6 equiv) along with 1% H_2O (relative to the equivalents of

Table 2
Conditions and yields of cyclization reaction of **1** by anhydrous TMSOTf

Entry	TMSOTf (equiv)	Time (h)	**2** (Yield%)	**3** (Yield%)
1	6	48	91	2
2	5	48	76	22
3	4	48	57	22
4	3	48	29	22
5	2	48	22 (24)[a]	20 (22)[a]
6	1	48	Trace	11 (16)[a]
7	0.3	48	0	2 (3)[a]

Condition: Et_3N (3 equiv), TMSOTf (6–0.3 equiv), 1,2-DCE (0.20 M), 95 °C and flame-dried glassware.

[a] Yields based on the recovery of starting material **1**.