2′-Amino-α-chloroacetophenone as a Valuable Tool for the Synthesis of Conveniently-Substituted α,β-Epoxychalcone Derivatives

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The synthesis of conveniently substituted 2′-amino-α,β-epoxychalcones is described. They were obtained through Darzens condensation of 2′-amino-3′,5′-dimethoxy-α-chloroacetophenone with benzaldehydes. The latter can undergo different cyclization possibilities and afford a variety of flavonoid analogs with biological potential.

Key words epoxychalcone; aurone; flavone; Darzens condensation

α,β-Epoxychalcones **2** (2,3-epoxy-1,3-diphenyl-1-propane) have received attention as potential precursors to different classes of flavonoids and some display biological activity; *e.g.* amino chalcones have been investigated for their antitumor activity.[1—3] The presence of a hydroxyl group at C-2′ makes the epoxychalcones difficult to isolate as they undergo a cyclisation to give dihydroflavonols formed by attack upon the β-carbon and auronols resulting from attack upon the α-carbon of the epoxide.[4] Dihydroflavonols and auronols formed can be easily dehydrated to afford flavones and aurones. The ease of cyclization of α,β-epoxychalcones has been questioned by Adam and collaborators.[5] In a 1990 report, Donnely and Franck studied the reactivity of 2′-amino-α,β-epoxychalcone (**2b**) and compared it with 2′-hydroxy-α,β-epoxychalcone (**2a**) and concluded that 2′-amino-α,β-epoxychalcones are stable and isolable.[6]

Epoxychalcones have been frequently prepared by epoxidation of chalcones.[7,8] These methods have some limitations, especially in the presence of sensitive-functions to oxidants. To a lesser extent, Darzens condensation of benzaldehydes with α-halophenacyl has been reported. However, the application of the latter method was generally limited to the synthesis of simple epoxychalcones (substituted only on the A-ring).[9,10]

We have been using 2′-amino-3′,5′-dimethoxy-α-chloroacetophenone **3** (Fig. 1) as an intermediate for the synthesis of bioactive azaflavonoids.[11,12] The presence of the two methoxy groups makes chloroacetophenone **3** very convenient to afford azaflavones and azaaurones bearing at the correct positions the most frequently found substituents (methoxy and hydroxy groups) met in naturally occurring flavones and aurones.

As part of our continuing effort to synthesize flavonoid analogs, we report here the use of **3** as a useful starting material for the synthesis of 2′-amino-α,β-epoxychalcones and derivatives, which can be elaborated to a variety of bioactive flavonoid analogs.

Results and Discussion

2′-Amino-α-chloroacetophenone **3** was prepared in multigram scale by condensation of 3,5-dimethoxyaniline with chloroacetonitrile according to the procedure described by Sugasawa.[13]

Condensation of **3** with an aldehyde in the presence of *t*-BuOK in *t*-BuOH gives the 2,3-epoxyketone **4** as the unique new compound (Chart 1). Based on the coupling constant between H-α and H-β (J=2 Hz), we concluded that the epoxide **4** is *trans*-disubstituted. The choice of the base and solvent is important. The use of aqueous, methanolic or ethanolic potassium hydroxide solutions provides respectively, α-hydroxyacetophenone, α-methoxyacetophenone and α-ethoxyacetophenone which were obtained by chlorine substitution. The attack of the amino group on the aldehyde may constitute a side reaction and explain the low yields. The results shown in Table 1 indicate that the reaction works better with weakly activated and deactivated aldehydes.

Except acetone, the condensation does not take place with ketones. Subjected to the same condensation conditions, an analog of **3** in which the amino group was replaced with a hydroxyl did not provide Darzens condensation but simply the 4,6-dimethoxybenzofuran-4-one (obtained by attack of the 2′-hydroxyl on the C-α).

The epoxide **4** is stable and no cyclization by attack of the amino group, even in the presence of a base, occurred. This is certainly due to the chelation and deactivation of the amino group by the adjacent ketone. The cyclization can be achieved by protecting the nitrogen; *e.g.* acetylation which induces a steric hindrance and makes the amino group adopt a configuration, in which the nitrogen atom is correctly positioned to attack on the epoxide ring (results not shown).

The utility of epoxide **4** is warranted as it allows access to a) 4-quinolones by attack of the amino group on the β-carbon,

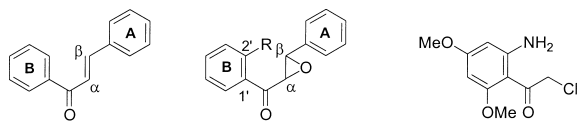

Fig. 1

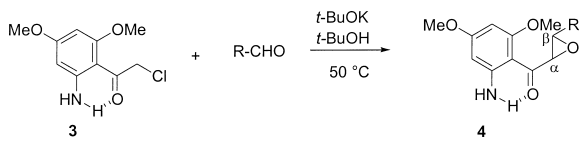

Chart 1

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Table 1. 2′-Aminoepoxychalcones **4** Prepared According to Chart 1

	Aldehyde	Yield (%)	Product, mp (°C), ^{1}H-NMR
1	Benzaldehyde	44	R=phenyl: 158 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.31 (5H, m), 6.41 (2H, s), 5.67 (1H, d, J=2.4 Hz), 5.61 (1H, d, J=2.0 Hz), 4.13 (1H, d, J=2.0 Hz), 3.86 (1H, d, J=2.0 Hz), 3.72 (3H, s), 3.31 (3H). MS m/z: 299 (M^+), 281, 270, 242, 180.
2	4-Methoxybenzaldehyde	15	R=4-methoxyphenyl: amorph, ^{1}H-NMR ($CDCl_3$) δ: 7.21 (2H, d, J=8.8 Hz), 6.86 (2H, d, J=8.4 Hz), 6.39 (2H, s), 5.67 (1H, d, J=2.4 Hz), 5.61 (1H, d, J=2 Hz), 4.13 (1H, d, J=2 Hz), 3.80 (1H, d, J=2.0 Hz), 3.77 (3H, s), 3.72 (3H, s), 3.35 (3H, s). MS m/z: 329 (M^+), 311, 300, 196, 279, 268.
3	4-Bromobenzaldehyde	46	R=4-bromophenyl: 128 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.44 (2H, d, J=8.8 Hz), 6.86 (2H, d, J=9.2 Hz), 6,41 (2H, s), 5.67 (1H, d, J=2.4 Hz), 5.61 (1H, d, J=2.4 Hz), 4.08 (1H, d, J=2 Hz), 3.82 (1H, d, J=2 Hz), 3.72 (3H, s), 3.35 (3H, s). MS m/z: 378 (M^+).
4	4-Isopropylbenzaldehyde	52	R=isopropylphenyl: 132 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.30 (2H, d, J=8.4 Hz), 7.25 (2H, d, J=8.4 Hz), 6.5 (2H, s), 5.75 (1H, d, J=2.4 Hz), 5.69 (1H, d, J=2.0 Hz), 4.22 (1H, d, J=2.0Hz), 3.92 (1H, d, J=2.0 Hz), 3.80 (3H, s), 3.41 (3H, s), 2.95 (1H, m), 1.27 (6H, d, J=6.8 Hz). MS m/z: 341 (M^+), 312, 284, 180, 164.
5	3-Methoxybenzaldehyde	39	R=3-methoxyphenyl: 138 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.29 (1H, m), 6.99 (1H, m), 6.89 (2H, m), 6.50 (2H, s), 5.75 (1H, d, J=2.0 Hz), 5.69 (1H, d, J=2 Hz), 4.18 (1H, d, J=2.0 Hz), 3.92 (1H, d, J=2.0 Hz), 3.84 (3H, s), 3.80 (3H, s), 3.42 (3H, s). MS m/z: 329 (M^+), 300, 272, 180, 164.
6	3-Fluorobenzaldehyde	72	R=3-fluorophenyl: 146 °C ; ^{1}H-NMR ($CDCl_3$) δ: 7.39 (1H, m), 7.28 (1H, m), 7.07 (2H, m), 6.5 (2H, s), 5.75 (1H, d, J=2.0 Hz), 5.69 (1H, d, J=2.0 Hz), 4.16 (1H, d, J=2.0 Hz), 3.93 (1H, d, J=2.0 Hz), 3.80 (3H, s), 3.42 (3H, s). MS m/z: 317 (M^+), 180, 164.
7	*n*-Propanal	45	R=ethyl: 90 °C; ^{1}H-NMR ($CDCl_3$) δ: 6.43 (2H, s), 5.78 (1H, d, J=2.4 Hz), 5.75 (1H, d, J=2.0 Hz), 4.03 (1H, d, J=1.2 Hz), 3.87 (3H, s), 3.82 (3H, s), 3.03 (1H, m); 1.85 (1H, m), 1.70 (1H, m), 1.09 (3H, dd, J_1=J_2=7.6 Hz). MS m/z: 251 (M^+), 180.
8	*n*-Butanal	54	R=*n*-propyl: 90 °C; ^{1}H-NMR ($CDCl_3$) δ: 6.35 (2H, s), 5.70 (1H, d, J=2.4 Hz), 5,67 (1H, d, J=2.4 Hz), 3.93 (1H, d, J=2.0 Hz), 3.77 (3H, s), 3.73 (3H, s), 2.95 (1H, m), 1.75 (1H, m), 1.50 (3H, m), 0.95 (3H, dd, J_1=J_2=7.6 Hz). MS m/z: 265 (M^+), 180.

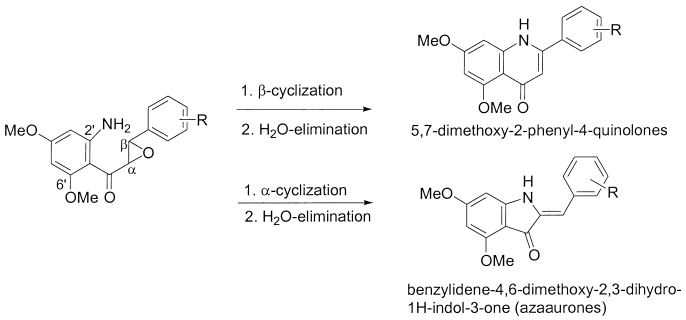

Chart 2

and b) azaaurones by attack of the amino group on the α-carbon (Chart 2). Further, the 6′-methoxy group can be selectively deprotected and the hydroxyl can take place in the cyclization process to afford 5′-aminoflavones and 4′-aminoaurones.

Typical Procedure for the Condensation of Chloroacetophenone 3 with Aldehydes *t*-BuOK (112 mg, 1 mmol) was added to a stirred solution of **3** (0.23 g, 1 mmol) and aldehyde (1 mmol, 1 eq. in *t*-butanol (10 ml). The solution was heated at 50 °C for 2 h and then *t*-butanol was evaporated under reduced pressure. The solution was hydrolyzed and extracted with CH_2Cl_2. The organic layer was collected, dried, evaporated, and purified by chromatography column (silica gel, cyclohexane : ethyl acetate 8 : 2), to provide the epoxychalcone **4** as a clear yellow powder.

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