Synthesis of 3-Aminoflavones from 3-Hydroxyflavones via 3-Tosyloxy- or 3-Mesyloxyflavones

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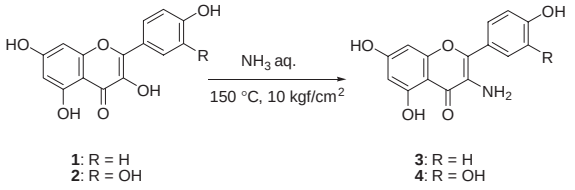
Reaction of 3-tosyloxy- or 3-mesyloxyflavones with ammonia or primary amines proceeded to give the corresponding 3-aminoflavones in high yields. 3-Aminoluteorin was efficiently prepared from rutin using this method.

Polyhydroxy-3-hydroxyflavones such as kaemferol **1** and quercetin **2** are known to metabolize in the small intestine of rat to the corresponding polyhydroxy-3-aminoflavones, i.e., 3-aminoapigenin **3** and 3-aminoluteorin **4**, respectively.[1] Our interest in examining the biological activities of the polyhydroxy-3-aminoflavones led us to the necessity of preparing a large amount of the 3-aminoflavones. Although the synthetic methods for 3-aminoflavones have been reported,[2] there seems to be no method for the preparation of polyhydroxy-3-aminoflavones in a large quantity. We describe herein a new method for the synthesis of 3-aminoflavones from 3-hydroxyflavones via 3-tosyl oxy- or 3-mesyloxyflavones, establishing a synthetic route to polyhydroxy-3-aminoflavones.

Attempted conversion of polyhydroxy-3-hydroxyflavones **1** and **2** to polyhydroxy-3-aminoflavones with aqueous ammonia under pressure resulted in less than 10% yield of the desired compounds **3** and **4** (Scheme 1).

Direct amination of flavonol to 3-aminoflavone with aqueous or liquid ammonia was also failed. Then, we tried to aminate 3-tosyloxy- or 3-mesyloxyflavone (**5** or **6**) with ammonia (Scheme 2). When **5** or **6** was reacted with liquid ammonia in THF at room temperature under pressure, the corresponding 3-aminoflavone **7** was obtained in high yield. The obtained **7** was acetylated with acetic anhydride in pyridine to afford **8**. Structures of the products **7** and **8** were confirmed on the bases of spectroscopic data and HRMS, respectively.[3,4]

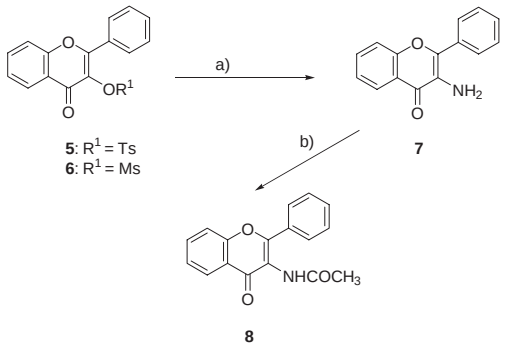
The results of reacting 3-tosyloxy- or 3-mesyloxyflavone with primary amines are listed in Table 1. Reaction of 3-tosyloxyflavone with methyl, *n*-butyl, benzyl, and *c*-hexylamine in THF at room temperature proceeded to give the corresponding 3-aminoflavones in high yields (Entries 1, 2, 4, 6, and 7). Reaction of 3-mesyloxyflavone with *n*-butylamine or benzylamine quantitatively afforded the corresponding 3-aminoflavones (Entries 3 and 5). In the case of reaction of 3-tosyloxyflavone with isopropylamine, a large excess of the amine was needed to completion of the reaction (Entry 7).



Scheme 1. Conversion of 3-hydroxyflavones to 3-aminoflavones under pressure.

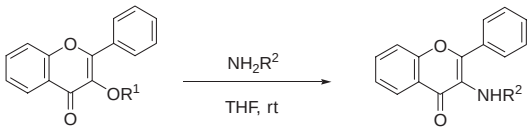
However, in the case of reaction of 3-tosyloxyflavone with *t*-butylamine or with aniline, no aminated product was obtained even under reflux condition in THF (Entries 8 and 9). Diethylamine was never reacted with 3-tosyloxy- or 3-mesyloxyflavone. Taking into consideration that the reaction of 3-tosyloxy- or 3-mesyloxyflavone with diethylamine did not proceed, the reaction mechanism for the formation of 3-aminoflavones may be proposed as follows (Scheme 3).

Michael addition of ammonia or primary amines might initially occur at the 2-position of 3-tosyloxy or 3-mesyloxyflavone (**5** or **6**) to give the adduct **9** which will easily cyclise to



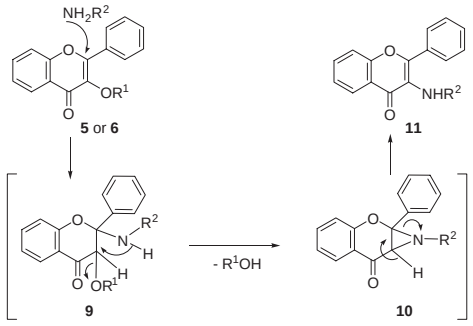
Scheme 2. Synthesis of 3-aminoflavone via 3-tosyloxy- or 3-mesyloxyflavone. Reagents and conditions: a) NH_3 liq., THF, rt, $\approx$10 kgf/cm^2, 93% (Ts) and 98% (Ms); b) $(CH_3CO)_2O$, pyridine, rt, 82%.

Table 1. Reaction of 3-tosyloxy- or 3-mesyloxyflavone with primary amines[a]

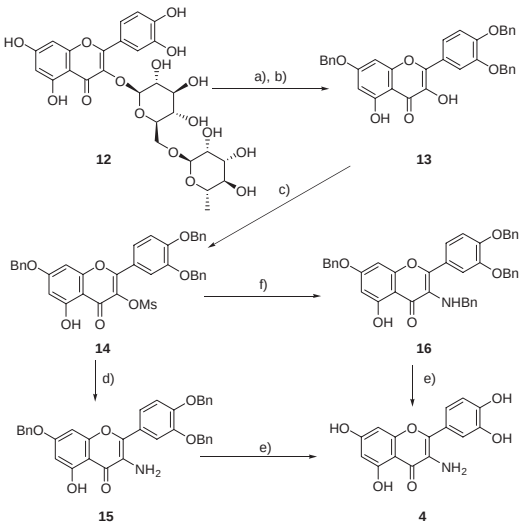


Entry	R^1	R^2	Reaction time/h	Yield/%
1	Ts	CH_3	26[b]	88
2	Ts	*n*-C_4H_9	92[b]	92
3	Ms	*n*-C_4H_9	72[b]	97
4	Ts	$PhCH_2$	95[b]	99
5	Ms	$PhCH_2$	5(days)[b]	99
6	Ts	*c*-C_6H_{11}	5(days)[b]	92
7	Ts	*i*-C_3H_7	23[c]	95
8	Ts	*t*-C_4H_9	7(days)[c]	0
9	Ts	Ph	7(days)[c]	0

[a]Reactions were carried out on a 0.2 mmol scale. [b]Amines (6–10 equiv.) were used. [c]More than 100 equiv. of amines were used.



Scheme 3. Plausible reaction mechanism.



Scheme 4. Reagents and conditions: a) BnCl, DBU, DMF, reflux and then b) HCl aq, EtOH, reflux, 30% (2 steps); c) MsCl, pyridine, rt, 94%; d) NH_3 liq., THF, $\approx$5 kgf/cm^2, and then e) H_2, cat. $Pd(OH)_2$, THF/EtOH, rt, 55% (2 steps); f) $BnNH_2$, THF, rt, 82% and then e) H_2, cat. $Pd(OH)_2$, THF/EtOH, rt, quant.

give the aziridine **10** with loss of toluenesulfonic or methanesulfonic acid. The aziridine ring of **10** may open to afford the 3-aminoflavones **11**. In this mechanism, secondary amines like diethylamine can not form the aziridine ring. At the moment we can not have any evidence of the intermediates **9** and **10** in terms of IR and NMR spectroscopies despite that the reaction proceeds slowly. Probably, the initial Micheal addition is in the rate-determining step.

We applied this method to the synthesis of 3-aminoluteorin **4** from commercially available quercetin **2** via the mesylated quercetin. Quercetin **2** was reacted with an excess of mesyl chloride in pyridine to give the compound mesylated at the 3, 5, 7, 3′, and 4′ positions of **2** which was treated with liquid ammonia at room temperature in DMF under pressure, yielding the corresponding 3-amino compound. However, the complete deprotection of the mesyloxy to hydroxyl groups in the 3-amino compound under alkaline condition was failed. Attempted selective mesylation at the 3-position of **2** with a limited amount of mesyl chloride in the presence of pyridine was also unsuccessful. Next, we tried to convert rutin into 3-aminoluteorin as shown in Scheme 4. Rutin **12** was initially benzylated and subsequently hydrolyzed to give the benzylated compound **13** which was selectively mesylated in pyridine at the 3-position of **13** to give the 3-mesyloxyflavone **14**. The mesyloxy compound **13** was treated with liquid ammonia under pressure to give the 3-amino compound **15** which was debenzylated to give 3-amminoluteorin[5] **4** in 55% yield (2 steps). However, in this route, some problems in purification process of **4** occurred due to the similar physicochemical properties between **4** and impurities. Then, the 3-mesyloxyflavone **14** was firstly reacted with benzylamine and the resulting benzylated compound **16** was hydrogenated to give the desired **4** in quantitative yield without any difficulty of purification.

Thus the present method provides an easy way to make a number of polyhydroxy-3-aminoflavones in a large quantity to test their biological activities.

References and Notes

1 Report appears in the patent literature: K. Kanazawa, M. Sasaki, Jpn. Kokai Tokkyo Koho 2004123728, **2004**; *Chem. Abstr.* **2004**, *140*, 350536.

2 a) D. Dauzonne, B. Folleas, L. Martines, G. G. Chabot, *Eur. J. Med. Chem.* **1997**, *32*, 71. b) T. Patonay, M. Rákosi, G. Litkei, R. Bognár, *Liebigs Ann. Chem.* **1979**, 161. c) R. Bognár, M. Rákosi, *Liebigs Ann. Chem.* **1966**, 225. d) C. O'Brien, E. M. Philbin, S. Ushioda, T. S. Wheeler, *Tetrahedron* **1963**, *19*, 373. e) A. Kasahara, *Nippon Kagaku Zasshi*, **1959**, *80*, 416; *Chem. Abstr.* **1961**, *55*, 27860.

3 3-Aminoflavone **7**: yellow solid, mp: 158–160 °C (differs from that of lit. 2: 136–138 °C, however, the following spectral data as well as those of **8** support the chemical structure of **7**); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (1H, ddd, J = 7.5, 7.2, 0.6 Hz), 7.25 (1H, d, J = 8.4 Hz), 7.48–7.55 (4H, m), 7.83–7.86 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.6, 121.9, 123.2, 124.1, 128.5, 128.8, 131.0, 131.5, 132.7, 133.0, 146.6, 161.9, 180.3; HRTOFMS (ESI): m/z 238.0866 (calcd for $C_{15}H_{12}NO_2$ $[M + H]^+$ 238.0862).

4 3-*N*-Acetylaminoflavone **8**: yellow solid, mp: 156–157 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (3H, s, CH_3), 7.19–7.26 (2H, m), 7.47–7.49 (3H, m), 7.58–7.64 (3H, m), 7.82 (1H, dd, J = 7.5, 0.9 Hz), 10.83 (1H, brs, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 113.1, 122.6, 123.0, 124.2, 128.1, 129.2, 130.1, 130.6, 136.0, 136.1, 136.5, 164.7, 169.5, 184.3; HRTOFMS (ESI): m/z 280.0979 (calcd for $C_{17}H_{14}NO_3$ $[M + H]^+$ 280.0968).

5 3-Aminoluteorin **4**: yellow resinous material; ^{1}H NMR (300 MHz, CD_3OD) δ 5.96 (1H, d, J = 1.3 Hz), 6.08 (1H, d, J = 1.3 Hz), 6.84 (1H, d, J = 8.4 Hz), 7.19 (1H, dd, J = 8.4, 1.6 Hz), 7.30 (1H, d, J = 1.6 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 90.7, 97.6, 107.4, 116.3, 117.2, 122.2, 125.3, 131.7, 146.3, 148.8, 149.5, 157.8, 165.2, 165.6, 179.1; HRTOFMS (ESI): m/z 302.0667 (calcd for $C_{15}H_{12}NO_6$ $[M + H]^+$ 302.0659).

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