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Comparison of divergent *vs.* convergent approaches for solid-phase synthesis of methylenedioxychalcones

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Introduction

Methylenedioxychalcones are attractive because of the presence of the 1,3-dioxolane ring in its structure, which is found in many natural and synthetic compounds of biological interest (Malcangio *et al.*, 1992). Therefore, the search and optimization of reaction conditions for obtaining methylenedioxychalcones in solid phase would allow to generate versatile intermediates for the construction of a variety of heterocyclic compounds of potential biological interest.

This paper aims to develop a comparative study between two methods for obtaining methylenedioxychalcones in solid phase, in the first one carboxybenzaldehyde is bound to the resin, and then, aldol condensation is carried out on the solid support (Scheme 1), the second consists of obtaining the chalcone in solution, and then direct chalcone/resin coupling is performed (Scheme 2).

The used resins (Rink **1** and Wang **10**) are labile under acid conditions, thus carrying out the separation of the compounds with a trifluoroacetic acid solution.

Results and Discussion

Coupling of 4-carboxybenzaldehyde **3** to the unprotected Rink resin **2** (Scheme 1) was carried out. Once the aldehyde was supported on the resin, the condensation step was started using the aminomethylenedioxyacetophenone **5a**, and the classical Claisen-Schmidt condensation in solution was applied for solid-phase synthesis, in which ethanol is used as solvent and a 20% NaOH solution, thus the presence of this base in the reaction medium giving rise to amide bond hydrolysis. Therefore, a new condensation test based on Marzinzik and Felder's approach (Marzinzik and Felder, 1998) with anhydrous dimethoxyethane as solvent and $LiOH.H_2O$ as catalyst, was used. It was necessary to make some changes in this approach, such as increase of temperature in order to improve catalyst solubility in the reaction medium.

Upon analysing the resin by ^{13}C-NMR in gel phase, a signal around 100 ppm was observed, assigned to the carbon of the methylenedioxy system, and also the carbonyl aldehyde carbon signal was observed, thus indicating that reaction conditions were not optimal for obtaining aminomethylenedioxychalcone. Then, another solid-phase aldol condensation strategy was tried, in which zinc acetate, 2,2'-bipyridine, DBU and NMP were used (Sensfuss, 2003). Better results were observed with this approach in terms of product proportion and decrease of the aldehyde signal, but the reaction did not show a significant progress.

When Marzinzik and Felder's modified approach was applied, but using the methylenedioxyacetophenone **5b** (Scheme 1), it was possible to obtain successfully Rink resin-coupled chalcone as shown in Fig. 1.

Negative results for condensation tests using the aminomethylenedioxyacetophenone **5a** were initially attributed to possible steric effects because of the amino group of the acetophenone, and to the large structural volume around Rink resin's linker. To verify these findings, a Wang resin was used; this shows a small size spacer, providing major freedom for condensation, but when performing the reaction, this was not successful.

Since the used methodologies failed to form aminomethylenedioxychalcone in solid phase, direct immobilization to Wang resin was tried (Scheme 2), *e.g.*, obtaining chalcone **8** in solution, and then acylation was carried out to generate compound **10** (Fig. 2).

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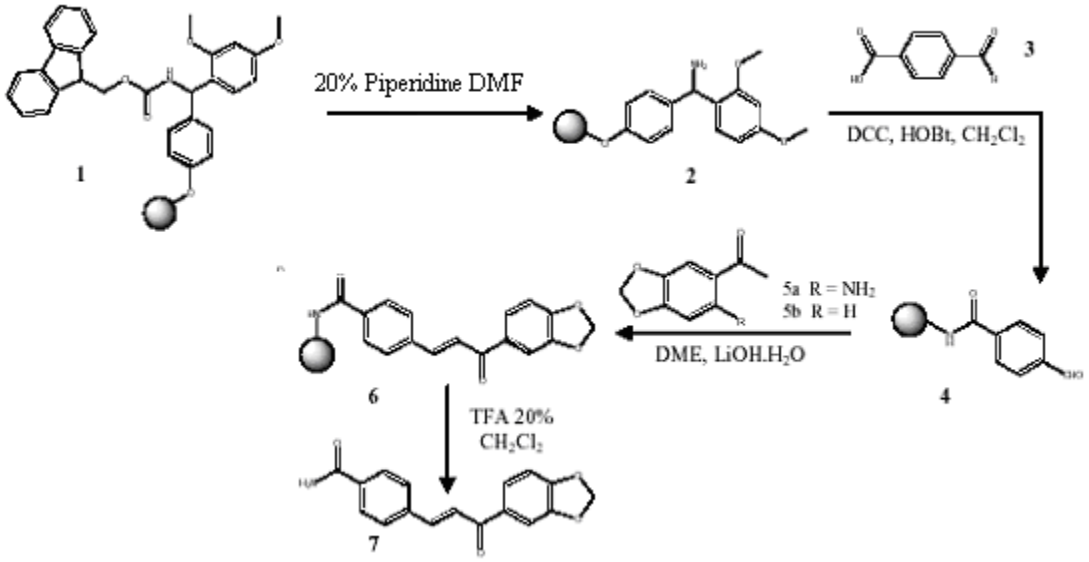

Scheme 1

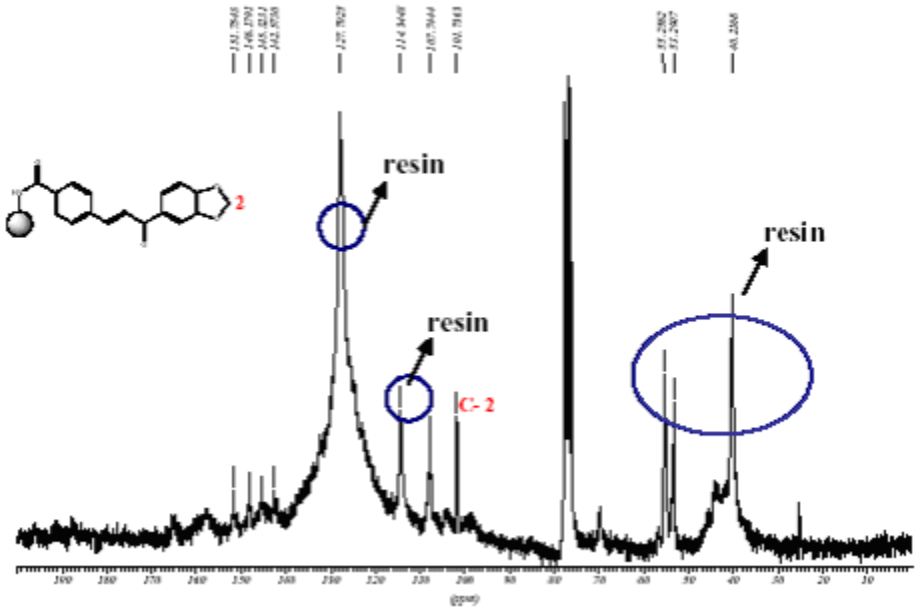

Figure 1. ^{13}C-NMR spectrum in gel phase for compound **6**.

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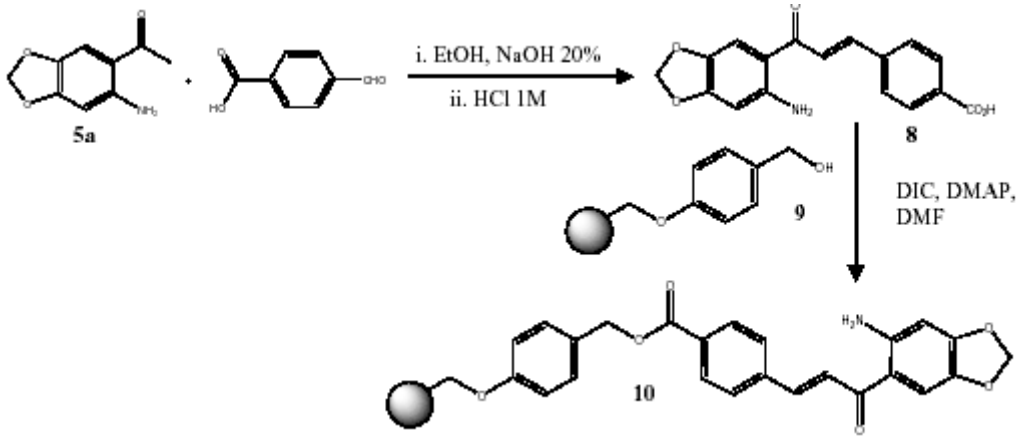

Scheme 2

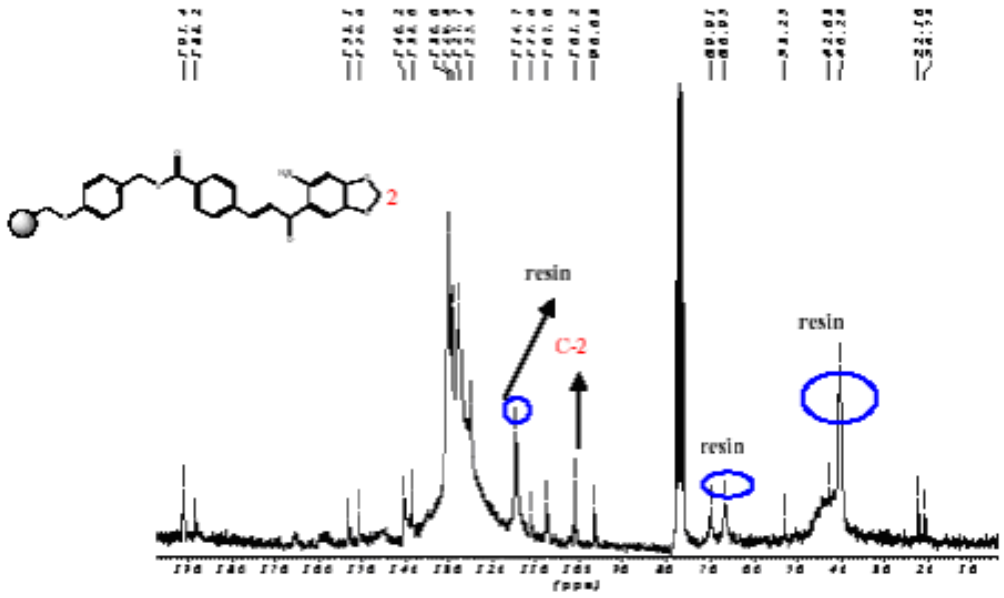

Figure 2. ^{13}C-NMR spectrum in gel phase for compound **10**.

Methodology

Rink-Fmoc resin deprotection

Compound **1** (0.4 g) was suspended in a 20% piperidine solution in DMF (5 ml), and stirred at room temperature for 1 hour. Then, filtered and washed with MeOH, DMF and DCM (3 times), and further dried in a vacuum desiccator. Kaiser test was performed to verify the presence of amino group, the result being positive.

Acylation of Rink-NH_2 resin with 4-carboxybenzaldehyde.

Deprotected Rink resin **2** (0.4 g) was acylated with 3 eq. of 4-carboxybenzaldehyde **3** in dry DCM. The suspension was stirred at room temperature under nitrogen atmosphere (after acid activation for 40 minutes with 3.3 eq. of DCC and 3.3 eq. of HOBt) for 4.5 hours. The resin was filtered and washed with MeOH, DMF and DCM (3 times). It was placed in a desiccator under vacuum. Kaiser's test was negative.

Methylenedioxychalcone 7. Claisen-Schmidt reaction of compound 4 and 3,4-methylenedioxyacetophenone 5b.

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Compound **4** (0.2 g) was suspended in anhydrous DME, then 20 eq. of $LiOH.H_2O$ and 20 eq. of 3,4-methylenedioxyacetophenone **5b** were added. The reaction mixture was stirred for 12 hours at a temperature of 60 ºC, and then stirred at room temperature for 16 hours. Then the resin was filtered and washed with acetic acid, DMF, isopropanol and DCM (3 times). It was dried in a vacuum desiccator.

The obtained compound was treated with a 20% solution of TFA in DCM, and further stirred at room temperature for 15 minutes. Then, the resin was vacuum filtered through a sintered glass funnel. Three washes with DCM were performed. The solvent was evaporated under reduced pressure to get compound **7**.

4-[3-(6-Amino-benzo[1,3]dioxol-5-yl)-3-oxo-propenyl]-benzoic acid

A solution of 6-amino-3,4-methylenedioxyacetophenone **5a** (0.5 g, 2.8 mmol), 4-carboxybenzaldehyde (0.42 g, 2.8 mmol) in ethanol (8 ml) and aqueous NaOH (0.5 ml, 20%) was heated under reflux for 5 hours, the obtained precipitate was filtered and further treated with a (1M) HCl solution; the solid was filtered and washed with water.

Wang resin-bound methylenedioxychalcone (10)

To a suspension of Wang resin **9** (0.1 g) in DMF the aminomethylenedioxychalcone (4 eq) in anhydrous DMF (3 ml) was added with stirring at room temperature under nitrogen atmosphere (after acid activation for 40 minutes with DIC (4 eq) and DMAP (0.1 eq) in anhydrous DMF for 12 hours. Then the resin was filtered and washed with MeOH, DMF and DCM (3 times), and an additional wash with MeOH, DCM (2 times) was performed.

The products were characterized by spectroscopic techniques, such as IR, and ^{13}C-NMR in gel phase, ^{1}H-NMR and ^{13}C-NMR.

Conclusions

The condensation of the aminomethylene dioxyacetophenone **5a** did not occur possibly because of molecule deactivation by the presence of the amino group, which reduces α-hydrogen availability for the ketone carbonyl group, being more difficult to abstract them by the used bases in the described approaches.

The comparison of both strategies allowed to draw the conclusion that the direct method is effective to generate the aminomethylene dioxychalcone **10**, since an aldol condensation is not necessary to be used with this acetophenone.

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