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# Solid-phase synthesis of 1,4-diketones by thiazolium salt promoted addition of aldehydes to chalcones†

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**Abstract**—The first report of thiazolium salt promoted Michael addition of aldehydes to chalcones (Stetter reaction) on solid-phase is reported. Reaction conditions have also been devised for cleaving the product 1,4-diketone from the solid-support in good yield and high purity. 

Parallel synthesis has developed into a powerful tool for the creation of new chemical entities for drug discovery.[1] Solid-phase synthesis has a number of advantages over conventional solution-phase synthesis and is extensively employed although considerable effort and time are required for optimising the reactions. There is an increasing need to expand both the number of available transformations on solid-phase to prepare libraries and the structural diversity present in those libraries. The cyanide ion[2] or thiazolium salt[3] catalysed addition of aldehydes to Michael acceptors in the presence of a base to afford 1,4-dicarbonyl compounds (Stetter reaction) is a transformation that permits generation of structural variety efficiently. A minimum of three elements of diversity, two from the Michael acceptor and one from the aldehyde, can be introduced into the product using this reaction. 1,4-Diketones are useful intermediates in the synthesis of cyclopentenones[4] and in the synthesis of heterocycles such as furans,[5] pyrroles,[6] thiophenes[7] and pyrrolidines.[8]

As a continuation of our studies[9] aimed at adapting strategically important processes to solid-phase, we disclose herein the first report of the preparation of 1,4-diketones by the thiazolium salt promoted addition of aliphatic, aromatic and heteroaromatic aldehydes to chalcones. The chalcones were chosen as the Michael acceptors because of the ease of their preparation and by virtue of their incorporating two elements of diversity, one each coming from an aldehyde and an acetophenone (Eq. (1)).

The chalcones **1A–D**, readily prepared[10] by aldol condensation in the solution-phase were anchored to the Wang resin through the phenolic group using the Mitsunobu protocol. After much experimentation, initially in the solution-phase and later on the solid-phase, optimal conditions were developed for the Stetter reaction. Thus refluxing the mixture of resin bound chalcone, aldehyde (9.0 equiv.), $Et_3N$ (9.0 equiv.), thiazolium salt (1.5 equiv.), in dioxane/EtOH (8:2, v/v) for 30 h under a nitrogen atmosphere afforded the 1,4-diketone in moderate to good yield after cleavage from the solid-support. A total of twelve diketones was prepared by reacting four chalcones (**1A–D**) with different aldehydes (Table 1). The reactions of aromatic and heteroaromatic aldehydes were promoted by thiazolium salt **I**[11] whereas reactions of aliphatic aldehydes were promoted by thiazolium salt **II**.[11] The following observations are worthy of note: the chalcones (**1B–D**) linked by the 3-OH group to the solid support reacted more readily to afford products in higher yield than the chalcone **1A** bound by the 4-OH group. Delocalisation of electrons from the resin bound ether oxygen to the carbonyl group in **1A** would make it a poorer Michael acceptor in comparison to chalcones **1B–D** wherein such a delocalisation of electrons is not possible. Aliphatic and heteroaromatic aldehydes afforded products in higher yield than aromatic aldehydes. This outcome was not surprising since cyanide catalysis was found to be most satisfactory for the reaction of aromatic aldehydes with chalcones in the solution-phase. Attempted cyanide ion catalysis of the reaction


(1)

*Keywords*: solid-phase; Stetter reaction; thiazolium salt; DDQ.

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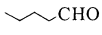
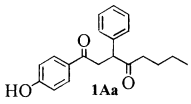
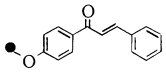
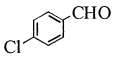
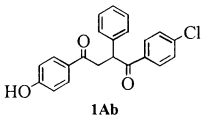
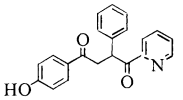
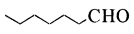
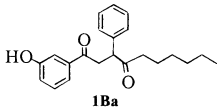
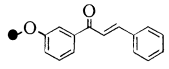
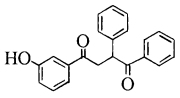
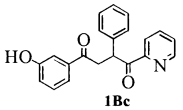
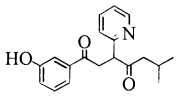
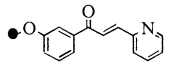
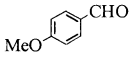
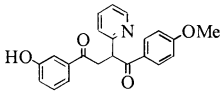
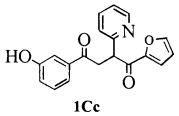
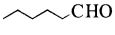
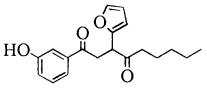
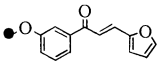
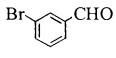
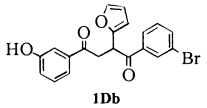
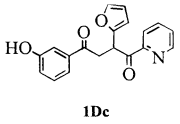
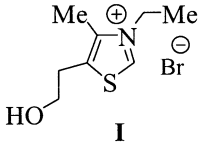
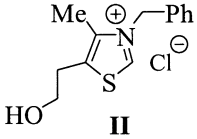
**Table 1.**

| Chalcone | Aldehyde | 1,4-Diketone | Yield (%) |
|---|---|---|---|
| |  |  **1Aa** | 70 |
|  **1A** |  |  **1Ab** | 55 |
| |  |  **1Ac** | 65 |
| |  |  **1Ba** | 75 |
|  **1B** |  |  **1Bb** | 57 |
| |  |  **1Bc** | 72 |
| |  |  **1Ca** | 70 |
|  **1C** |  |  **1Cb** | 55 |
| |  |  **1Cc** | 71 |
| |  |  **1Da** | 70 |
|  **1D** |  |  **1Db** | 60 |
| |  |  **1Dc** | 55 |

with aromatic aldehydes in DMF as the solvent failed to give any 1,4-diketone after cleavage from the solid support. While the products elaborated from chalcones **1A**–**C** could be cleaved with 25% TFA/DCM in high yield and purity, identical conditions led to a complex mixture of products from **1D**. DDQ[12] in DCM/water was used to liberate products elaborated from **1D** in high yield and purity.



**I**



**II**

In conclusion, we have adapted the important C–C bond forming Stetter reaction, to solid-phase. The product 1,4-diketones are important intermediates in the synthesis of heterocycles and cyclopentenone.

## Typical experimental procedure and data for representative examples

**Mitsunobu reaction**: To the suspension of Wang resin (1 g, 1.7 meq./g, 150–300 μM, 2% DVB) in THF (10 mL), the chalcone **1B** (1.14 g, 5.1 mmol) and triphenylphosphine (1.34 g, 5.1 mmol) were added and gently stirred at 0°C for 15 min. DEAD (0.89 g, 5.1 mmol) was added dropwise and the mixture was stirred for 16 h gradually allowing it to attain rt. The resin was collected by filtration and washed successively with THF (3×20 mL), dioxane (3×20 mL), DCM (3×20 mL), 1:1 DCM/MeOH (3×20 mL), MeOH (3×20 mL), DCM (3×20 mL) and finally with ether (3×20 mL). The resin was dried in vacuo and used in the next step.

**Aromatic/heteroaromatic aldehyde addition**: The catalyst **I** (80 mg, 0.32 mmol), $Et_3N$ (0.42 g, 5.67 mmol) and benzaldehyde (0.6 g, 5.67 mmol) were added successively to the resin (0.5 g, 1.26 meq./g) suspended in dioxane/EtOH (5 mL, 8:2, v/v) and heated at reflux. Another portion (80 mg) of the thiazolium salt was added at the end of 10 and 20 h and the mixture refluxed for a total of 30 h from the commencement of the reaction. The resin was then filtered and washed as mentioned above to afford the diketone **1Bb** on the solid support.

**Cleavage using TFA**: The resin bound product **1Bb** (0.2 g, 1.1 meq./g) was suspended in 25% TFA/DCM and stirred at rt for 4 h. The resin was filtered and washed with DCM (3×10 mL). The combined filtrates were evaporated and the residue dissolved in DCM and washed successively with satd aq. $NaHCO_3$, water and brine. Drying over $Na_2SO_4$ and evaporation of the solvent gave a crude product which was purified by column chromatography on silica gel using EtOAc/pet. ether as the eluent to afford **1Bb** (41 mg, 57%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.97 (d, $J=6.7$ Hz, 2H), 7.47–6.96 (m, 12H), 5.26 (dd, $J=10.4$, 3.7 Hz, 1H), 4.12 (dd, $J=18.6$, 10.4 Hz, 1H), 3.19 (dd, $J=18.6$, 3.7 Hz, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 199.9, 198.6, 156.4, 138.2, 137.5, 136.2, 133.0, 129.6, 129.1, 128.8, 128.4, 128.1, 127.3, 120.7, 120.2, 114.7, 48.7, 43.8. $m/z$ (EI) 330 (5), 225 (100), 121 (50).

**1Aa**: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.50 (d, $J=4.1$ Hz, 1H), 7.67–7.0 (m, 8H), 4.60 (dd, $J=9.6$, 5.5 Hz, 1H), 3.95 (dd, $J=19.2$, 9.6 Hz, 1H), 3.25 (dd, $J=19.2$, 5.5 Hz, 1H), 2.68–2.35 (m, 2H), 1.68–1.47 (m, 2H), 1.21–1.12 (m, 2H), 0.80 (t, $J=8.2$ Hz, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 211.2, 197.2, 161.3, 137.9, 130.6, 129.1, 128.8, 128.3, 127.5, 115.4, 53.4, 42.0, 41.7, 25.6, 22.0, 13.7. $m/z$ (FAB) 311 (65), 281 (28), 121 (100).

**1Cc**: $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 9.20 (brs, 1H), 8.50 (m, 1H), 7.64–6.92 (m, 9H), 6.50 (m, 1H), 5.25 (dd, $J=9.5$, 4.4 Hz, 1H), 4.10 (dd, $J=18.3$, 9.5 Hz, 1H), 3.42 (dd, $J=18.3$, 4.4 Hz, 1H). $^{13}$C (50 MHz, $CDCl_3$+DMSO-$d_6$) $\delta$ 196.5, 185.2, 156.7, 151.0, 148.6, 145.8, 136.7, 136.1, 128.6, 122.3, 121.3, 119.7, 118.1, 117.6, 113.7, 111.4, 50.2, 46.0. $m/z$ (EI) 321 (50), 201 (100).

**Cleavage using DDQ**: To the resin-bound product **1Db** on the solid support (0.2 g, 1.03 meq./g) suspended in DCM/water (4.0 mL, 9.5:0.5, v/v), DDQ (0.14 g, 0.6 mmol, 3.0 equiv.) was added and the mixture stirred at rt for 4 h. The resin was filtered and washed thoroughly with DCM. The combined filtrates were washed successively with aq. satd $NaHCO_3$, water and brine. Drying over sodium sulfate and evaporation afforded the crude product which was purified by column chromatography to afford **1Db** (50 mg, 60%). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.13 (s, 1H), 7.96 (d, $J=8.2$ Hz, 1H), 7.62 (d, $J=8.2$ Hz, 1H), 7.48 (d, $J=8.2$ Hz, 1H), 7.40–7.20 (m, 4H), 7.0 (d, $J=8.2$ Hz, 1H), 6.25 (m, 1H), 6.10 (m, 1H), 5.30 (dd, $J=9.6$, 2.8 Hz, 1H), 4.05 (dd, $J=17.8$, 9.6 Hz, 1H), 3.34 (dd, $J=17.8$, 2.8 Hz, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 197.5, 195.5, 156.1, 150.6, 142.5, 137.9, 137.5, 131.8, 131.1, 130.2, 129.9, 127.4, 122.9, 120.9, 120.7, 111.2, 110.2, 107.2, 42.3, 40.7. $m/z$ (EI) 398 (5), 121 (25).

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