HETEROCYCLES, Vol. 97, No. 2, 2018, pp. 785 - 792. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 14th February, 2018, Accepted, 17th April, 2018, Published online, 11th May, 2018
DOI: 10.3987/COM-18-S(T)51

CONSTRUCTION OF AZAISOFLAVONE DERIVATIVES BY HYPERVALENT IODINE REAGENT-MEDIATED OXIDATIVE REARRANGEMENT OF 2'-NITROCHALCONE‡

Akira Nakamura, Reo Takane, Junki Tanaka, Junya Morimoto, and Tomohiro Maegawa*

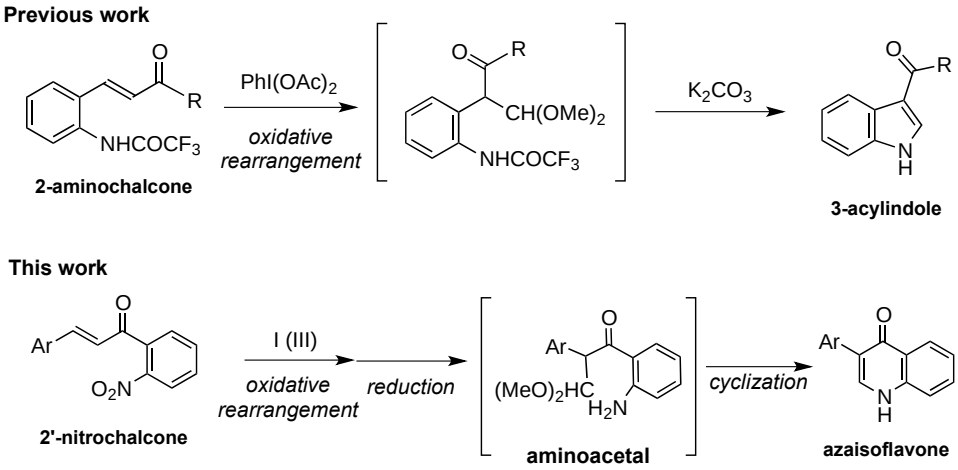
School of Pharmaceutical Sciences, Kindai University, 3-4-1 Kowakae, Higashi-osaka, Osaka, 577-8502, Japan. E-mail: maegawa@phar.kindai.ac.jp

Abstract – Fabrication of a synthetic azaisoflavone skeleton from 2'-nitrochalcone was done using oxidative rearrangement with a hypervalent iodine reagent. A key intermediate compound, aminoacetal, was prepared from readily available 2'-nitrochalcone via a PhI(OH)OTs-mediated rearrangement, followed by reduction of the nitro group. A variety of azaisoflavones were obtained in moderate to high yields by treatment of the intermediate compound under acidic conditions.

INTRODUCTION

Azaisoflavones (3-arylated quinolin-4(1*H*)-ones) are known as quinolone analogs, in which the oxygen of isoflavone skeletons is replaced with nitrogen, and a number of azaisoflavone analogs have been designed and evaluated based on their biological activities.[1] Numerous synthetic strategies for the construction of azaisoflavones have been developed,[2] including methods involving a chalcone rearrangement reaction. However, azaisoflavone synthesis via oxidative rearrangement of 2'-aminochalcone requires thallium (III) nitrate, which is highly toxic.[1a,3] Another reaction using an epoxide derivative of 2'-nitrochalcone via acid-mediated rearrangement has also been reported.[4] Our current research focuses on the development of synthetic methodologies based on the rearrangement of chalcone using hypervalent iodine reagents.[5] Recently, we reported a concise synthesis of 3-acylindole derivatives from 2-aminochalcone via $PhI(OAc)_2$-mediated rearrangement and cyclization under basic conditions (Scheme 1).[6] Herein, we report an application of the oxidative rearrangement method using hypervalent iodine reagent to synthesize azaisoflavones from 2'-nitrochalcones.

‡This paper is dedicated to Prof. Kiyoshi Tomioka on the occasion of his 70th birthday.

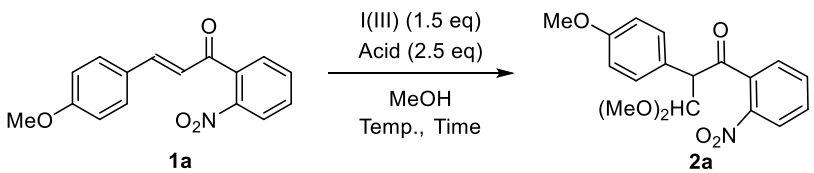


Scheme 1. Previous our work and the synthesis plan of azaisoflavones

RESULTS AND DISCUSSION

In our initial study, 2'-nitrochalcone **1a** was chosen as a model substrate and the reaction conditions were optimized for the rearrangement process (Table 1). The reaction conditions using $PhI(OAc)_2$ (1.5 equiv) and $BF_3{\cdot}OEt_2$ (2.5 equiv) in $CH(OMe)_3$ at room temperature, employed for indole synthesis,[6] were inefficient and did not yield any rearranged product **2a** (Entry 1). In the absence of acid, no reaction occurred even at reflux conditions (Entry 2). **2a** was obtained at a 56% yield with *p*-TsOH, while no reaction occurred using trifluoroacetic acid (TFA; Entries 3 and 4). Next, the reaction was conducted other hypervalent iodine reagents. The most chalcone **(1a)** was recovered using $PhI(OCOCF_3)_2$, and no rearranged product was obtained. On the other hand, the yield was greatly improved with PhI(OH)OTs and **2a** was isolated at a 79% yield (Entry 6). Finally, **2a** was obtained in a quantitative yield when the reaction was performed at 50 °C (Entry 7).

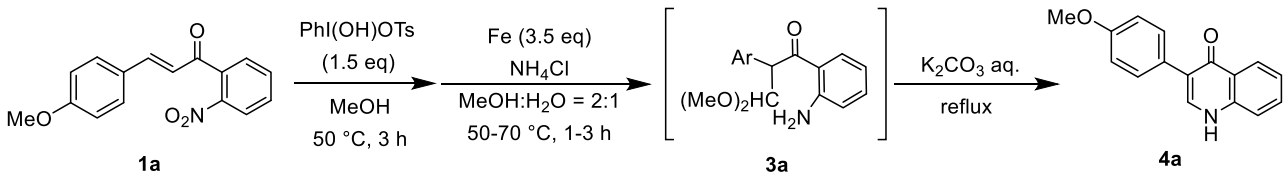
Table 1. Hypervalent iodine reagent-mediated oxidative rearrangement of 2'-nitrochalcone **1a**



Entry	I(III)	Acid	Temp.	Time	Yield
1[a]	$PhI(OAc)_2$	$BF_3{\cdot}Et_2O$	rt	2 h	-
2	$PhI(OAc)_2$	-	reflux	24 h	N.R.[b]
3	$PhI(OAc)_2$	*p*-TsOH	50 °C	4 h	56%
4	$PhI(OAc)_2$	TFA	reflux	24 h	N.R.[b]
5	$PhI(OCOCF_3)_2$	-	rt	24 h	(91%)[c]
6	PhI(OH)OTs	-	rt	24 h	79%
7	PhI(OH)OTs	-	50 °C	3 h	99%

[a] $CH(OMe)_3$ was used instead of MeOH. [b] No reaction. [c] The yield of recovered **1a**.

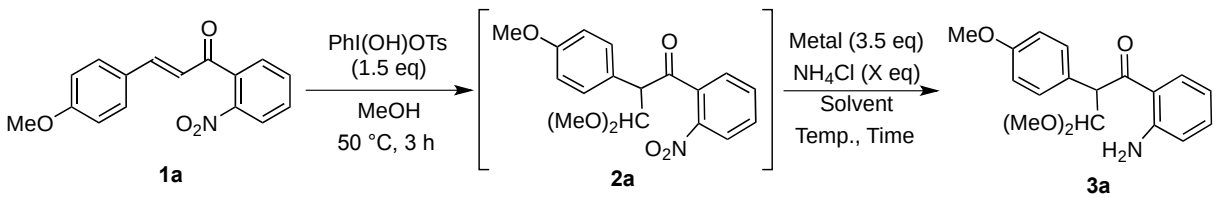
Similar to our previous findings,[6] the isolated **2a** was not stable and gradual decomposition was observed. Therefore, we next used a one-pot procedure and attempted the direct synthesis of azaisoflavones from 2'-nitrochalcone (Scheme 2). After completion of rearrangement, iron powder and NH_4Cl were added to the reaction mixture and subsequent treatment with K_2CO_3 aqueous solution led to the desired azaisoflavone **4a**, but only a trace amount of **4a** was obtained. Based on thin layer chromatography (TLC) analysis, the reaction progressed as expected until the reduction step, at which point there seemed to be a problem with the cyclization step.



Scheme 2. Attempted one-pot synthesis of azaisoflavone **4a**

Next, we examined the isolation of reductant **3a**, which turned out to be relatively stable since the intramolecular hydrogen bonding between the ketone and amine group in **3a** contributes to stability (Table 2). After the oxidative rearrangement step, reduction of **2a** was conducted with iron powder and NH_4Cl. The reaction proceeded slowly at 50 °C and **3a** was isolated at a 54% yield (Entry 1). The use of zinc powder was not effective for this reduction (Entry 2). The yield increased to 77% when the reaction was performed at 70 °C (Entry 3). To make the experimental operation easier, we added saturated NH_4Cl aqueous solution instead of solid NH_4Cl. Finally, the best result was obtained at 60 °C with an 86% yield of **3a** (Entry 4).

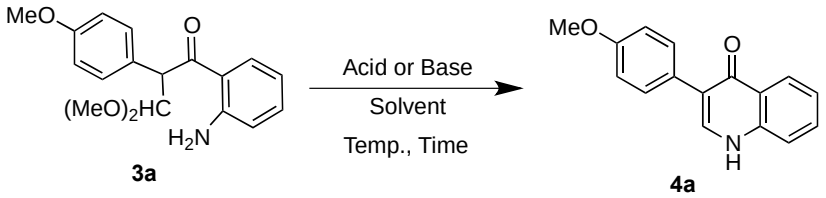
Table 2. Sequential reactions of oxidative rearrangement and reduction



Entry	Metal	X	Solvent	Temp.	Time	Yield
1	Fe	10 eq	MeOH-H_2O = 2:1	50 °C	24 h	54%
2	Zn	10 eq	MeOH-H_2O = 2:1	50 °C	1 h	-
3	Fe	-	MeOH-NH_4Cl aq. = 2:1	70 °C	1 h	77%
4	Fe	-	MeOH-NH_4Cl aq. = 2:1	60 °C	2 h	86%

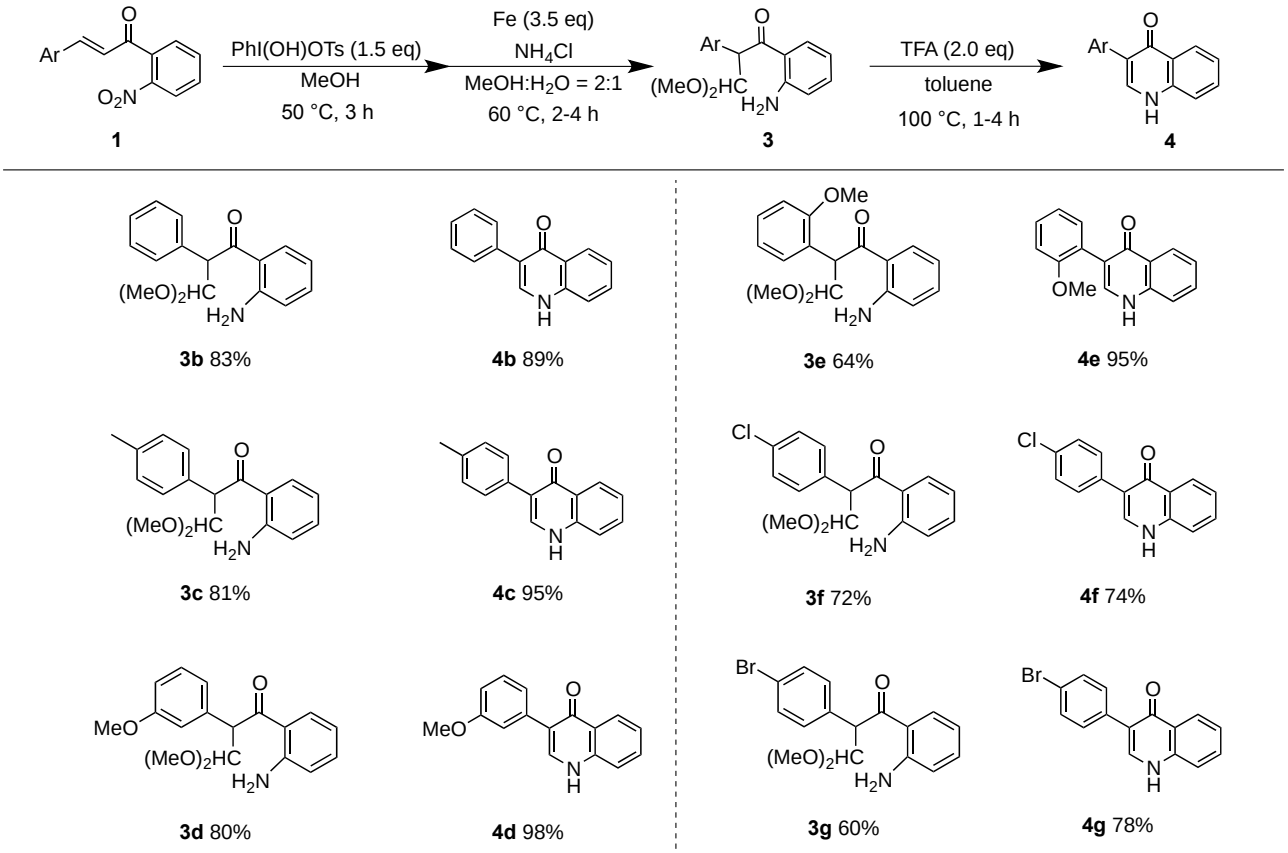
Next, we examined the reaction conditions for the formation of azaisoflavone **4a** by cyclization and aromatization (Table 3). Basic conditions were investigated but only a trace amount of **4a** was obtained under these conditions (Entries 1 and 2). The reaction proceeded rapidly with a 96% yield in the presence of two equivalents of TFA at 100 °C, whereas only a trace amount of **4a** was observed when using an excess amount of AcOH at the same reaction temperature (Entries 3 and 4).[7,8]

Table 3. Screening of reaction conditions for the formation of azaisoflavone **4a**



Entry	Acid or Base	Solvent	Temp.	Time	Yield
1	K_2CO_3 (excess)	THF	60 °C	4 h	trace
2	LiOH (2.0 eq)	THF-H_2O	80 °C	9 h	trace
3	TFA (2.0 eq)	toluene	100 °C	1 h	96%
4	AcOH (excess)	toluene	100 °C	9 h	trace

Table 4. Scope of substrates



With optimal reaction conditions in hand, the scope of this method was investigated with a variety of 2'-nitrochalcones and the results are summarized in Table 4. The oxidative rearrangement reaction proceeds well in the presence of an electron-donating group on the migrating aromatic ring, and good results were obtained under these conditions (**3b–d**). **3b–d** were then converted to azaisoflavones **4b–d** in high yields. The 2'-nitrochalcone bearing a methoxy group on the *ortho* position, however, was less favored and **3e** was obtained at a 64% yield. During both rearrangement and reduction, decomposition was observed in the TLC analysis, since steric hindrance of the *ortho*-methoxy group may affect the lack of stability. However, the cyclization process was not affected by steric hindrance and azaisoflavone **4e** was isolated at a 95% yield. The reaction of **1g** with chlorine on the benzene ring, and of **1f** with bromine on the benzene ring, yielded **3f** and **3g** at slightly lower yields (60% and 72%) due to partial decomposition under the reducing conditions. The removal of a small amount of impurities was difficult but recrystallization afforded pure azaisoflavones **4f** (74% yield) and **4g** (78% yield).

In conclusion, we have developed an azaisoflavone synthesis method using hypervalent iodine reagent-mediated oxidative rearrangement. A variety of 2'-nitrochalcones can be synthesized easily from the corresponding benzaldehydes and 2-nitroacetophenones. Intermediate **3**, bearing an acetal and amino group, is relatively stable and subsequent treatment with acid produces azaisoflavone at a high yield.

EXPERIMENTAL

Typical procedure for oxidative rearrangement and reduction of 2'-nitrochalcones: To the solution of **1** in MeOH (0.1 M) was added PhI(OH)OTs (1.5 eq) at 50 °C, which was then stirred at the same temperature for 3 h. To the resulting mixture were added Fe (3.5 eq) and saturated aq. NH_4Cl, then the whole was stirred at 60 °C for 2 h. The reaction was quenched with saturated aq. $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under the reduced pressure. The residue was purified by silica-gel column chromatography to give **3**.

Typical procedure for the formation of azaisoflavones: TFA (2 eq) was added to the solution of **3** in toluene (0.1 M), which was then stirred at 100 °C for 1 h. After cooling to room temperature, the solid was filtered to produce high amounts of **4**. Saturated aq. $NaHCO_3$ was added to the filtrate and the mixture was extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to isolate the remaining **4**. The total yield of **4** was calculated based on the combined amounts.

3-(4-Methoxyphenyl)quinolin-4(1*H*)-one (4a)

mp 224-225 °C; ^{1}H-NMR (DMSO-d_6) δ 3.78 (3H, s), 6.96 (2H, d, J = 8.8 Hz), 7.33 (1H, ddd, J = 0.8,

7.6, 8.4 Hz), 7.58 (1H, d, *J* = 8.4 Hz), 7.62-7.68 (3H, m), 8.10 (1H, d, *J* = 6.0 Hz), 8.20 (1H, d, *J* = 7.6 Hz), 12.00 (1H, d, *J* = 6.0 Hz); ^{13}C-NMR (DMSO-d_6) δ 55.1, 113.3, 118.1, 119.5, 123.1, 125.6, 125.7, 128.4, 129.5, 131.4, 137.4, 139.2, 158.0, 174.8; IR 1022, 1180, 1348, 1508, 1560, 1614, 1628, 3011, 3061, 3092 cm^{-1}; HRFABMS: calcd for $C_{16}H_{14}O_2N$ $[M+H]^+$: 252.1025, found 252.1014.

3-Phenylquinolin-4(1*H*)-one (4b)

mp 241-242 °C; ^{1}H-NMR (DMSO-d_6) δ 7.28 (1H, t, *J* = 7.2 Hz), 7.33-7.41 (3H, m), 7.59 (1H, d, *J* = 7.6 Hz), 7.66 (1H, t, *J* = 7.0 Hz), 7.73 (2H, d, *J* = 7.2 Hz), 8.16 (1H, d, *J* = 5.2 Hz), 8.21 (1H, d, *J* = 7.6 Hz), 12.07 (1H, s); ^{13}C-NMR (DMSO-d_6) δ 118.2, 119.7, 123.3, 125.6, 125.8, 126.3, 127.8, 128.4, 131.6, 136.2, 138.1, 139.3, 174.7; IR 1296, 1362, 1447, 1516, 1560, 1628, 3011, 3059, 3092 cm^{-1}; HRFABMS: calcd for $C_{15}H_{11}ON$ $[M]^+$: 221.0841, found 221.0831.

3-(*p*-Tolyl)quinolin-4(1*H*)-one (4c)

mp 252-253 °C; ^{1}H-NMR (DMSO-d_6) δ 2.33 (3H, s), 7.19 (2H, d, *J* = 8.4 Hz), 7.34 (1H, t, *J* = 7.2 Hz), 7.57-7.67 (4H, m), 8.12 (1H, d, *J* = 6.4 Hz), 8.20 (1H, d, *J* = 8.0 Hz), 12.02 (1H, d, *J* = 5.6 Hz); ^{13}C-NMR (DMSO-d_6) δ 20.8, 118.1, 119.7, 123.1, 125.6, 125.8, 128.2, 128.4, 131.4, 133.2, 135.4, 137.7, 139.2, 174.8; IR 1352, 1476, 1508, 1516, 1558, 1624, 2967, 3007, 3059 cm^{-1}; HRFABMS: calcd for $C_{16}H_{13}ON$ $[M]^+$: 235.0997, found 235.1018.

3-(3-Methoxyphenyl)quinolin-4(1*H*)-one (4d)

mp 232-233 °C; ^{1}H-NMR (DMSO-d_6) δ 3.79 (3H, s), 6.84-6.87 (1H, m), 7.29-7.37 (4H, m), 7.60 (1H, d, *J* = 8.0 Hz), 7.66 (1H, t, *J* = 7.6 Hz), 8.18-8.22 (2H, m), 12.09 (1H, s); ^{13}C-NMR (DMSO-d_6) δ 55.0, 111.9, 114.1, 118.2, 119.4, 120.6, 123.3, 125.6, 125.9, 128.8, 131.6, 137.5, 138.3, 139.2, 158.9, 174.7; IR 1043, 1215, 1346, 1508, 1558, 1630, 2862, 2945, 3001 cm^{-1}; HRFABMS: calcd for $C_{16}H_{14}O_2N$ $[M+H]^+$: 252.1025, found 252.1016.

3-(2-Methoxyphenyl)quinolin-4(1*H*)-one (4e)

mp 231-232 °C; ^{1}H-NMR (DMSO-d_6) δ 3.71 (3H, s), 6.96 (1H, t, *J* = 7.4 Hz), 7.05 (1H, d, *J* = 8.4 Hz), 7.28-7.34 (3H, m), 7.56 (1H, d, *J* = 8.4 Hz), 7.65 (1H, dt, *J* = 1.6, 8.4 Hz), 7.92 (1H, d, *J* = 5.6 Hz), 8.14 (1H, d, *J* = 8.0 Hz), 11.86 (1H, d, *J* = 6.0 Hz); ^{13}C-NMR (DMSO-d_6) δ 55.4, 111.2, 117.8, 118.1, 119.9, 123.0, 125.1, 125.4, 125.6, 128.2, 131.4, 131.8, 138.9, 139.4, 157.1, 174.7; IR 1022, 1360, 1616, 1624, 1734, 3032, 3096, 3246 cm^{-1}; HRFABMS: calcd for $C_{16}H_{14}O_2N$ $[M+H]^+$: 252.1025, found 252.1017.

3-(4-Chlorophenyl)quinolin-4(1*H*)-one (4f)

mp 290-291 °C; ^{1}H-NMR (DMSO-d_6) δ 7.36 (1H, t, *J* = 7.2 Hz), 7.44 (1H, d, *J* = 8.8 Hz), 7.60 (1H, d, *J* = 8.4 Hz), 7.67 (1H, t, *J* = 7.4 Hz), 7.80 (2H, d, *J* = 8.8 Hz), 8.20-8.23 (2H, m), 12.14 (1H, d, *J* = 5.2 Hz); ^{13}C-NMR (DMSO-d_6) δ 118.26, 118.29, 123.5, 125.6, 125.8, 127.8, 130.0, 130.8, 131.7, 135.0, 138.4, 139.3, 174.6; IR 1096, 1296, 1350, 1479, 1487, 1518, 1628, 3013, 3044, 3063; HRFABMS: calcd for $C_{15}H_{11}ONCl$ $[M+H]^+$ 256.0529, found 256.0536.

3-(4-Bromophenyl)quinolin-4(1*H*)-one (4g)

mp 284-285 °C; ^{1}H-NMR (DMSO-d_6) δ 7.36 (1H, t, J = 7.6 Hz), 7.58-7.61 (3H, m), 7.67 (1H, t, J = 7.6 Hz), 7.74 (1H, d, J = 8.0 Hz), 8.20-8.23 (2H, m), 12.14 (1H, d, J = 5.2 Hz); ^{13}C-NMR (DMSO-d_6) δ 118.2, 118.3, 119.3, 123.5, 125.6, 125.8, 130.3, 130.7, 131.7, 135.4, 138.3, 139.2, 174.5; IR 1296, 1348, 1518, 1560, 1628, 3011, 3061, 3092; HRFABMS: calcd for $C_{15}H_{11}ON^{79}Br$ $[M+H]^+$ 300.0024, found 300.0002.

ACKNOWLEDGEMENTS

This work was generously supported by Grant-in-Aid for Young Scientists (B) (15K18840) from the Japan Society for the Promotion of Science (JSPS) and also by the MEXT-Supported Program for the Strategic Research Foundation at Private Universities, 2014–2018 (S1411037). We thank Kindai University Joint Research Center for use of facilities.

REFERENCES AND NOTES

1. (a) G. H. Jin, S. K. Ha, H. M. Park, B. Kang, S. Y. Kim, H. D. Kim, J. H. Ryu, and R. Jeon, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4092; (b) R. M. Cross, A. Monastyrskyi, T. S. Mutka, J. N. Burrows, D. E. Kyle, and R. Manetsch, *J. Med. Chem.*, 2010, **53**, 7076; (c) K. Biswas, T. A. N. Peterkin, M. C. Bryan, L. Arik, S. G. Lehto, H. Sun, F. Y. Hsieh, C. Xu, R. T. Fremeau, and J. R. Allen, *J. Med. Chem.*, 2011, **54**, 7232; (d) C. Pidathala, R. Amewu, B. Pacorel, G. L. Nixon, P. Gibbons, W. D. Hong, S. C. Leung, N. G. Berry, R. Sharma, P. A. Stocks, A. Srivastava, A. E. Shone, S. Charoensutthivarakul, L. Taylor, O. Berger, A. Mbekeani, A. Hill, N. E. Fisher, A. J. Warman, G. A. Biagini, S. A. Ward, and P. M. O'Neill, *J. Med. Chem.*, 2012, **55**, 1831; (e) S. Sinha, P. Mishra, H. Amin, B. Rah, D. Nayak, A. Goswami, N. Kumar, R. Vishwakarma, and S. Ghosal, *Eur. J. Med. Chem.*, 2013, **60**, 490; (f) H. J. Gim, H. Li, S. R. Jung, Y. J. Park, J.-H. Ryu, K. H. Chung, and R. Jeon, *Eur. J. Med. Chem.*, 2014, **85**, 107; (g) A. Nilsen, G. P. Miley, I. P. Forquer, M. W. Mather, K. Katneni, Y. Li, S. Pou, A. M. Pershing, A. M. Stickles, E. Ryan, J. X. Kelly, J. S. Doggett, K. L. White, D. J. Hinrichs, R. W. Winter, S. A. Charman, L. N. Zakharov, I. Bathurst, J. N. Burrows, A. B. Vaidya, and M. K. Kiscoe, *J. Med. Chem.*, 2014, **57**, 3818; (h) R. M. Cross, D. L. Flanigan, A. Monastyrskyi, A. N. LaCrue, F. E. Saenz, J. R. Maignan, T. S. Mutka, K. L. White, D. M. Shackleford, I. Bathurst, F. R. Fronczek, L. Wojtas, W. C. Guida, S. A. Charman, J. N. Burrows, D. E. Kyle, and R. Manetsch, *J. Med. Chem.*, 2014, **57**, 8860; (i) M. J. Capper, P. M. O'Neill, N. Fisher, R. W. Strange, D. Moss, S. A. Ward, N. G. Berry, A. S. Lawrenson, S. S. Hasnain, G. A. Biagini, and S. V. Antonyuk, *Proc. Natl. Acad. Sci. U.S.A.*, 2015, **112**, 755; (j) C. Praveen, K. Parthasarathy, P. S. Kumar, and P. T. Perumal, *Ind. J. Chem.*, 2015, **54B**, 373.

2. (a) Y. Moon, D. Kwon, and S. Hong, *Angew. Chem. Int. Ed.*, 2012, **51**, 11333; (b) F. Chen, Z. Feng, C.-Y. He, H. Y. Wang, Y. L. Guo, and X. Zhang, *Org. Lett.*, 2012, **14**, 1176; (c) S. Messaoudi, J.-D. Brion, and M. Alami, *Org. Lett.*, 2012, **14**, 1496; (d) C. Xia, Y. Yang, Z. Wei, W. Yu, H. Liao, C. Shen, and P. Zhang, *Catal. Lett.*, 2015, **145**, 1634; (e) M. Ravi, P. Chauhan, R. Kaut, S. K. Shukla, and P. P. Yadav, *J. Org. Chem.*, 2015, **80**, 5369; (f) J. Pinto, V. L. M. Silva, A. M. G. Silva, L. M. N. B. F. Santos, and A. M. S. Silva, *J. Org. Chem.*, 2015, **80**, 6649.
3. A. L. Tőkés and S. Antus, *Liebigs Ann. Chem.*, 1993, **8**, 927.
4. (a) C. Praveen, K. Parthasarathy, and P. T. Perumal, *Synlett,* 2010, 1635; (b) S. Wang, C. Zhao, T. Liu, L. Yu, F. Yang, and J. Tang, *Tetrahedron,* 2016, **72**, 7025.
5. (a) Y. Miki, S. Kobayashi, N. Ogawa, and H. Hachiken, *Synlett*, 1994, 1001; (b) Y. Miki, R. Fujita, and K. Matsushita, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2533.
6. A. Nakamura, S. Tanaka, A. Imamiya, R. Takane, C. Ohta, K. Fujimura, T. Maegawa, and Y. Miki, *Org. Biomol. Chem.*, 2017, **15**, 6702.
7. We examined one-pot synthesis from **1a** and the desired product **4a** was obtained using acidic conditions, but the yield was lowered because it is difficult to separate the residue of iron and the solid product due to the low solubility.
8. A possible reaction mechanism of azaisoflavone formation under acidic conditions was considered that the oxonium cation would be formed from acetal moiety and subsequent cyclization and elimination afforded azaisoflavone. On the other hand, no cyclization occurred under basic conditions, which was employed in our previous indole synthesis from similar acetal intermediate (See the Supporting Information).