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Report

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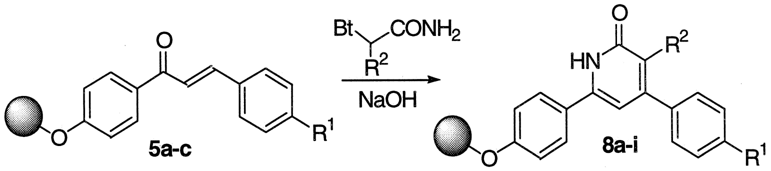

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Reports

Solid-Phase Synthesis of 4,6-Disubstituted and 3,4,6-Trisubstituted Pyrid-2-ones

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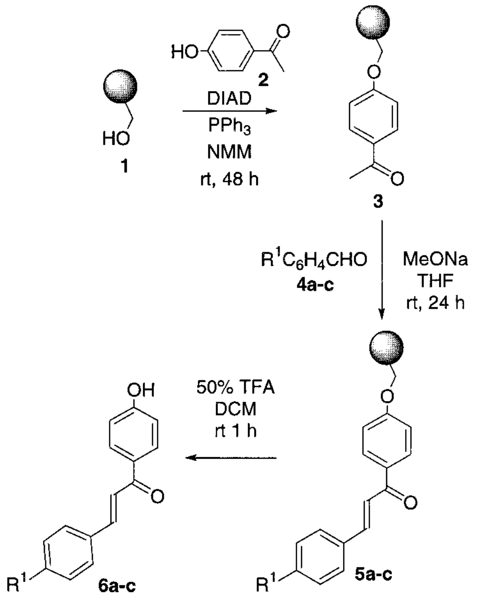
Introduction. During the past 2 decades, combinatorial chemistry has appeared as one of the most valuable tools used to accelerate drug discovery and lead optimization processes. The emergence of this new field has promoted the transfer of solution-phase functional group transformations to the solid phase.[1−3] Among the preparations of libraries of low molecular weight compounds, nitrogen-containing heterocycles are of particular interest as recognized pharmacophores.[4−6] Pyridones constitute valuable scaffolds allowing the potential introduction of diversity by functionalization of the carbonyl moiety. To the best of our knowledge, solid-phase syntheses of pyridones have been restricted to four reports. Two of them concern the preparation of 2,3-dihydropyrid-4-ones by (i) reactions of Danishefsky's diene with imine resins[7] and (ii) the acylation of pyridines followed by the condensation with Grignard reagents.[8,9] In the third report (iii), pyrid-4-ones have been obtained by reaction of acetylketene with polymer-bound enamines.[10] A more recent example (iv) involves the reaction of resin-bound chalcones with 1-(methoxycarbonylmethyl)-pyridinium bromide and ammonium acetate to give pyrid-2-ones.[11] Recently, we disclosed the solution-phase synthesis of 4,6-disubstituted and 3,4,6-trisubstituted pyrid-2-ones by the condensation of chalcones with 2-(benzotriazol-1-yl)-acetamide and 2-alkyl-2-(benzotriazol-1-yl)acetamides.[12] We now report the successful transfer of this protocol to the solid phase.

Scheme 1



6	a	b	c
R^1	Me	OMe	F
Purity* (%)	95	95	90
Yield** (%)	87	85	79

* Determined by HPLC (UV detection, 254 nm)
** Yield of the crude products based on the initial loading of the resin

Results and Discussion. We selected Wang resin **1** for the elaboration of our library because of the ease of subsequent cleavage with trifluoroacetic acid (TFA) from this support. The resin-bound chalcones **5a**−**c** were prepared by the linkage of 4-hydroxyacetophenone **2** to Wang resin **1** using our modified Mitsunobu protocol[13] followed by the

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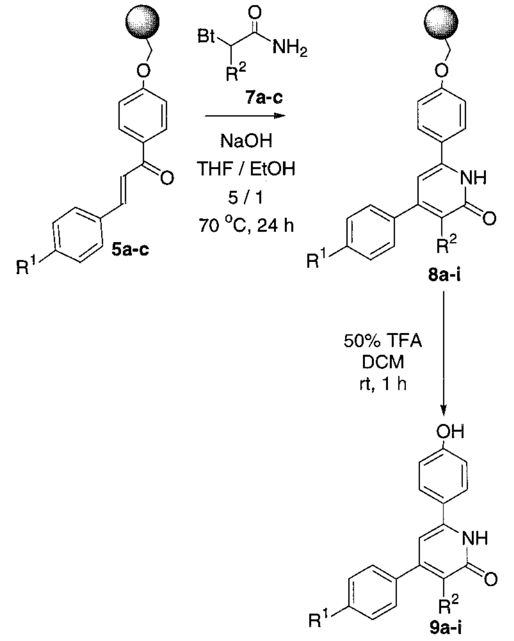
Scheme 2



9	a	b	c	d	e	f	g	h	i
R^1	Me	OMe	F	Me	OMe	F	Me	OMe	F
R^2	H	H	H	Me	Me	Me	Et	Et	Et
Purity * (%)	90	95	95	90	95	90	70	95	90
Yield** (%)	87	80	81	84	81	79	85	83	82

* Determined by HPLC (UV detection, 254 nm)
** Yield of the crude products based on the initial loading of the resin

condensation with the aromatic aldehydes **4a**−**c** in the presence of sodium methoxide in THF at room temperature for 24 h. The expected resin-bound chalcones **5a**−**c** were obtained in 79−87% yields and 90−95% purities as shown by LC−MS analysis of the cleaved residues **6a**−**c** (Scheme 1).

Chalcones **5a**−**c** were reacted with 2-(benzotriazol-1-yl)-acetamides **7a**−**c** (20 equiv, 0.25 mmol/mL) in the presence of sodium hydroxide (40 equiv, 0.5 mmol/mL) in a 1:5 mixture of ethanol and THF at 70 °C for 24 h. The resins **8a**−**i** obtained were washed using a standard protocol (2 × H_2O, 2 × H_2O/THF = 1:1, 2 × THF, 4 × DCM/MeOH, and MeOH) and were cleaved by 50% solution of TFA in DCM for 1 h at room temperature. According to ^{1}H NMR and LC−MS analyses, the desired pyridones **9a**−**i** were obtained in 79−87% yields and with 70−95% purities independently of the nature of substituents R^1 and R^2 in chalcones **5a**−**c** (R^1 = Me, MeO, F) and acetamides **7a**−**c** (R^2 = H, Me, Et) molecules (Scheme 2).

When the condensation of resin **5a** with acetamide **7a** was attempted in the presence of sodium methoxide in boiling THF for 24 h, the expected pyridone **9a** was not detected in the cleaved material. Analogous condensation performed in 2-methoxyethanol at 70 °C resulted in the formation of a complex mixture of degradation products.

Conclusions. In conclusion, the condensation of resin-bound chalcones **5a**−**c** with 2-(benzotriazol-1-yl)acetamide **7a** has been described. This protocol allows for the first time the solid-phase synthesis of 4,6-disubstituted pyrid-2-ones **8a**−**c**. Extension of this method to 2-alkyl-2-(benzotriazol-1-yl)acetamides **7b,c** offers an entry to 3,4,6-trisubstituted pyrid-2-ones **8d**−**i**.

Supporting Information Available. General experimental procedures and NMR and LC−MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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