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Letter

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Solid-Supported Cross-Metathesis and a Formal Alkane Metathesis for the Generation of Biologically Relevant Molecules

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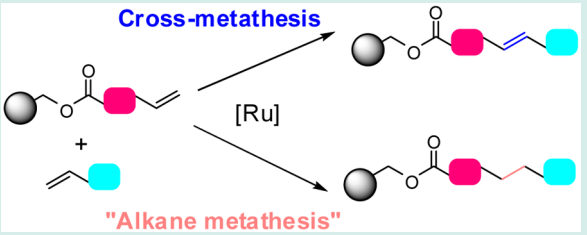
Supporting Information

ABSTRACT: Solid-phase synthetic strategies toward the generation of libraries of biologically relevant molecules were developed using olefin cross-metathesis as a key step. It is remarkably the formal alkane metathesis based on a one-pot, microwave-assisted, ruthenium-catalyzed cross-metathesis and reduction to obtain C_{sp^3}–C_{sp^3} linkages.



KEYWORDS: *olefin metathesis, solid-phase organic synthesis, chalcones, β-phenylpropiophenone derivatives, microwave heating*

The application of metal-catalyzed cross-coupling reactions to solid-phase organic synthesis has increased substantially in the past decade.[1] This has been caused by the emergence of new and more efficient catalysts and the inherent advantages of solid-supported chemistry, including an increase in selectivity.[2] Since the desired product is immobilized on a resin, undesirable side reactions that take place in solution are easily washed away by a simple filtration. In addition, spatial separation between the reactive sites (pseudo high dilution conditions)[3] make intramolecular macrocyclization a suitable reaction that could be carried out efficiently on solid-phase rather than in solution. An extra benefit of the solid-phase synthesis is obtained when it is applied to cross-coupling reactions: unwanted homodimeric products can be either easily removed or not formed at all. The nonimmobilized substrate can be added in excess in order to complete the reaction since the corresponding homodimer remains in solution and can be eliminated by a simple filtration. Similarly, homodimerization of the immobilized substrate is a less favorable process due to the isolation between the reactive sites.[4]

On the other hand, studies related to the synthesis and properties of small molecules remains an essential strategy for identifying lead compounds for treatment of diseases.[5] There is a growing interest in the development of new ways to obtain such small molecules not only for their use in traditional drug discovery but also for the use in dissecting protein–protein interactions and for understanding signaling pathways.[6] Thus, one of the methodologies for a rapid and efficient construction of diversity-based small molecules is parallel solid-phase synthesis which, after an initial use in the preparation of peptides, is now extensively employed in the preparation of biologically interesting molecules including heterocycles and natural product scaffolds,[7] becoming an important tool to improve the efficiency of drug discovery.[8]

Regarding the likelihood of identifying new active structures in drug discovery, recent analyses have demonstrated that current compound collections exhibit a low incidence of sp^3 carbon atoms in their molecules, and the tendency is even more marked in the last 15 years.[9] A high level of carbon bond saturation, defined the fraction sp^3 (Fsp^3), indicates a more three-dimensional, less "flat" structure.[10] Many recent studies, supported by computational analysis, have suggested that larger Fsp^3 values can improve the possibility of finding new drug candidates.[11]

Among structures that show a wide spectrum of beneficial biological activities, chalcones (**1**) occupy an important place (Figure 1). They are versatile synthetic and natural scaffolds found in antibacterial,[12] antifungal,[13] antituberculosis,[14] anti-inflammatory,[15] and especially, in antitumor agents, that is,

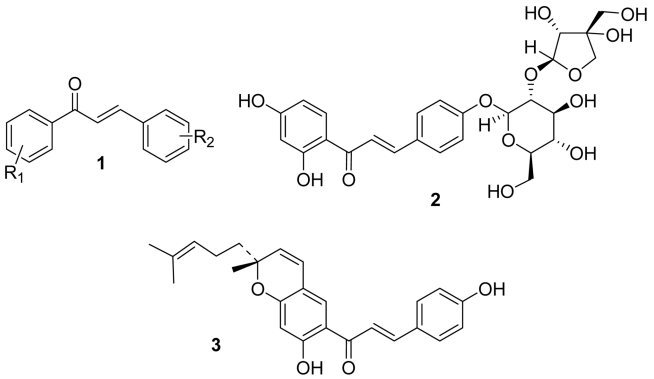


Figure 1. Some chalcone derivatives of biological interest.

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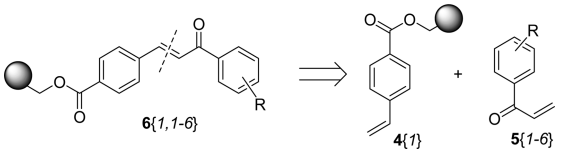
isoliquiritin apioside (**2**) and isolespeol (**3**) (Figure 1).[16] All previous solid-phase synthesis of chalcones were based on aldol condensation between ketones and aldehydes, usually employing strong bases.[17] Despite of the mild conditions of solid-supported cross-metathesis, its application to the chalcone synthesis has not yet been reported. In this work we have developed an efficient solid-supported methodology useful for generating libraries of chalcones and an alkane metathesis[18] based on a tandem, one-pot, ruthenium-catalyzed cross-metathesis and reduction,[19] to obtain biologically interesting β-phenylpropiophenone derivatives.[20]

We initially analyzed the ruthenium catalyzed cross-metathesis between polymer supported 4-vinylbenzoic acid (**4**{*1*}) and nonimmobilized α,β-unsaturated ketones **5**{*1*−*6*} to obtain the corresponding chalcones (**6**{*1,1*−*6*}) (Scheme 1).

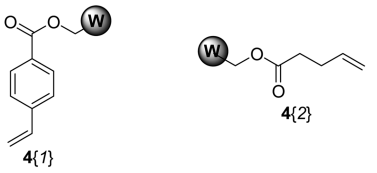
Scheme 1. Strategy for the Solid-Phase Synthesis of Chalcones



To study the cross-metathesis reaction, we chose olefin **5**{*1*} as a model substrate and two different ruthenium-carbene precatalysts [Grubbs' second generation (**7**) and Hoveyda−Grubbs' (**8**)] (Scheme 2 and Figure 2). While resin **4**{*1*} was obtained by coupling 4-vinyl benzoic acid to Wang resin by a standard coupling procedure, nonimmobilized olefin **5**{*1*} was synthesized, starting from anisole (**9**{*1*}), by a sequence Friedel−Crafts acylation/dehydrohalogenation (Scheme 2). Thus, anisole (**9**{*1*}) was treated with 3-bromopropionyl chloride (**10**) in the presence of aluminum chloride to obtain the 3-bromopropanone derivative **11**{*1*}. This Friedel−Crafts acylation was followed by the dehydrohalogenation using triethylamine to obtain α,β-unsaturated ketone **5**{*1*}.

Regarding the cross-metathesis coupling, every time precatalyst **7** was employed under a variety of reaction conditions, no desired product was detected, leaving the unreacted starting olefin **4**{*1*}. However, when precatalyst **8** was used, formation of the expected chalcone (**6**{*1,1*}) was successful. This promising result was clearly observed through gel-phase ^{13}C NMR experiments [55.6 (OMe), 124.1 (CH-vinyl), 142.3 (CH-vinyl), 174.3 (CO, ester), 203.8 ppm (CO, ketone)]. After a short optimization process, the best conditions for this reaction were established: resin **4**{*1*} was treated with 5 mol % of precatalyst **8** and 5 equiv of olefin **5**{*1*} in toluene at 75 °C for 1 h.

Polymer supported olefins 4



Non-inmobilized olefins 5

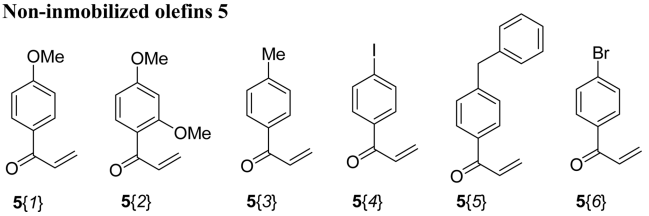


Figure 2. Structures and numbering of building blocks.

A library of chalcones was then developed employing the synthetic pathway described above. The products were cleaved from the resin by treatment with 10% trifluoroacetic acid in CH_2Cl_2 during 1 h at room temperature and the carboxylic acid moiety was esterificated with diazomethane. To our surprise, the analysis of the reaction crudes by ^{1}H NMR showed a mixture of compounds consisting in the desired chalcones and unknown byproducts. Besides, yields of the isolated chalcones **14**{*1,1*−*3*} were lower than we expected (entries 1−3, Table 1). Interestingly, in the case of compound **5**{*4*} (R^1 = I, R^2 = H, entry 4), after cleavage, methylation and purification by column chromatography, we isolated a product that, after analysis by ^{1}H NMR, ^{13}C NMR, 2D NMR experiments and mass spectrometry, was unequivocally assigned as the 2-pyrazoline **12**{*1,4*} (Figure 3). This type of compounds could be generated by an 1,3-dipolar cycloaddition of diazomethane to the α,β-unsaturated double bound.[21]

To avoid the formation of byproducts derived from the use of diazomethane, we decided to directly purify compounds **13**{*1,1*−*6*} which contains the free carboxylic acid moiety (Table 1, entries 5−9). The corresponding chalcones were

Scheme 2. Solid-Phase Synthesis of Chalcones Based on Olefin Cross-Metathesis

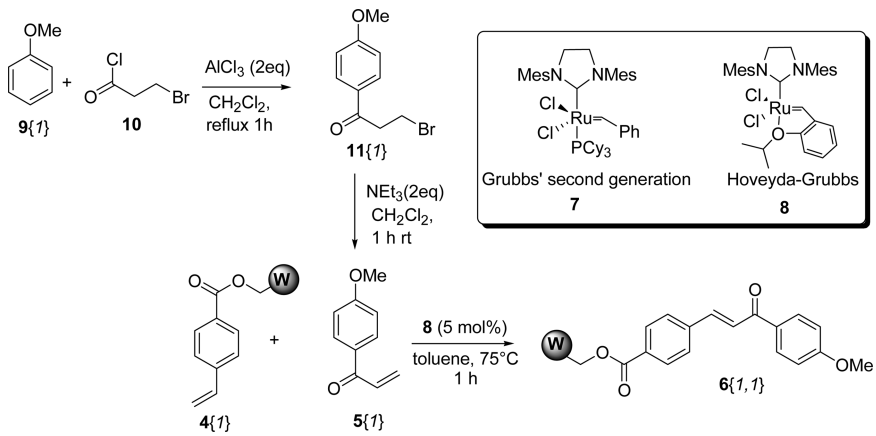


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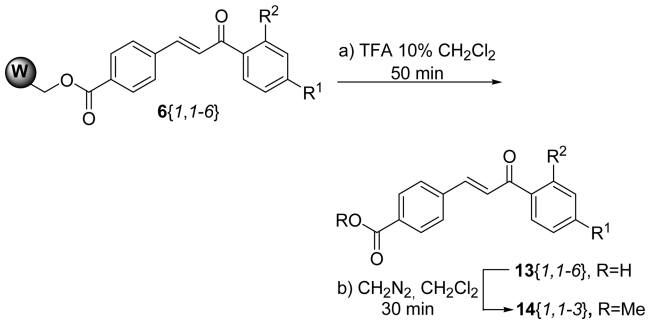
Table 1. Solid-Phase-Based Library of Chalcones



entry	R^1	R^2	product	yield (%)
1	OMe	H	**14**{*1,1*}	36[a]
2	OMe	OMe	**14**{*1,2*}	55[a]
3	Me	H	**14**{*1,3*}	35[a]
4	I	H	**12**{*1,4*}	36[a]
5	OMe	H	**13**{*1,1*}	83[b]
6	Me	H	**13**{*1,3*}	78[b]
7	I	H	**13**{*1,4*}	65[b]
8	CH_2Ph	H	**13**{*1,5*}	85[b]
9	Br	H	**13**{*1,6*}	63[b]

[a]Overall isolated yield after flash column chromatography (based on loading of resin **4**{*1*}). [b]Overall isolated yield after reverse-phase flash column chromatography (based on loading of resin **4**{*1*}).

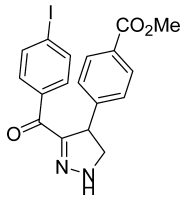


Figure 3. 2-Pyrazoline obtained by reaction of the corresponding chalcone and diazomethane.

obtained in very good overall yields, after isolation by reverse phase column chromatography.

Once the immobilized chalcones **6**{*1,1−6*} were successfully achieved, we decided to hydrogenate these *α,β*-unsaturated alkenes to obtain biologically interesting *β*-phenylpropiophenone derivatives. The synthetic pathway chosen was a "hydrogen-free" reduction of *α,β*-unsaturated alkenes employing carbene-ruthenium precatalyst in a nonmetathetic role and Et_3SiH as reducing agent.[19] Using previously reported conditions, which are based on Grubbs' second generation catalysis (**7**) and microwave heating,[19] the immobilized chalcone **6**{*1,1*} was selectively reduced to the corresponding immobilized saturated ketone **15**{*1,1*} (Scheme 3). The appearance of methylene signals (30.3 and 39.5 ppm) instead of the vinyl ones (142.3 and 124.1 ppm) in the gel phase ^{13}C NMR of resin **15**{*1,1*} provided evidence of the convenience of this strategy. Final release from the solid support, methylation and isolation by column chromatography afforded **16**{*1,1*} in 47% yield for the sequential cross-metathesis/olefin reduction process (Scheme 3). Additionally, we found that catalyst replacement by Hoveyda-Grubbs (**8**) gave compound **16**{*1,1*} in similar yield.

To improve the efficiency of the whole sequence, we tried a one-pot cross-metathesis/reduction version.[22] Since precatalyst **7** was inefficient for the cross-metathesis step, the one-pot strategy was performed using precatalyst **8**. Thus, the solid-supported olefin **4**{*1*}, precatalyst **8**, and the nonimmobilized olefin **5**{*1*}, suspended in anhydrous dichloromethane, were irradiated under microwave conditions during 10 min at 75 °C. After this time, the microwave vial was purged with nitrogen to remove the generated ethylene and the reaction was irradiated again for 20 min. Then, triethylsilane was added and the reaction mixture was irradiated during 30 min at 150 °C. Under this one-pot protocol, an small library of *β*-phenylpropiophenone **16**{*1,1−5*} was afforded in good overall yields, after releasing from the resin, methylation and isolation by column chromatography (entries 1−4, Table 2). Unfortunately, when 1-(4-bromo-phenyl)-propenone (**5**{*6*}) was used as the solution-phase olefin, decomposition products were obtained after cleavage (entry 5). The efficacy of our formal alkane metathesis methodology was also demonstrated varying the starting immobilized olefin. With this purpose, 4-pentenoic acid linked to Wang resin (**4**{*2*}), preparing by standard DIC/DMAP coupling, was subjected to the optimal one-pot conditions with nonimmobilized olefins **5**{*1−5*} to generate the saturated methyl esters **18**{*1,1−5*} with very good overall yields (entries 6−9, Table 2).

In summary, we report an efficient solid-supported protocol toward the generation of libraries of biologically relevant chalcone scaffolds. This is the first cross-metathesis-based chalcone synthesis applying solid phase, which is especially useful for cross-coupling reaction because of the spatial separation of substrates achieved by immobilization on the resin, that avoids undesired homocoupling products. In addition, a formal alkane metathesis was developed by a tandem, one-pot, microwave-assisted, ruthenium-catalyzed cross-metathesis and reduction. This remarkable procedure was successfully applied to the synthesis of biologically interesting *β*-phenylpropiophenone and other acetophenone derivatives. We think that this study is an important contribution for a more general application of solid-phase strategies, particularly to the generation of $C_{sp^3}-C_{sp^3}$ bonds,

Scheme 3. Hydrogen-Free Reduction of *α,β*-Unsaturated Ketones by Ruthenium Precatalyst and Et_3SiH

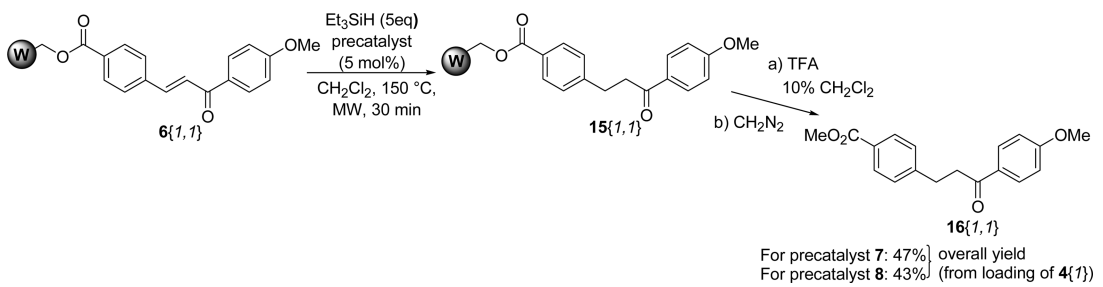


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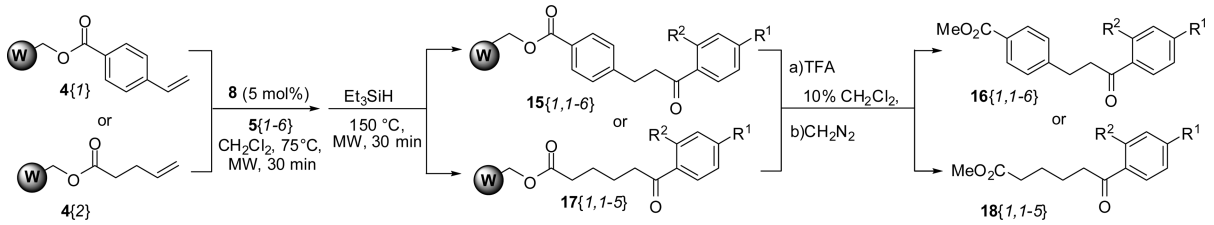
Table 2. Formal Alkane Metathesis by Solid-Phase, One-Pot Cross-Metathesis/Reduction



entry	starting immobilized resin	R^1	R^2	product	yield (%)
1	4{*1*}	OMe	H	**16**{*1,1*}	40[a]
2	4{*1*}	Me	H	**16**{*1,3*}	34[a]
3	4{*1*}	I	H	**16**{*1,4*}	32[a]
4	4{*1*}	CH_2Ph	H	**16**{*1,5*}	40[a]
5	4{*1*}	Br	H	**16**{*1,6*}	-[b]
6	4{*2*}	OMe	H	**18**{*1,1*}	50[c]
7	4{*2*}	Me	H	**18**{*1,3*}	46[c]
8	4{*2*}	I	H	**18**{*1,4*}	30[c]
9	4{*2*}	CH_2Ph	H	**18**{*1,5*}	60[c]

[a]Overall isolated yield after flash column chromatography (four steps based on loading of resin 4{*1*}). [b]After cleavage decomposition products were obtained. [c]Overall isolated yield after flash column chromatography (five steps based on loading of Wang resin).

which are progressively more required for increasing F_{sp^3} value in the search for new drug candidates.

EXPERIMENTAL PROCEDURES

Representative procedure for the solid-phase synthesis of chalcones: Resin-bound vinyl benzoic acid 4{*1*} (100 mg, 0.11 mmol) was placed in a 25 mL round-bottom flask, purged with dry nitrogen, suspended in anhydrous toluene (3.0 mL) and olefin **5**{*5*} (166.6 mg, 0.55 mmol) dissolved in anhydrous toluene (3.0 mL) was added via syringe. After addition of precatalyst **8** (3.4 mg, 5.5 μmol, 5 mol %), the flask was fitted with a condenser with a cannula adapted so as to allow the elimination of the generated ethylene during the reaction. Being a reversible process, elimination of ethylene helps to displace the reaction toward the desired products.[4b] The system was heated at 75 °C for 1 h under nitrogen atmosphere. Resin was filtered and washed with toluene (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), MeOH (3 × 5 mL), and CH_2Cl_2 (3 × 5 mL) and dried under high vacuum. Resin **6**{*1,5*} (98.5 mg, 77.8 μmol, 0.79 mmol/g) was treated with 5 mL of 10% TFA in CH_2Cl_2 for 1 h. The mixture was filtered and the filtrate was evaporated under reduced pressure to give the crude product. The solvent was evaporated under reduced pressure and the crude material was purified by flash reversed column chromatography (H_2O–acetonitrile) to provide 13.4 mg of chalcone **13**{*1,5*} (85% yield, calculated yield from linker 4{*1*}).

Representative procedure for one-pot cross-metathesis/reduction: Immobilized vinyl benzoic acid 4{*1*} (100 mg, 0.11 mmol) was placed in a 10 mL microwave vial, precatalyst **8** (3.4 mg, 5.5 μmol, 5 mol %) and olefin **5**{*5*} (166.6 mg, 0.55 mmol) dissolved in anhydrous CH_2Cl_2 (2 mL) were added under nitrogen atmosphere. The vial was placed in the microwave reactor with the appropriate cover. The reaction was irradiated during 10 min at 75 °C (maximum power = 300 W) in closed system with magnetic stirring. After this time the vial was removed from the microwave reactor and was purged with nitrogen in order to remove the generated ethylene. Then, the reaction was irradiated 20 min more under the same conditions. The vial was removed from the reactor, triethylsilane (88 μL, 0.55 mmol) was added and the reaction medium was irradiated during 30 min at 150 °C (maximum power = 300 W). Resin was filtered and washed with CH_2Cl_2 (3 × 5 mL), AcOEt (3 × 5 mL), MeOH (3 × 5 mL), and CH_2Cl_2 (3 × 5 mL) and dried under high vacuum. Resin **15**{*1,5*} (112.6 mg, 83.3 μmol, 0.74 mmol/g) was treated with 5 mL of 10% TFA in CH_2Cl_2 for 1 h. The mixture was filtered and the filtrate was evaporated under reduced pressure to give the crude product. This crude material was dissolved in CH_2Cl_2 and treated with ethereal solution of diazomethane at 0 °C until yellowish coloration is achieved. The reaction was stirred for 30 min and diazomethane was quenched by addition of AcOH until discoloration was achieved. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography (hexane–AcOEt) to provide 6.3 mg of **16**{*1,5*} (40% yield, calculated yield from linker 4{*1*}).

ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data: ^1H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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