A SHORT METHOD FOR THE SYNTHESIS OF 4,6-DIMETHOXY-1-AZAAURONES

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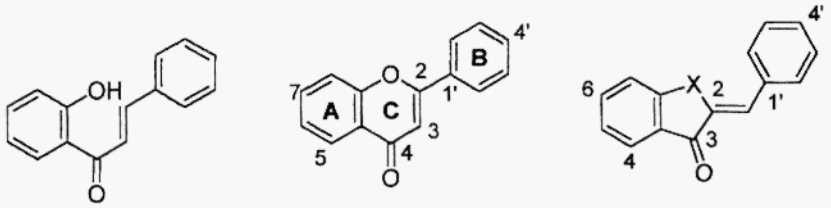
Abstract: Aurones (Benzylidenebenzofuran-3(2*H*)-one) are naturally occurring compounds, which are isomers of the well known flavones. Like flavones, ring A dioxygenated aurones especially on 4 and 6 positions are frequently found in nature and this substitution pattern is surely responsible for aurones bioactivity. In the present communication, we report the synthesis of ring A-oxygenated 1-azaaurones. These molecules adopt conformations very close to aurones and the presence of the nitrogen can allow derivitization for SAR studies and also making ammonium salts, suitable for the molecule hydrosolubility. The synthesis of 4,6-dimethoxy-1-azaaurones was achieved by condensation of a benzaldehyde derivative with 1-acetyl-4,6-dimethoxy-2,3-dihydro-1*H*-indole-3-one. The latter was prepared in three steps starting from 3,5-dimethoxyaniline and chloroacetonitrile. If the benzaldehyde derivative is appropriately chosen, the method can allow the preparation of a large number of azaaurones.

Introduction

Aurones are secondary metabolites belonging to the flavonoid family of naturally occurring compounds (1). In the plant arena, these 2-phenylidenebenzofuranone which are structurally isomeric of flavones contribute to plants color. The biological activities of flavones are well investigated. In particular, ring A methoxylated or hydroxylated flavones are of current interest (2-4). Compared to flavones, aurones still poorly investigated as therapeutics (5-7). Our interest in the biological properties of ring-A methoxylated and/or hydroxylated flavonoids prompted us to investigate the synthesis of 4,6-oxygenated aurones and their 1-azaanalogs (azaaurones) (8). The latter are structurally similar to the naturally occurring aurones and in addition, they also have an available nitrogen for further extension and for branching different substituents that may give rise to beneficial interactions with the biological active site. Therefore, the search for an approach toward 4,6-dimethoxy-1-azaaurones was undertaken in the framework of a project related to the synthesis of biologically active flavonoid analogs (9-11).



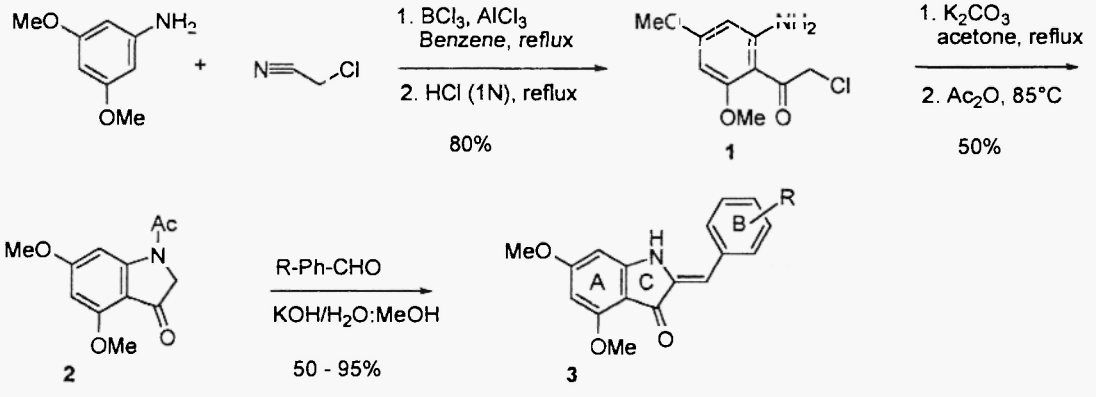
chalcone flavone X = O, aurone
X = NH, 1-azaaurone

Figure 1.

The literature survey indicated that only simple azaaurones (unsubstituted or monosubstituted on the A-ring) have been investigated (12). Owing to the important role played by the simultaneous presence of hydroxyl or methoxy groups on 5 and 7 positions, we report herein a simple method for preparation of 4,6-dimethoxyazaaurones.

Results and Discussion:

Azaaurones were prepared from 1-acetyl-4,6-dimethoxy-2,3-dihydro-1*H*-indole **2** by base-catalyzed condensation with a benzaldehyde derivative. Oxindole **2** was prepared starting from 3,5-dimethoxyaniline and chloroacetonitrile (Scheme 1).

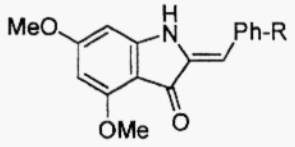


Scheme 1. Synthesis of 4,6-dimethoxy-1-azaaurones

Ketone **1** was synthesized by a specific ortho chloroacetylation of 3,5-dimethoxyaniline, according to the method reported by Sugasawa (13). Cyclisation of **1** with K_2CO_3 in acetone followed by acetylation with acetic acid anhydride gave 1-acetyl-4,6-dimethoxy-2,3-dihydro-1*H*-indole-3-one **2** in 50% yield. It should be mentioned that analogs of **2** (mono or unsubstituted on ring-A) have been used as starting blocks for the synthesis of biologically active compounds (14-17). The key intermediate **2** can be easily prepared in multi-grams scale without yield lowering. The final step is the condensation of **2** with a benzaldehyde derivative which gives directly the desired 4,6-

dimethoxyazaaurone. The structure of azaaurones **3** were determined by NMR and mass spectrometry. The configuration of the double bond is exclusively Z as can be assigned on the basis of the chemical shift of the olefinic proton (δ 6.7 ppm) and by comparing with literature (18).

Table 1. Structures and physicochemical data of synthesized 4,6-dimethoxy-1-azaaurones **3**.



R	Yield (%)[a,b]	mp (°C)	^{1}H-NMR ($CDCl_3$) δ
4'-H	75	152 - 154	7.5 (dd, 2H, J_1 = 7.7 Hz, J_2 = 1.4 Hz); 7.4 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz, H-4'); 7.3 (dd, 2H, J_1 = 7.7 Hz, J_2 = 1.4 Hz); 6.8 (Sl, 1H, NH); 6.7 (s, 1H); 6.1 (d, 1H, J = 1.9 Hz,); 5.9 (d, 1H, J = 1.9 Hz,), 3.9 (s, 3H); 3.8 (s, 3H).
4'-Et	70	215 - 217	7.45 (dd, 2H, J_1 = 8.2 Hz, J_2 = 0.4 Hz); 7.25 (dd, 2H, J_1 = 8.2 Hz, J_2 = 0.4 Hz); 7.1 (sl, 1H); 6.7 (s, 1H); 6.1 (d, 1H, J = 1.8 Hz); 5.9 (d, 1H, J = 1.8 Hz), 3.9 (s, 3H); 3.8 (s, 3H); 2.7 (q, 2H, J = 6 Hz); 1.3 (t, J = 6 Hz).
4'-SMe	60	228 - 230	7.4 (dd, 2H, J_1 = 8.5 Hz, J_2 = 0.4 Hz); 7.3 (dd, 2H, J_1 = 8.5 Hz, J_2 = 0.4 Hz); 6.8 (sl, 1H); 6.7 (s, 1H); 6.1 (d, 1H, J = 1.6 Hz, H-5); 5.9 (d, 1H, J = 1.6 Hz), 3.9 (s, 3H); 3.8 (s, 3H); 2.5 (s, 3H).
4'-Cl	80	146 - 148	7.4 (dd, 2H, J_1 = 8.5 Hz, J_2 = 0.4 Hz); 7.3 (dd, 2H, J_1 = 8.5 Hz, J_2 = 0.4 Hz); 6.6 (s, 1H); 6.1 (d, 1H, J = 1.6 Hz); 5.85 (d, 1H, J = 1.6 Hz), 3.85 (s, 3H); 3.8 (s, 3H).
2',4',6'-triOMe	60	109 - 111	7.6 (sl, 1H); 6.95 (s); 6.7 (s, 1H); 6.55 (s, 1H); 6.0 (d, 1H, J = 1.8 Hz); 5.85 (d, 1H, J = 1.8 Hz), 3.9 (5s, 15H).
Ph-R = 2-naphtyl	63	254 - 256	7.9 (ddd, 2H, J_1 = 8.7 Hz, J_2 = 1.5 Hz, J_3= 0.4 Hz); 7,8 (dd, 2H, J_1 = 8.7 Hz, J_2 = 1.5 Hz); 7.6 (dd, 1H, J_1 = 8.7 Hz, J_2 = 0.4 Hz); 7.4 (dd, 2H, J_1 = 8.7 Hz, J_2 = 0.4 Hz); 7.15 (Sl, 1H); 6.85 (s, 1H); 6.1 (d, 1H, J = 1.5 Hz); 5.9 (d, 1H, J = 1.5 Hz), 3.9 (s, 3H); 3.8 (s, 3H).

[a]Reported yields are those of purified compounds. [b]Mass spectrometry performed on intermediates and final compounds gave satisfactory analysis.

In conclusion, if appropriately substituted benzaldehydes are selected, our synthetic approach constitutes a simple and high yield procedure for the synthesis of diverses 4,6-dimethoxy-1-

azaaurones which can be used as analogs of aurones, especially in studying aurones structure-activity relationship.

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