Facile Synthesis of 2,3-Diacetoxyflavanones from 3-Aminoflavones

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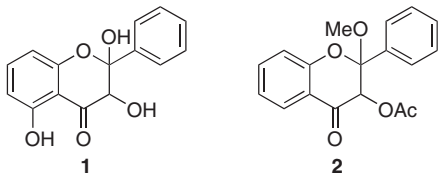
3-Aminoflavone reacts with isopentyl nitrite in acetic acid to give 2,3-diacetoxyflavanone in good yield. 3-Aminoflavone, the starting material, is readily available, and this method is a powerful tool for the synthesis of 2,3-dihydroxyflavanone derivatives.

Flavonoids consist one of the largest groups of natural compounds. Many flavones, not only the natural ones but also the artificial ones have very interesting biological activity.[1] In 2003, a new type of flavonoid, 2,3,5-trihydroxyflavanone (**1**) (Scheme 1), was discovered in the ethanol extract of *L. polygalifolium* subsp. *polygalifolium*.[2] The derivative of 2,3-dihydroxyflavanone was synthesized via the epoxidation of flavone by dimethyldioxirane.[3] Bernini et al. reported a new synthesis of 3-acetoxy-2-methoxyflavanones (**2**), some of which have antifungal activities against *Trichoderma koningii* et al.[4] The key step in their procedures is the oxidation of flavone by CH_3ReO_3. However, the oxidants used in the above two methods are expensive or difficult to handle.

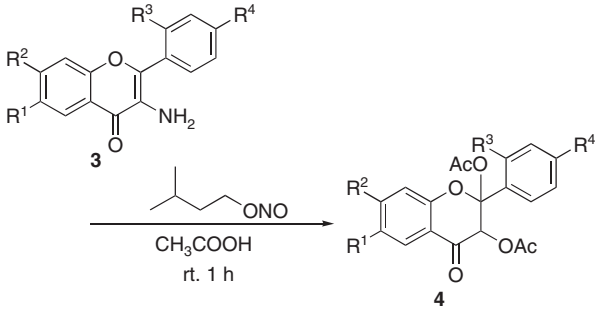


Scheme 1.

During our study of the synthetic use of 3-aminoflavone (**3**), which is readily prepared from 3-bromoflavone or similar material by reaction with aqueous NH_3,[5] 3-aminoflavone (**3**) reacts with isopentyl nitrite[6] or $NaNO_2$ in acetic acid to give 2,3-diacetoxyflavanone (**4**). 2,3-Diacetoxyflavanone, which is a derivative of 2,3-dihydroxyflavanone, has a similar structure to the 3-acetoxy-2-methoxyflavanone mentioned above. In this paper, we report on a new synthesis of 2,3-diacetoxyflavanones from 3-aminoflavones.

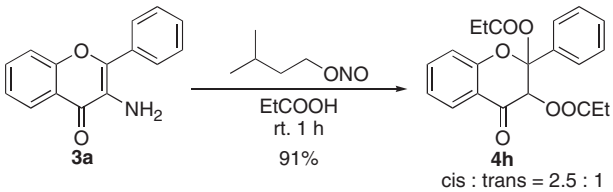
The procedures of this transformation are quite simple. When isopentyl nitrite is added to an acetic acid solution of 3-aminoflavone at 0 °C, the reaction proceeds smoothly to give 2,3-diacetoxyflavanone in good yield. The results are summarized in Table 1.

Table 1. Synthesis of 2,3-diacetoxyflavanone



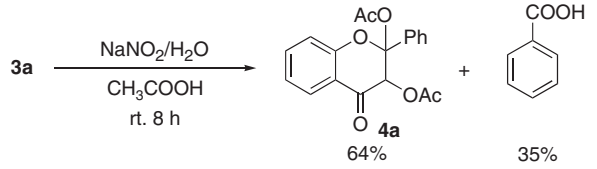
Entry	R^1	R^2	R^3	R^4	Product	Isolated yield/%	cis:trans
1	H	H	H	H	**4a**	83	2.1:1
2	Me	H	H	H	**4b**	66	2.1:1
3	Cl	H	H	H	**4c**	83	2.5:1
4	Br	H	H	H	**4d**	89	2.2:1
5	H	OMe	H	H	**4e**	61	2.1:1
6	Me	H	H	*t*-Bu	**4f**	98	1.3:1
7	Br	H	Cl	H	**4g**	68	2.4:1

When propionic acid was used instead of acetic acid, 2,3-dipropanoyloxyflavanone was obtained in a 91% yield (Scheme 2). An aqueous solution of $NaNO_2$ also gave **4** in somewhat lower yield, and a considerable amount of benzoic acid was obtained (Scheme 3). The reaction in alcoholic solvent in the presence of an acid gave unidentified mixtures.



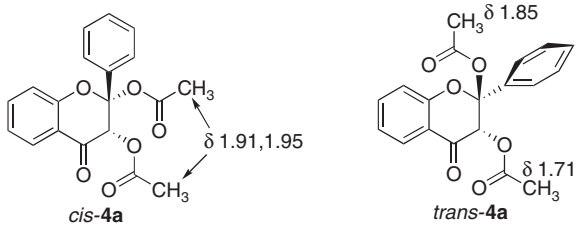
Scheme 2.

The reaction predominantly gave the cis isomer. The approximate diastereomeric ratios, determined by ^{1}H NMR, are shown in Table 1. The structure of the diastereomers was deduced as follows. The ^{1}H NMR chemical shift of the 3-acetoxy group was influenced by the aromatic ring (B ring). For the trans isomer, the ring current of the aromatic B ring causes the upfield shift of the methyl proton of the 3-acetoxy group (Scheme 4). Similar results were observed in the ^{1}H NMR data of the 2-methoxy-3-acetoxyflavanones.[4]

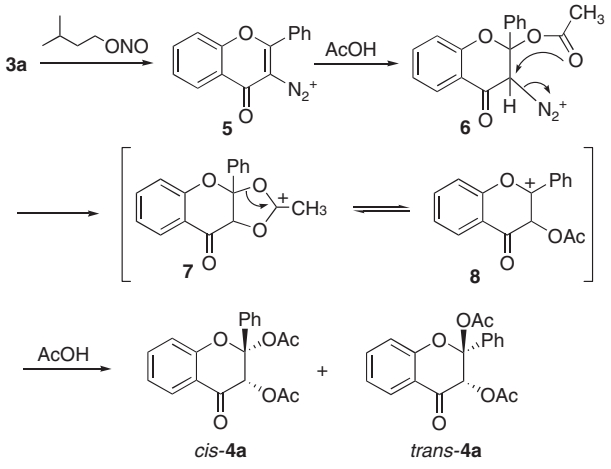


Scheme 3.

A plausible mechanism for this reaction is as follows (Scheme 5). The reaction of **3a** with isopentyl nitrite gives diazonium salt **5**. The conjugate addition of acetic acid proceeds to



Scheme 4.



Scheme 5.

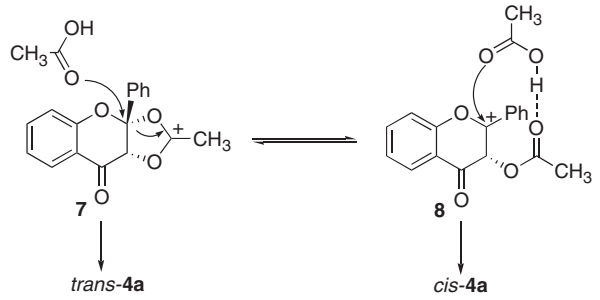
give **6**. The diazonium **6** is presumed to be unstable and readily decomposes with the generation of N_2; the decomposition is accompanied with the migration of the acetoxy group to give **7** or **8**. These cations react with acetic acid to give **4a**.

If the cation **7** reacts with acetic acid, the reaction proceeds with inversion of configuration to give *trans*-**4a** (Scheme 6). However, the reaction proceeds with moderate cis selectivity, meaning that the mechanism described above does not prevail. An alternative pathway to cis isomer is as follows. Interaction of **8** with acetic acid causes a nucleophilic attack from the same face as the 3-acetoxy group to give cis isomer *cis*-**4a** predominantly.

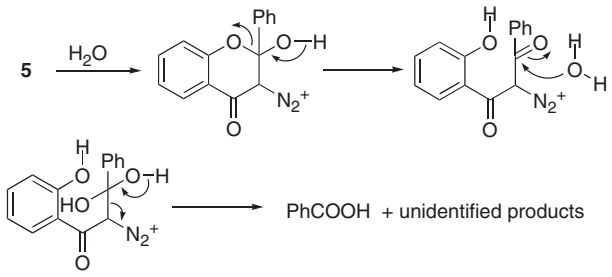
Plausible reasons why the presence of alcohol lowers the yield of **4a** include the following. Alcohol is more nucleophilic than acetic acid, and the nucleophilic addition of alcohol to **5** proceeds much faster than that of acetic acid. However, the intramolecular replacement of N_2^+ is not as fast as that of the acetoxy group, and decomposition occurrs to give unidentified mixtures.

In the presence of water, the conjugate addition of water to **5** occurrs, and the following C–C bond cleavage shown in Scheme 7 gives benzoic acid and unidentified products.

2,3-Diacetoxyflavanone is considered to be a precursor of flavonol. However, as far as we have studied, the conversion into



Scheme 6.



Scheme 7.

flavonol or 2,3-dihydroxyflavone is not facile. When **3a** is treated with NaOH or amines, unidentified mixtures are obtained. Further studies on these compounds are under investigation.

The following are typical procedures for the synthesis of 2,3-diacetoxyflavanone. To an acetic acid (1.5 mL) solution of **3a** (0.163 g, 0.69 mmol), isopentyl nitrite (0.097 g, 0.87 mmol) was added at room temperature and stirred for one hour. The mixture was poured into water (5 mL) and extracted with ethyl acetate. After the usual workup, the crude product was purified by column chromatography on silica gel to give **4a** (0.191 g, 0.56 mmol) in 83% yield.

References

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