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

Yi-Ru Chen, Yu Cheng Cho, Tzenge-Lien Shih *

Department of Chemistry, Tamkang University, Tamsui Dist., 25137 New Taipei City, Taiwan, ROC

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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

* Corresponding author. Tel./fax: +886 2 86315024; e-mail address: tlshih@mail.tku.edu.tw (T.-L. Shih).

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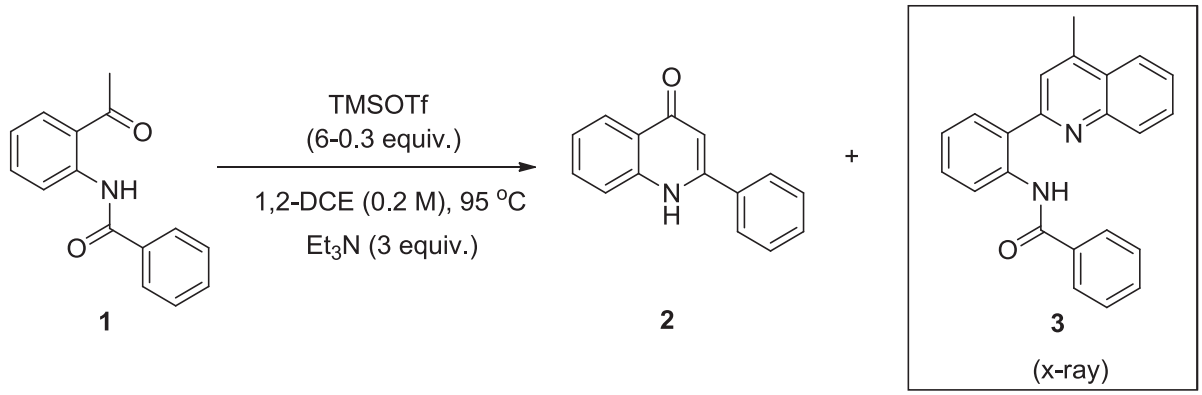


Scheme 1. The TMSOTf mediated cyclization of **1**. Intramolecular cyclization versus intermolecular self condensation.

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**.

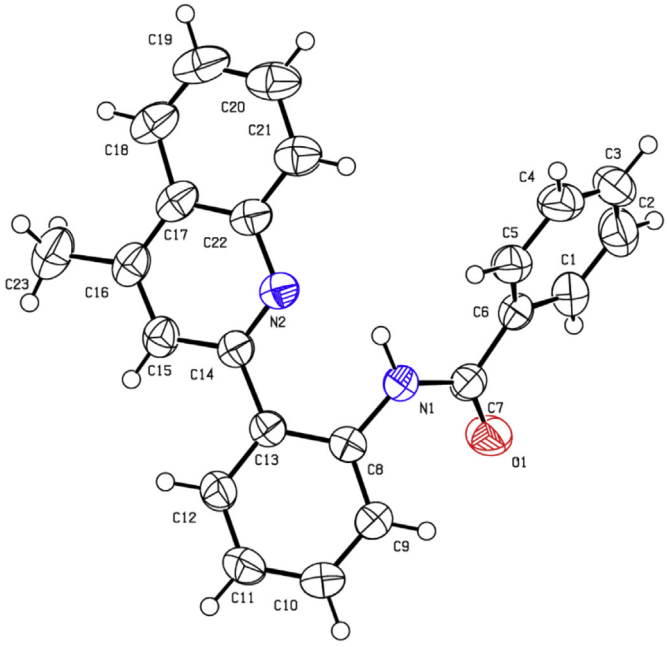


Fig. 1. Single crystal X-ray structure of **3**.

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**.

Table 3
Yields of cyclization reaction of **1** by 'TMSOTf' under moist condition

Entry	'TMSOTf' (equiv)	Time (h)	**2** (Yield%)	**3** (Yield%)
1	6	48	18	47
2	5	48	23	27
3	4	48	20	34
4	3	48	21	19
5	2	48	20 (20)[a]	15 (16)[a]
6	1	48	Trace	6 (15)[a]
7	0.3	48	0	2 (9)[a]

Condition: Et_3N (3 equiv), 'TMSOTf' (6–0.3 equiv), 1,2-DCE (0.20 M), 95 °C and non-flame-dried glassware.
[a] Yields based on the recovery of starting material **1**.

TMSOTf) and heated for 30 h. At this stage, part of the TMSOTf was decomposed to afford TMSOH and TfOH. Compounds **2** and **3** were isolated with 17% and 29% yields, respectively. Although the combined yields was slightly lower, this indeed demonstrated that TfOH was essentially needed for **1** in favor of formation of **3**.

In order to discern the role of TMS group during the reaction course, we used anhydrous TfOH as the only source of Brønsted acid in reaction (Table 4). No compound **2** was isolated throughout the reactions at any event. We observed that the extended reaction time (72 h) was needed and relatively lower yields of **3** were obtained in comparison to the data of Table 3. When analogous **4** was treated with anhydrous TfOH (Scheme 2) in the same condition as in Table 4, the intermolecular condensation adduct **6** (Fig. 2)was received in comparable yields (Table 5). However, these reactions also required longer reaction time and did not complete in the absence of TMS group. Again, no intramolecular cyclization compound **5** was detected through the studies. In addition, when methanesulfonic acid (MsOH, 6–0.3 equiv) was replaced for TfOH in Table 4, neither **2** nor **3** were formed and **1** was fully recovered. We assumed that the acidity of MsOH was not strong enough to mediate intermolecular self condensation of **1** to furnish **3**.

Table 4
Conditions and yields of cyclization reaction of **1** by anhydrous TfOH

Entry	TfOH (equiv)	Time (h)	**2** (Yield%)	**3** (Yield%)
1	6	72	0	40 (53)[a]
2	5	72	0	34 (45)[a]
3	4	72	0	15 (17)[a]
4	3	72	0	19 (46)[a]
5	2	72	0	5 (9)[a]
6	1	72	0	3 (4)[a]
7	0.3	72	0	3 (13)[a]

Condition: Et_3N (3 equiv), TfOH (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**.

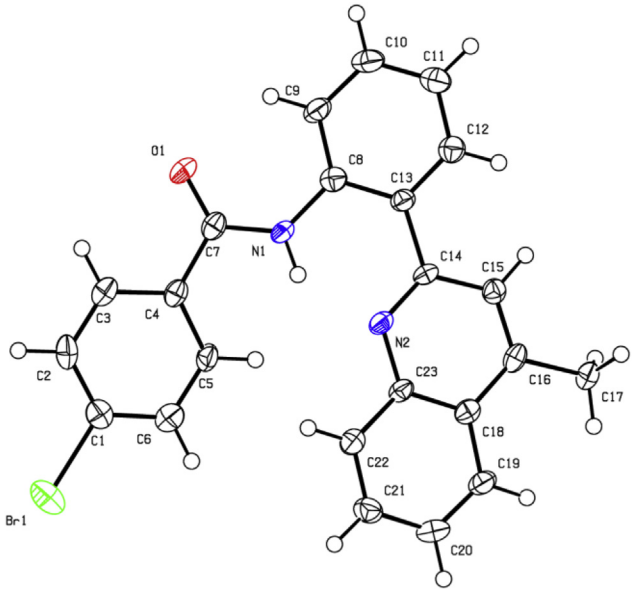


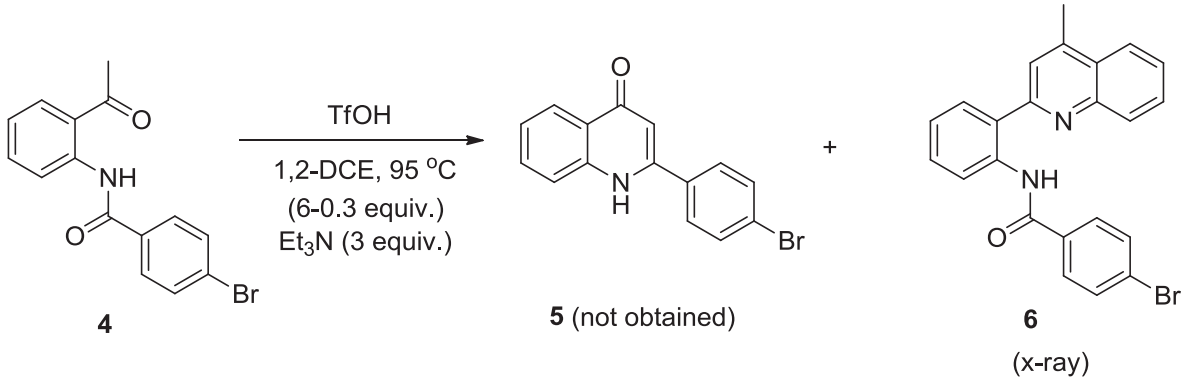
Fig. 2. Single crystal X-ray structure of **6**.

Table 5
Conditions and yields of cyclization reaction of **4** by anhydrous TfOH

Entry	TfOH (equiv)	Time (h)	**5** (Yield%)	**6** (Yield%)
1	6	72	0	50 (57)[a]
2	5	72	0	38 (49)[a]
3	4	72	0	19 (41)[a]
4	3	72	0	10 (28)[a]
5	2	72	0	11 (30)[a]
6	1	72	0	13 (22)[a]
7	0.3	72	0	10 (22)[a]

Condition: Et_3N (3 equiv), TfOH (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 **4**.

We found two or less equivalents of TMSOTf were not enough to complete reactions in Table 1–3. Therefore, it was more reasonable that the reaction required at least 3 equiv of TMSOTf because the same equivalent amounts of Et_3N were used. The plausible mechanism of formation **3** from **1** by treating with 'TMSOTf' (3 equiv) is depicted in Fig. 3. Two equivalents of TMS groups complexed with both oxygens of amide and ketone to form either TMS-enol **7** or **7′**. The resulting TfOH (cat) arose from the partial decomposition of the rest 1 equiv of TMSOTf by the moisture. Equilibrium occurred



Scheme 2. Cyclization reaction of **4** by anhydrous TfOH to lead to the intermolecular self-condensation compound **6**.

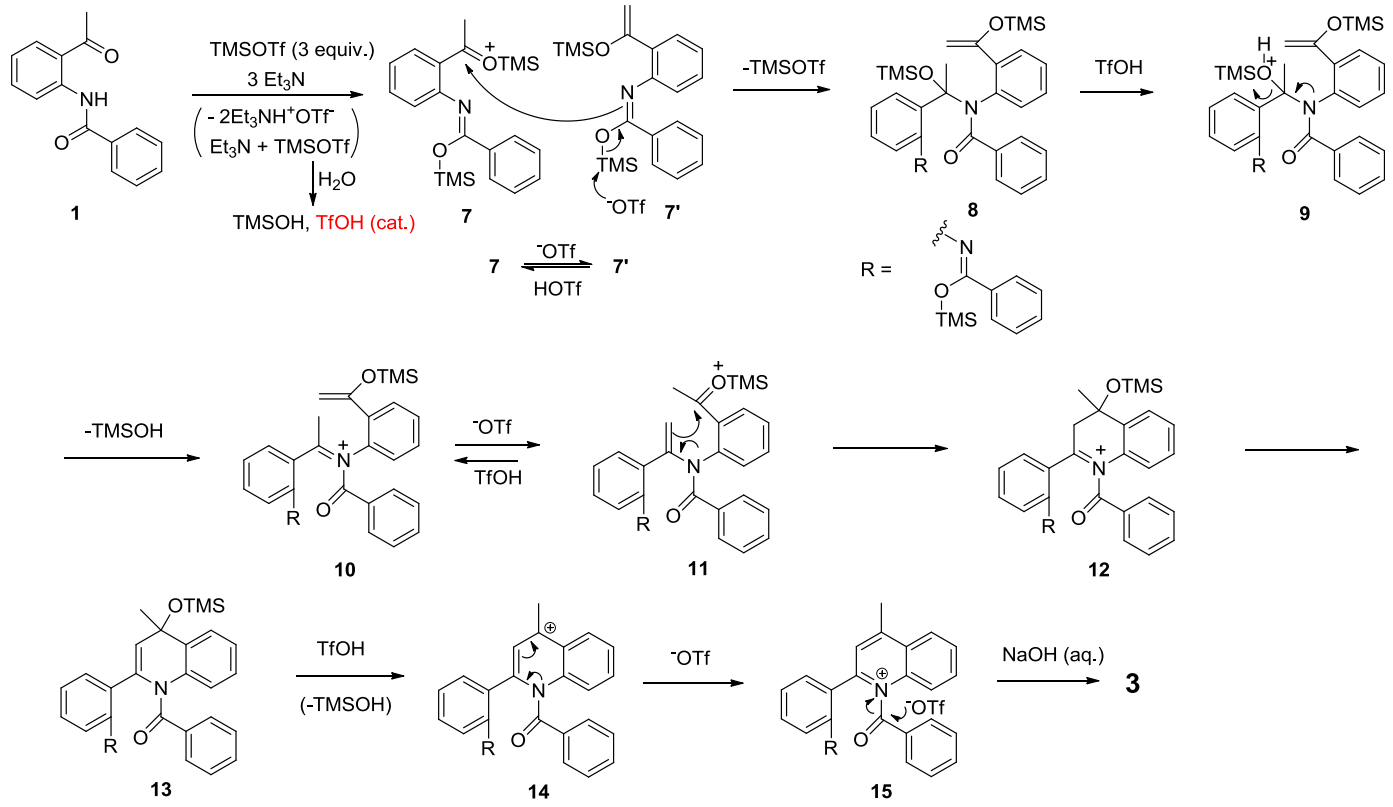


Fig. 3. Plausible mechanism of cyclization reaction of **1** mediated by 'TMSOTf'. The intermolecular self-condensation reaction of **1** facilitated by TfOH (cat.) to furnish **3**.

between **7** and **7′** while TfOH presented. The presence of $^{-}$OTf sequentially removed TMS of 7′ to trigger the intramolecular self condensation of **1** to lead to compound **3**. The similar mechanism is also applicable to the cyclization of **4** to provide **6** while the TMS group(s) in Fig. 3 were replaced with H^{+}.

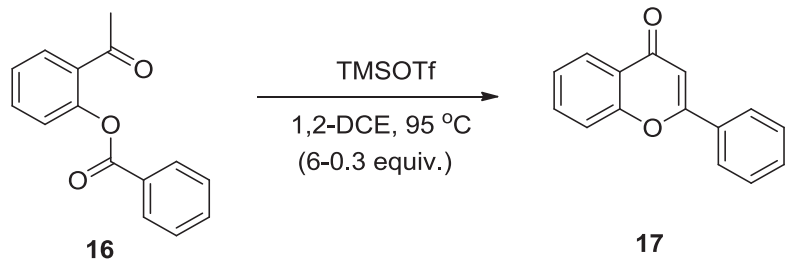
Table 6
Conditions and yields of cyclization reaction of **1** by TMSOTf or moist 'TMSOTf' under different concentrations

Entry	Condition	Time (h)	**2** (Yield%)	**3** (Yield%)
1	a	24	63	8
2	b	24	53	11
3	c	18	49	18
4	d	4	47	43

Condition: a. Et_3N (3 equiv), TMSOTf (6 equiv), 1,2-DCE (0.05 M), 95 °C and flame-dried glassware. b. Et_3N (3 equiv), 'TMSOTf' (6 equiv), 1,2-DCE (0.05 M), 95 °C and flame-dried glassware. c. Et_3N (3 equiv), 'TMSOTf' (6 equiv), 1,2-DCE (0.05 M), 95 °C and non-flame-dried glassware. d. Et_3N (3 equiv), 'TMSOTf' (6 equiv), 1,2-DCE (0.5 M), 95 °C and non-flame-dried glassware.

The reaction concentration used throughout these studies were 0.2 M instead of those in the literature (0.1 M) based on starting materials **1**. A question might arise from the higher concentration media leading to higher yields of **3**. Therefore, the conditions in Tables 1–3 (Entry 1) were repeated except the reaction concentrations were reduced to 0.05 M (Table 6, Entry1–3). In presence of moisture of 'TMSOTf' (Entry 3), yields of **2** were dominated over **3** of which yield was slightly increased and less reaction time was needed to compare with Entry1–2. When the concentration was 0.5 M, compounds **2** and **3** were received almost equivalent yields (Entry 4). The above-mentioned results and in Table 3 (Entry 1) clearly demonstrated that the reaction was most likely concentration dependent to form **3**. Especially, the moist TfOH along with TMS group and higher concentration (0.2–0.5 M) were without doubt in favor of compound 3.

In order to determine whether cyclization reaction could occur for **16** by TMSOTf, compound **16** was treated with the same conditions as in Tables 1 and 2 (Scheme 3). The cyclized adduct **17** was



Scheme 3. Intramolecular cyclization of **16** by TMSOTf.

formed while TMSOTf was used (6–0.3 equiv) for **16** (Table 7). The yields of **17** declined as the equivalents of TMSOTf reduced. We observed **16** also gradually decomposed during **17** was forming that accounted for its lower yields in prolonged reaction time. When 'TMSOTf' was used, the relatively lower yields of **17** were received (Table 8). It was probably the resulting TfOH in reaction mixture to decompose compound **16**. That explained why we observed compound **16** immediately decomposed by TLC monitoring when TfOH (6–0.3 equiv) was added. We suspected that the ester moiety of **16** might be too labile to survive under strong Brønsted acid conditions. Unlike the cyclization reactions of **1** and **4**, we have to point out that the intermolecular self condensation of **16** did not occurred. When MsOH was used as the only proton source (6–0.3 equiv), compound **16** was fully recovered and no cyclized adduct **17** was received.

3. Conclusion

In conclusion, we have investigated in details the mechanism of formation of **3** from *ortho*-amidoacetophenone **1** by moist TMSOTf. It is noteworthy that the TMS group, catalytic moist TfOH and higher concentration media (0.2–0.5 M) play essential roles to facilitate the formation of **3**. The combined yields of **2** and **3** were moderate to good with at least 3 equiv of TMSOTf (Tables 1–3). The yields of compound **3** and **6** were moderate to low and required longer reaction times by using TfOH as the only proton source (Tables 4 and 5). We found the only TfOH could not drive the reactions in completion without the TMS group's assistance. This is an example of Lewis-acid-assisted and Brønsted-acid-catalyzed cyclization.

4. Experimental section

All chemicals were purchased from either Aldrich Chemical Co. or Arcos companies and used without further purification. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on Bruker Advance 600 spectrometer. The melting points were determined on Fargo MP-2D and not corrected. Column chromatography was conducted under flash pressure and the silica gel was used 230–400 mesh (Macherey–Nagel, MN Kiesegel 60) except otherwise stated. The chemical shifts were reported in parts per million (ppm) and referenced to the residual protonated solvent: CD_3OD (^{1}H: 3.31 ppm; ^{13}C: 49.2 ppm) or CD_2Cl_2 (^{1}H: 5.32 ppm; ^{13}C: 54.0 ppm). The HRMS (FAB) data were recorded on Finnigan MAT-95S.

Table 7
Conditions and yields of cyclization reaction of **16** by anhydrous TMSOTf

Entry	TMSOTf (equiv)	Time (h)[a]	**17** (Yield%)
1	6	6	53
2	5	8	49
3	4	7	36
4	3	10	22
5	2	13	16
6	1	14	10
7	0.3	24	1

Condition: Et_3N (3 equiv), TMSOTf (6–0.3 equiv), 1,2-DCE (0.20 M), 95 °C and flame-dried glassware.
[a] Reaction was terminated until compound **16** was consumed by TLC detection.

Table 8
Conditions and yields of cyclization reaction of **16** by 'TMSOTf'

Entry	'TMSOTf' (equiv)	Time (h)[a]	**17** (Yield%)
1	6	8	27
2	5	9	23
3	4	9	22
4	3	10	18
5	2	11	15
6	1	15	8
7	0.3	26	Trace

Condition: Et_3N (3 equiv), 'TMSOTf' (6–0.3 equiv), 1,2-DCE (0.20 M), 95 °C and flame-dried glassware.
[a] Reaction was terminated until compound **16** was consumed by TLC detection.

4.1. *N*-(2-(4-Methylquinolin-2-yl)phenyl)benzamide (3)

A set of two-necked round-bottom flask equipped with a condenser was flame-dried under vacuum then charged with **1** (132 mg, 0.55 mmol). After the flask was evacuated and purged with N_2 for three times, anhydrous 1,2-dichloroethane (2.8 mL), anhydrous triethylamine (0.24 mL, 1.66 mmol), and TMSOTf (0.60 mL, 3.32 mmol) were added sequentially. This mixture was heated at 95 °C for 48 h. At the end of reaction time, MeOH (5 mL) was added to quench the reaction. The solvent was removed under reduced pressure, diluted with EtOAc (20 mL), and washed with 2 M $NaOH_{(aq)}$ (3×10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2:Hexane=1:2–19:1) to afford **3** as a white solid (4 mg, 2%); Mp=132–134 °C. Then the eluent was changed (CH_2Cl_2:MeOH=20:1) to afford **2** as a yellow solid (112 mg, 91%); Mp=251–253 °C (lit.[10]>230 °C). For **3**: ^{1}H NMR (600 MHz, CD_3OD) δ 8.61 (d, J=8.3 Hz, 1H), 8.07 (d, J=8.3 Hz, 1H), 7.45 (dd, J=7.4, 1.6 Hz, 4H), 7.84 (s, 1H), 7.72 (t, J=8.0 Hz, 1H), 7.57–7.62 (m, 2H), 7.51 (t, J=7.7 Hz, 2H), 7.47 (t, J=8.2 Hz, 1H), 7.28 (t, J=7.7 Hz, 1H), 5.47 (s, 1H), 2.75 (s, 3H). ^{13}C NMR (150 MHz, CD_3OD) δ 168.2, 159.1, 148.3, 147.4, 139.3, 136.9, 133.3, 131.3 (×2), 131.1, 130.9 (×2), 129.8 (×2), 127.9, 125.5, 125.4, 123.1, 122.6, 19.2. HRMS (ESI) calcd for $C_{23}H_{18}N_2O$ $[M]^+$ 339.1497; found: 339.1490.

4.2. 4-Bromo-*N*-(2-(4-methylquinolin-2-yl)phenyl)benzamide (6)

Purification by flash column chromatography (Hexane:CH_2Cl_2=2:1–0:1). Mp=135–136 °C. ^{1}H NMR (600 MHz, CD_2Cl_2) δ 13.69 (s, 1H), 8.79 (d, J=8.3 Hz, 1H), 8.08 (d, J=8.3 Hz, 1H), 8.04 (d, J=8.3 Hz, 1H), 7.93 (d, J=8.5 Hz, 3H), 7.80 (t, J=8.7 Hz, 2H), 7.66–7.62 (m, 3H), 7.51 (t, J=7.5 Hz, 1H), 7.28 (t, J=7.5 Hz, 1H), 2.80 (s, 3H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 165.0, 158.2, 147.0, 146.3, 138.9, 135.4, 132.2 (×2), 130.7, 130.5, 129.9 (×2), 129.6 (×2), 128.9, 127.1, 126.5, 126.2, 124.5, 124.0, 122.0, 121.9, 19.31. HRMS (FAB) calcd for $C_{23}H_{18}BrN_2O$ $[M+1]^+$ 417.0603; Found: 417.0605.

Acknowledgements

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Supplementary data

Supplementary data (Copies of ^{1}H, ^{13}C NMR spectra and X-ray data of compounds **3** and **6**) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.02.068.

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