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# Stereoselective Synthesis of Highly Functionalised Pyrrolidines *via* 1,3-Dipolar Cycloaddition Reactions on a Solid Support.

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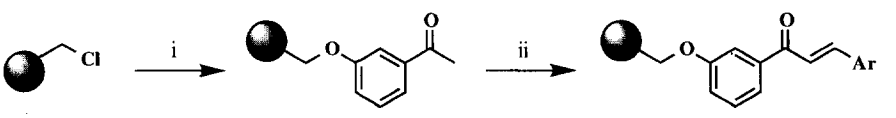
**Abstract:** Resin bound 3-hydroxyacetophenone **2** was condensed (NaOMe/MeOH/THF) with aryl aldehydes to afford α,β-unsaturated ketones **3a-e**. Subsequent reaction with azomethine ylid **5** in the presence of LiBr/DBU provided pyrrolidines **6a-d**. These were subsequently acylated and cleaved from the solid support to afford highly functionalised pyrrolidines **8a-d**.


Solid phase synthesis has become an increasingly important tool for the rapid synthesis of libraries comprising large numbers of compounds for screening as potential drug candidates.[1] Currently this overall approach is limited to some degree due to the nature of the chemistry which may be applied to solid phase, which ultimately may influence the structural class of compounds available in this manner. As a part of our own combinatorial research effort we have been interested in broadening the scope of reactions which lend themselves to this technique to facilitate the synthesis of diverse libraries of complex organic molecules.

The mild reaction conditions of 1,3-dipolar cycloadditions[2] (often ambient temperature) and the construction of multiple bonds in a single transformation made this chemistry highly attractive for the solid phase synthesis of heterocyclic compounds. There has been success regarding the polymer supported 1,3-dipolar cycloaddition reaction of nitrile oxides.[3] Recent reports[4] relating the synthesis of pyrrolidines *via* 1,3-dipolar cycloaddition reactions of resin bound Schiff bases has prompted us to disclose our own results in this area.

The preparation of pyrrolidines *via* cycloaddition reactions of azomethine ylids has been extensively studied.[2] Nevertheless, there are few reports[5] of the reaction of azomethine ylids with α,β-unsaturated ketones and this transformation was chosen for an initial investigation of this chemistry on a solid support.

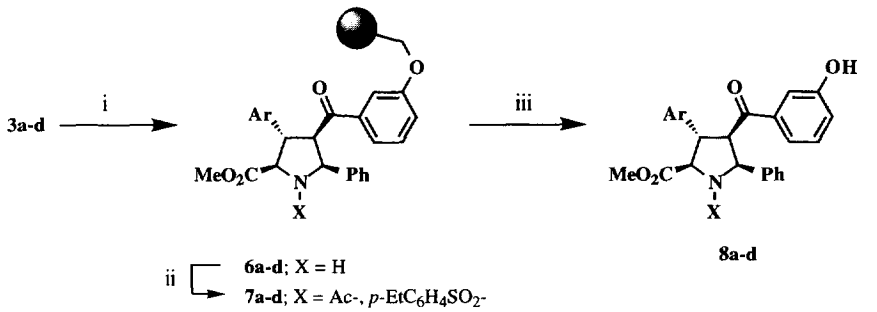



| | Ar |
|---|---|
| a | p-$C_6H_4OMe$ |
| b | p-$C_6H_4Br$ |
| c | o,p-di$Cl_2C_6H_4$ |
| d | 1-napthyl |
| e | p-$PhC_6H_4$ |

i. 3-Hydroxyacetophenone, $Cs_2CO_3$, NaI, DMF. ii. ArCHO (12 equiv.), NaOMe (0.5M solution in MeOH, 12 equiv.), THF. iii. TFA-$CH_2Cl_2$

3-Hydroxyacetophenone was coupled to chlorinated Wang resin[6] **1** with $Cs_2CO_3$/NaI in DMF to give **2**. The loading capacity was determined to be 0.49 mmol/g (starting Wang resin was 0.93 mmol/g) by TFA hydrolysis of a known amount and subsequent HPLC analysis. Initial attempts to condense resin bound 3-hydroxyacetophenone **2** with aldehydes employing KOH-THF-$H_2O$ or KO$^t$Bu-THF conditions failed. NaOMe (as a 0.5M solution in MeOH) was found to be the base of choice. However a co-solvent with suitable resin swelling properties is necessary to ensure complete conversion to enone product. Both toluene and THF were found to be satisfactory, although THF gave more consistent results with larger scale reactions. Typically 12 equivalents of both aldehyde and NaOMe (0.5M in MeOH) were added to resin (pre-swelled in an equal volume of THF) to afford the required enones **3a-e**. Cleavage by TFA hydrolysis provided clean hydroxy enones **4a-e** (by comparison with authentic material prepared independently by standard solution methods[7]).

Enones **3a-d** were subjected to standard 1,3-dipolar cycloaddition reaction conditions[2] with N-metallated azomethine ylid **5** in the presence of DBU and a Lewis acid. In our hands LiBr[8] proved to be the catalyst of choice[9] and provided highly substituted pyrrolidine products **6a-d** with high regio- and diastereoselectivity[10], consistent with results observed in solution by Pätzel.[5]




i. $PhCH{=}NCH_2CO_2Me$ **5**, LiBr, DBU, THF. ii. acylating agent, py, DMAP, $CH_2Cl_2$. iii. TFA-$CH_2Cl_2$

**Table 1. Yields of Purified Products Following Resin Cleavage**

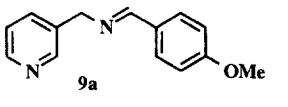
| product | Ar | acylating agent X | Yield‡(%) |
|---|---|---|---|
| **8a** | **p-$C_6H_4OMe$** | **AcCl** | **45** |
| **8b** | **p-$C_6H_4Br$** | **AcCl** | **32** |
| **8c** | **o,p-di$Cl_2C_6H_4$** | **p-$EtC_6H_4SO_2Cl$** | **68** |
| **8d** | **1-napthyl** | **p-$EtC_6H_4SO_2Cl$** | **31** |

‡yields are for purified products and are calculated from acetophenone resin **2** and are unoptimised

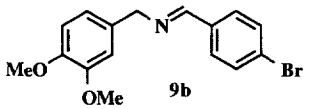
The pyrrolidines **6a-d** could also be conveniently reacted with acid chlorides and sulphonyl chlorides as shown in Table 1. Cleavage from the resin (TFA-$CH_2Cl_2$) yielded the highly functionalised crude pyrrolidine products **8a-d**[11] (see Table 1) which could be purified by chromatography or crystallisation.

However, when imines **9a** or **9b** were reacted under analagous conditions (LiBr, DBU, THF) with resin bound enones **3c** or **3e** the 1,3-dipolar cycloaddition reaction products **10a** or **10b** were not observed upon TFA mediated cleavage, and the enones **4c** and 4e, respectively, were isolated. This was also the result

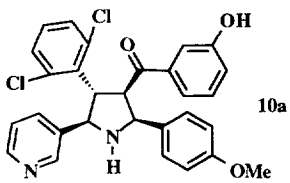
when AgOAc was employed as the Lewis acid during the reaction of **9a** with **4e**, although there is literature precedent for reaction of similar aryl imines.[2f] This may be a consequence of steric problems associated with the resin.



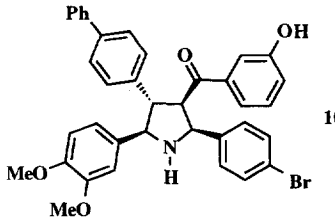

**9a**




**9b**




**10a**




**10b**

In summary we have been able to demonstrate the solid phase synthesis of highly substituted pyrrolidines *via* 1,3-dipolar cycloaddition chemistry, which exemplifies the utility of this general technique for the preparation of libraries of complex molecules in a combinatorial fashion.

**Acknowedgement.** We would like to thank Thomas Mitchell for analytical support and Steven E. Hall for constructive comments during the preparation of this manuscript.

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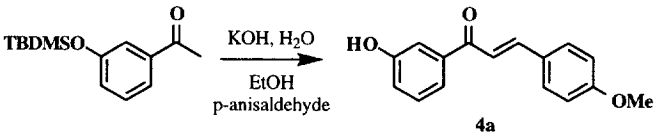
7. For example, compound **4a** was prepared according to the following scheme:




4a

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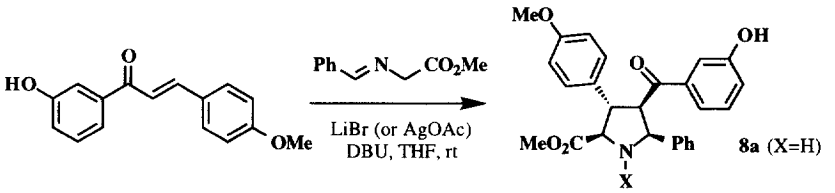
9. AgOAc reportedly affords higher stereoselectivity in some cases as compared to LiBr (see ref. 5) and is sometimes the favored catalyst (see refs. 2a-c). For most examples to date the major diastereisomer has been formed with > 85% selectivity when LiBr has been employed as the Lewis acid.

10. TFA hydrolysis of resin at this point afforded (following basic work-up to free base the TFA salt) N-unsubstituted pyrrolidines (**8a-d**, X=H), also prepared independently in solution. For example, **8a** was synthesised *via* the following scheme:




11. A typical experimental procedure for the synthesis of **8a**: A solution of NaOMe in MeOH (31.3 mL of a 0.5M solution in MeOH, 15.6mmol: *ex* Aldrich) was added to a mixture of acetophenone resin **2a** (2.66g) and *p*-anisaldehyde (2.36g, 15.6mmol) in anhydrous THF (30 mL). The flask was capped and placed on an orbital shaker for 4 days. The reaction mixture was filtered and washed sequentially with the following solvents (50 mL of each): THF, MeOH, THF, MeOH and finally THF. The resin was dried with air pulling through the Buchner funnel to give 3.0g of resin **3a**. Resin **3a** (1g) was suspended in anhydrous THF. To this was added sequentially imine **5** (Ar'=Ph) (434 mg as a solution in dry THF), LiBr (255 mg, 2.94mmol) and DBU (372 mg, 2.45mmol). The reaction mixture was slowly stirred for 3 days at which time the resin was filtered and washed sequentially (20 mL of each) with MeOH, THF, MeOH, THF, MeOH, THF, $CH_2Cl_2$ and air dried to give resin **6a**. A portion (300 mg) was suspended in anhydrous methylene chloride and DMAP (3 mg), pyridine (190 ul, 2.35mmol) and acetyl chloride (1.18 mL of a 1M solution in methylene chloride, 1.175mmol) were added in sequence. The mixture was stirred at ambient temperature for 20hr, at which time the resin was filtered and washed (10 mL of each) with $CH_2Cl_2$, DMF, MeOH, DMF, MeOH, DMF, $CH_2Cl_2$. The resin was air dried and suspended in a 1:1 (v/v) mixture of $CH_2Cl_2$:TFA and stirred at ambient temperature for 20hr. The supernatant liquid was removed by filtration and the resin washed several times with methylene chloride. The filtrates were evaporated *in vacuo* to yield a crude brown foam (90 mg) which was purified by chromatography ($SiO_2$, 3:2 EtOAc-hexanes) to afford pyrrolidine **8a** (31 mg, 45%), which could be recrystallised from methanol. FAB MS 474 (M+1). HRMS calcd. for $C_{28}H_{28}NO_6$ (M+1) 474.19108. Found 474.19107. IR (KBr) 1739, 1675, 1621 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\partial_H$ 1.85 (3H, s), 3.67 (3H, s), 3.70 (3H, s), 4.25 (1H, t, J=11.5Hz), 4.54 (1H, d, J=11.1Hz), 4.77 (1H, dd, J=8.8, 12.1Hz), 5.48 (1H, d, J=8.36Hz), 6.70 (2H, d, J=8.7Hz), 7.03-7.41 (11H, m). Anal. Calcd. for $C_{28}H_{27}NO_6.0.3H_2O$: C 70.22. H 5.81. N 2.92. Found C 70.52. H 6.05. N 2.85.

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