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# A Solid Phase Synthesis of Chalcones by Claisen-Schmidt Condensations

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**Abstract:** In order to accelerate the development of relatively inexpensive antimalarials that are effective against chloroquine-resistant strains of *Plasmodium falclparum*, a methodology for the solid phase synthesis of chalcone (l, 3-diphenyl-2-propen-l-one) analogues in reasonably high yields has been developed.

**Keywords:** Solid phase synthesis, chalcones, antimalarial.

In previous papers[1,2], we reported our recent findings that chalcone (l,3-dipheny1-2-propen-1-one) derivatives are novel potential antimalarials that are active against chloroquine-resistant strains of *Plasmodium falciparum*. According to our structure-activity relationships (SAR) and computer modeling data[1,2], we expect the chalcone derivatives with hydroxyl functionality on one of the aromatic rings and with some other appropriate substitutions on the other ring will be even more potent as antimalarials. Consequently, we have developed solid phase methodology to accelerate the development of cost-effective antimalarials.

## Experimental

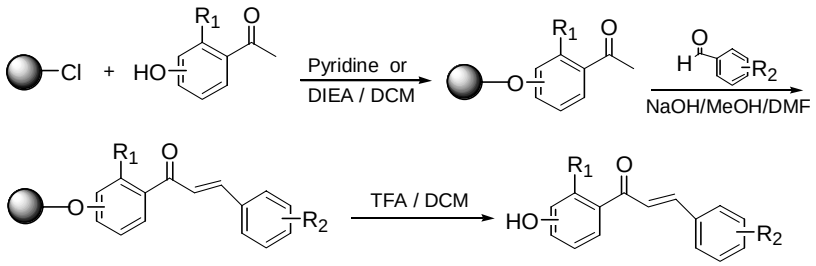
Manual peptide synthesis vessels were oven-dried, and all reactions were performed under an argon atmosphere. 2-Chlorotrityl chloride resin and methylketones were dried over KOH pellets in a desiccator under vacuum before use. $^{l}$H NMR spectra at 300 MHz were recorded on a General Electric QE-300 spectrometer. Chemical Ionization Mass Spectrometry (CIMS) spectra were obtained at the UCSF Mass Spectrometry Facility (VG-70E EI/CIMS and CONCEPT-LSIMS) by director, A. L. Burlingame. HPLC were performed on a HP-l050 system. FT-IR (Nicolet Impact 400) was used to monitor and optimize the Claisen-Schmidt condensation reactions. All starting materials were purchased from Aldrich Chemical Company, Inc. 2-Cholorotrityl chloride resin was purchased from Novabiochem, La Jolla, CA.

***General procedure for the synthesis of chalcone derivatives:*** In a manual peptide synthesis vessel, a mixture of 3- or 4-hydroxyacetophenone or hydroxybenzaldehyde (5 to l0 eq.), pyridine or diisopropyl ethylamine (2 eq.) and 2-chlorotritylchloride resin (l00

mg, l.l-l.6 mmol/g) in anhydrous dichloromethane (3 mL) was shaken for l h at room temperature. Resin was washed with DMF (3x), MeOH (2x) and DCM (3x) and dried *in vacuo*. The resin-attached aldehydes (l eq.) or methylketones (l eq.) were condensed with either substituted methylketones (l0 eq.) or substituted aldehydes (l0 eq.) with NaOH (0.1 eq.) in l0% MeOH-DMF (3 mL total) at room temperature for 24 h. Resins were washed in the same sequence as the first step described above. The product was cleaved with TFA/DCM at room temperature for 20 min.

***Determination of product purity by HPLC:*** Column. Hewlett Packard ODS hypersil, 5 μm, 100 x 4.6 mm. Gradient. A from 100% to 0% and B from 0% to l00 in 20 min (A: 0. l% TFA in $H_2O$; B: MeCN).

**Scheme 1.**




●-Cl : 2-chlorotrityl chloride resin; $R_1$=H, $CH_3$; $R_2$=H, $CH_3$, $CH_3O$, F, Cl, Br, or fuzed heterocycles

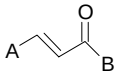
## Results and Discussion

Our solid phase synthesis of chalcone derivatives was effected *via* carbon-carbon bond formation using a Claisen-Schmidt condensation reaction shown in **Scheme 1**. In our previous procedures[1], based on condensations in solution, methanol was used as solvent and sodium hydroxide as catalyst. The reaction was monitored by a more sophisticated FT-IR spectrometer[5]. In this work, we used KBr pellets of the resins for analysis of the intermediates using a conventional FT-IR spectrometer. Even though *ca.* 10 mg of resin is required for the analysis, it is still more convenient than analyzing the resin cleaved intermediate by other methods, such as $^1$H NMR. FT-IR by observing the disappearance of the carbonyl stretch from aldehydes or methylketones (l680- l700 $cm^{-1}$) and appearance of the carbonyl stretch from α,β-unsaturated ketones (l650-1670 $cm^{-1}$) monitored the Claisen-Schmidt condensations. For example, the KBr pe1let of the resin-attached *p*-hydroxyacetophenone showed a carbonyl stretch at 1683.8 $cm^{-1}$ while the product of the Claisen-Schmidt condensation, chalcone, showed a carbonyl stretch at l654.1 $cm^{-1}$. Products of formation of the α,β-unsaturated ketones always yielded the *trans*-alkene (E-form) under these conditions as judged by $^1$HNMR spectroscopy.

In conclusion, we have developed a solid phase synthetic method for a carbon-carbon bond formation giving chalcones in reasonably high yields. The methodology of this Claisen-Schmidt condensation on solid phase may apply for synthesis of other α, β-unsaturated ketones and for other chalcones of biological

interest[6,7]. Chalcones generated by this solid phase method may also be used as key intermediates for other molecular targets in a combinatorial fashion.

**Table 1**. Structures of chalcone (l, 3-diphenyl-2-propen-l-one) analogues




| Entry | A | B | Yield (%)[a] | Purity (%)[b] |
|---|---|---|---|---|
| 1 |  |  | Quantitative | >99 |
| 2 |  |  | Quantitative | >99 |
| 3 |  |  | 97 | 90 |
| 4 |  |  | 82 | 89 |
| 5 |  |  | 79 | 75 |
| 6 |  |  | 96 | >99 |
| 7 |  |  | 83 | 90 |
| 8 |  |  | 76 | 82 |
| 9 |  |  | 88 | >99 |
| 10 |  |  | 93 | >99 |
| 11 |  |  | 90 | 96 |
| 12 |  |  | 87 | 93 |

[a]Yields based on an average 70% loading of hydroxyacetophenone on to the resin.
[b] Purity determined by HPLC (see experimental section for conditions).

## Acknowledgments

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## References and notes

1. R. Li, G. L. Kenyon, F. E. Cohen, *et al*., *J. Med. Chem.*, **1995**, *38*, 503l.
2. R. Li, X. Chen, B. Gong, *et al*., *Biomed. Chem*., **1996**, *4*, l421.
3. S. P. Hollinshead, *Tetrahedron Lett.* **1996**, *37*, 9157.
4. C. Chen, L. A. Randall, R. B. Miller, *et al*., *J. Am.. Chem. Soc.*, **l994**, *1l6*, 266l.
5. B. Yan, G. Kumaravel, H. Anjaria, *et al*., *J. Org. Chem.*, **l995**, *60*, 5736.
6. M. E. Zwaastra, H. Timmerman, M. Tamura, *et al*., *J. Med. Chem.*, **l997**, *40*, l075.
7. F. Herencia, M. L. Ferrandiz, A. Ubeda, *et al*., *Bioorg. Medchem. Lett*., **l998**, *8*, ll69.
8. **Compd.3:** [l]HNMR ($d_6$-DMSO) δ 7.l4 (d, *J* = 7.9 Hz, l H), 7.43 (dd, *J* = 8.0 Hz, l H), 7.7l (d,

*J* = 7.6 Hz, l H), 7.80 (dd, *J* = 8.0 Hz, l H), 7.92 (dd, *J* = 7.5 Hz, l H), 8.18 (d, *J* =7.l Hz, l H), 8.21 (d, *J* = l6.0Hz,1H), 8.27 (d, *J* = 4.8 Hz,1H), 8.40 (d, *J* = 7.6Hz, l H), 8.48 (d, *J* = 15.3 Hz,1H) and 9.11 (d, *J* = 4.8 Hz,1H); CIMS for $C_{18}H_{13}NclO_2$[M + $H^+$], calcd, 310.1; found, 310.0.**Compd.4:** $^1$HNMR ($d_6$-DMSO) δ 6.94 (d, *J* =8.1 Hz, 2H), 7.72 (dd, *J* = 7.4 Hz, 1H), 7.87 (dd, *J* = 7.2 Hz, 1H), 7.96-8. l5 (m, 6 H), 9.24 (s, l H) and 10.57 (br. s,1H), CIMS for $C_{18}H_{13}NClO_2$ [M + $H^+$], calcd. 310.1; found, 310.0.**Compd.5:** $^1$H NMR ($d_6$-DMSO) δ 2.49 (s, 3 H), 6.75 (d, *J* = 8.0 Hz, 2H), 7.72-8.10 (m, 8 H), 9.20 (s, l H) and 10.25 (br. s,1H), CIMS for $C_{19}H_{14}NClO_2$ [M + $H^+$],calcd. 324.1; found, 324.0. **Compd.9:** $^1$H NMR ($d_6$-DMSO) δ 6.95 (d, *J* = 8.7 Hz, 2H), 7.66 (dd, *J* = 7.7 Hz, l H), 7.74 (d, *J* = l5.5Hz, l H), 7.78-8.04 (m, 3 H), 8.l2 (d, *J* = 8.6 Hz, 2 H), 8.26 (d, *J* = 8.5 Hz, l H), 8.35 (d, *J* = l5.6 Hz, l H), 8.55 (d, *J* = 8.6 Hz, l H) and 10.50 (br. s, l H), CIMS for $C_{18}H_{14}NO_2$, [M + $H^+$], calcd. 276. 1; found, 276.0. **Compd.11:** $^1$H NMR ($d_6$-DMSO) δ 6.95 (d, *J* = 8.7 Hz, 2H), 7.84 (dd, *J* = 8.l Hz, l H), 7.98-8.01 (m, l H), 8.l4-8.20 (m, 3 H), 8.25 (d, *J* = l5.4 Hz, l H), 8.30 (d, *J* = 5.1 Hz, l H), 8.4l (d, *J* = l4.8 Hz, l H), 8.47 (d, *J* = 7.6 Hz, l H) and 9.l6 (d, *J* = 5.0 Hz, l H); CIMS for $C_{18}H_{14}NO_2$, [M + $H^+$], calcd. 276. l, found, 276.0. **Compd.12:** $^1$H NMR ($d_6$-DMSO) δ 7.l l (d, *J* = 8.0 Hz, l H), 7.4l (dd, *J* = 7.9 Hz, 1 H), 7.53 (s, l H), 7.69-7.78 (m, 3 H), 7.9l (d, *J* = 7.0 Hz, l H) and 8.02-8.ll (m, 5 H); CIMS for $C_{18}H_{14}NO_2$, [M + $H^+$], calcd. 276.1; found, 276.0.

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