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Solid phase synthesis of α-acylamino-α,α-disubstituted ketones

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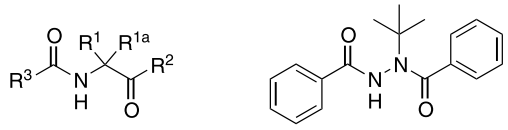
Abstract—α-Acylamino-α,α-disubstituted ketones are of interest as ecdysone agonists. Solid phase synthesis of prototypical α-acylamino-α,α-disubstituted ketones on two different solid supports is described. In both cases the ketone was formed by reaction of a Grignard reagent with an *N*-acyl-α,α-disubstituted amino acid immobilized through its carboxylate as a Weinreb amide derivative.

As part of a program to discover ecdysone agonists for use in systems to control gene expression via natural and engineered ecdysone receptors, we became interested in α-acylaminoketones of general structure **1**. With appropriate substituents at the R^1, R^{1a}, R^2 and R^3 positions, these compounds are potentially bioisosteric with known diacyl hydrazine ecdysone agonists e.g. **2** (Fig. 1).[1,2] To investigate this hypothesis we sought a solid phase synthesis of **1** which would be sufficiently general to allow production of a library of compounds for biological screening.



1 **2**

Figure 1. α-Acylamino-α,α-disubstituted ketones **1** and diacylhydrazine **2**.

A number of solid phase syntheses of ketones,[3–22] including α-acylaminoketones,[10–22] have been reported in the literature. The syntheses of α-acylaminoketones have utilized a variety of strategies to link the synthetic intermediates to the polymeric support including linking through the nitrogen,[10–12] through a functional group remote from the ketone,[13–17] through the ketone itself as a hydrazone derivative[18–20] or employing a carboxylic acid derivative as the incipient ketone.[21,22]

We were particularly attracted to the last approach since it would allow complete construction of the desired compounds **1** on solid phase (Scheme 1). Thus, resin bound Weinreb amides **3** could plausibly be assembled from *N*-protected α,α-disubstituted amino acids **6** and carboxylic acids **7**. Treatment of **3** with Grignard reagents **4** should liberate the desired α-acylaminoketones **1**. Large numbers of carboxylic acids **7** and certain *N*-protected α,α-disubstituted amino acids **6** and Grignard reagents **4** are commercially available rendering production of a large library a practical undertaking. However, α,α-disubstituted amino acids are known to be problematic in peptide synthesis because of their steric bulk[23] and we anticipated that we might encounter similar difficulties using them. Furthermore, during the course of this work, O'Donnell and Scott reported that *t*-BuMgBr failed to give any of the desired ketone when reacted with a resin bound intermediate not dissimilar to **3**, suggesting that the addition of a Grignard reagent to a resin bound Weinreb amide is susceptible to steric hindrance.[22] Nonetheless, we embarked upon an effort to reduce the

Abbreviations: Aib, α-aminoisobutyric acid; DIC, *N*,*N*′-diisopropylcarbodiimide; EDC, 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide; Fmoc, 9-fluorenylmethoxycarbonyl; HOAt, 1-hydroxy-7-azabenzotriazole; HATU, *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridino-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; *i*-Pr_2Net, *N*,*N*-diisopropylethylamine; NMP, *N*-methylpyrrolidin-2-one; PAS-FTIR, photoacoustic Fourier transform infrared spectroscopy; TFA, trifluoroacetic acid; TFFH, tetramethylfluoroformamidinium hexafluorophosphate.

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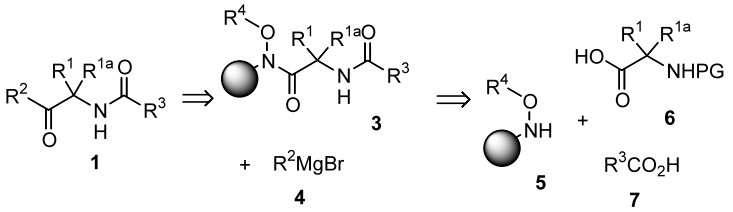
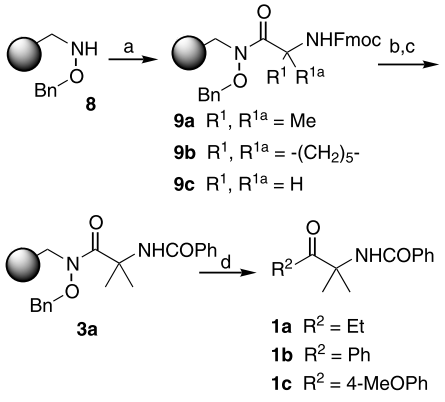


Scheme 1. Retrosynthesis of α-acylamino-α,α-disubstituted ketones **1**.

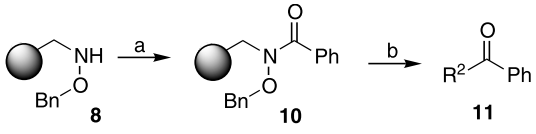
approach outlined retrosynthetically in Scheme 1 to practice, initially using the benzyloxyamino resin **8** reported by Salvino[8] and subsequently employing the commercially available Weinreb amide resin **13** developed by Martinez.[24]

Benzyloxyamino resin **8** (Scheme 2) was prepared from Wang resin following the literature procedure[8] and the intermediates were characterized by PAS-FTIR. Product resin **8** itself was characterized both by PAS-FTIR and by cleavage of a portion with TFA/CH_2Cl_2 (1:1) to afford $C_6H_5CH_2ONH_2$. Fmoc-Aib-OH (**6a**) was selected as a prototypical α,α-disubstituted amino acid for coupling to **8** and the extent of conversion of **8** to **9a** was estimated based on PAS-FTIR.[25] A number of standard peptide coupling conditions were explored and failed to give satisfactory conversion to the amide **9a** (Table 1, entries 1–6). Use of the amino acid fluoride prepared in situ using TFFH (entry 7) or isolated from reaction of Fmoc-Aib-OH and DAST (entry 8)[26] afforded slightly improved conversion. Proceeding through the synthetic sequence with incompletely loaded samples of **9a** proved problematical. Benzyloxyamino groups that had not reacted with **6a** were available for coupling with benzoic acid (**7a**) affording **10** (Scheme 3). Grignard reagents effectively converted **10** to phenyl ketones **11**. Finally, significantly improved loading was effected using the symmetrical anhydride of **6a**, prepared in situ by treatment of **6a** with 0.5 equiv. of DIC in a mixture of CH_2Cl_2 and DMF (entry 9).[27] Submitting the resin to a second cycle of coupling increased the level of conversion of **8** to **9a** to 91% (entry 10). The Fmoc protecting group was removed from **9a** under standard conditions and benzoic acid was smoothly coupled to the free amino group using DIC/HOAt to afford **3a**. Resin bound intermediates **9a** and **3a** exhibited satisfactory PAS-FTIR spectra. Treatment of **3a** with excess EtMgBr afforded **1a** in 60% yield based on the initial functionalization of the resin. The chemistry was successfully extended to aromatic Grignard reagents. Reaction of **3a** with excess of PhMgBr afforded **1b** in 31% yield. The major impurity in the crude product was biphenyl derived from the Grignard solution used. Examination of the spent resin from this reaction by PAS-FTIR revealed the presence of peaks corresponding to unreacted **3a**, possibly accounting for the low yield. Reaction of **3a** with 4-methoxyphenylmagnesium bromide failed to give **1c**; ^{1}H NMR and LC MS indicated that the major component in the crude product was 4,4′-dimethoxy-1,1′-biphenyl, present in the Grignard solution used. Furthermore, application of the optimum coupling conditions developed for Fmoc-Aib-OH to Fmoc protected 1-aminocyclohexane-1-carboxylic acid (**6b**) gave only 37% conversion to amide **9b** by PAS-FTIR.

The difficulties in effecting complete coupling of **6a** to **8** and in achieving efficient reaction of **3a** with Grignard reagents were apparently due at least in part to steric hindrance around the benzyloxyamino functionality. This prompted us to explore the use of methoxyamino resin **13**, available by deprotection of commercially available **12** (Scheme 4). The methoxyamino group in **13** is presumably more accessible than the benzyloxyamino group in **8**. Acylation of **13** with Fmoc-Aib-OH (**6a**) was carried out using the symmetric anhydride of **6a** under conditions described above (Table 1, entry 10) to afford **14** with 66% conversion. Removal of the Fmoc protecting group with piperidine in DMF gave **15** and coupling benzoic acid (**7a**) to the free amino group afforded **16**. Treatment of **16** with excess of EtMgBr (**4a**) provided **1a** in 51% yield based on the



Scheme 2. (a) FmocNHCR^{1}R^{1a}CO$_2$H (**6**, 10 equiv.), DIC (5 equiv.), CH_2Cl_2/DMF (7:3), 3 days, rt; (b) piperidine/DMF (1:4), 20 min, rt; (c) PhCO$_2$H (**7a**, 10 equiv.), DIC (10 equiv.), HOAt (10 equiv.), 5 h, rt; (d) R^{2}MgBr (**4**, 10 equiv.), THF$_{(anh)}$, 18 h, rt.

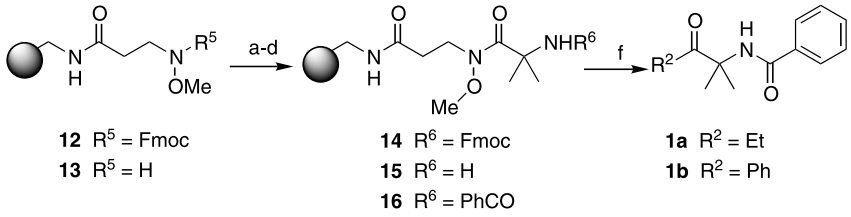


Scheme 3. (a) PhCO$_2$H (10 equiv.), DIC (10 equiv.), HOAt (10 equiv.), 5 h, rt; (b) R^{2}MgBr (**4**, 10 equiv.), THF$_{(anh)}$, 18 h, rt.

Table 1. Optimization of loading Fmoc-Aib-OH (**6a**) onto resin **8**[a]

Entry	Reagents (equivs)	Solvent	Time (days)	Conversion[b]
1	**6a** (4), DIC (4), HOAt (4)	DMF	3	28
2	**6a** (4), DIC (4), HOAt (4)	DMF	2 × 3	32
3	**6a** (4), HATU (4), *i*-Pr_2NEt (8)	DMF	3	20
4	**6a** (5), EDC (5)	DMF	3	15
5	**6a** (5), EDC (5), HOAt (4.5)	DMF	3	30
6	**6a** (5), DIC (5), HOAt (5), *i*-Pr_2NEt (5)	NMP	3	20
7	**6a** (5), TFFH (5), *i*-Pr_2NEt (10)	DMF	2	40
8	Fmoc-Aib-F (5)[c]	DCM	1	42
9	$(Fmoc\text{-}Aib)_2O$ (5)[d]	DCM/DMF (7:3)	3	83
10	$(Fmoc\text{-}Aib)_2O$ (5)[d]	DCM/DMF (7:3)	2 × 3	91

[a] All reactions were run at room temperature.
[b] The conversion was measured by photoacoustic infrared spectroscopy. See Ref. 25.
[c] Fmoc-Aib-F, the acid fluoride of **6a**, was prepared from **6a** and DAST. See Ref. 26.
[d] $(Fmoc\text{-}Aib)_2O$, the symmetrical anhydride of **6a**, was prepared immediately prior to use by treatment of **6a** with 0.5 equiv. of DIC. See Ref. 27.



Scheme 4. (a) piperidine/DMF (1:4), 20 min, rt; (b) Fmoc-Aib-OH (**6a**, 10 equiv.), DIC (5 equiv.), CH_2Cl_2/DMF (7:3), 3 days, rt; (c) piperidine/DMF (1:4), 20 min, rt; (d) $PhCO_2H$ (**7a**, 10 equiv.), DIC (10 equiv.), HOAt (10 equiv.), 5 h, rt; (e) R^2MgBr (**4**, 10 equiv.), $THF_{(anh)}$, 18 h, rt.

initial functionalization of the resin while excess PhMgBr (**4b**) afforded **1b** in 36% yield.[28] Again, the major impurity in **1b** was biphenyl and examination of the spent resin revealed the presence of peaks corresponding to unreacted **16**. Based on these results, resin **13** did not offer any improvement over **8**.

In conclusion, we demonstrated solid phase synthesis of prototypical α-acylamino-α,α-disubstitutedketones **1a** and **1b**. However, the purity of the crude products, resulting from inefficient conversion in certain steps and the presence of typical side-products formed during the Grignard reactions in the cleavage solution, does not make this route the most suitable for library production.

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25. To provide a reference standard, Fmoc-Gly-OH (**6c**) was coupled to resin **8** to afford **9c** (Scheme 2). Complete conversion was demonstrated by magic angle spinning ^{1}H NMR. The carbamate (1722 cm^{-1}) and amide carbonyl (1665 cm^{-1}) stretches in the PAS-FTIR of **9c** were integrated and normalized with respect to the aromatic C=C stretch (1611 cm^{-1}). Comparison of the normalized integrals of the carbamate and amide carbonyl stretches in samples of **9a** allowed % conversion to be estimated. These values were confirmed in certain cases by measuring the UV absorbance of the piperidine–dibenzofluvene adduct released when the Fmoc group was removed from **9a**.
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28. The following experimental procedure is representative. **Preparation of 16.** Fmoc-Aib-OH (**6a**, 0.615 g, 1.89 mmol, 10 equiv.) and DIC (0.146 mL, 0.945 mmol, 5 equiv.) were dissolved in 3 mL of CH_2Cl_2/DMF (7:3). The mixture was stirred at room temperature for 10 min, the resultant precipitate (*N*,*N*′-diisopropylurea) was removed by filtration, and the filtrate was added to methoxyamino resin **13** (0.3 g, 0.189 mmol, 0.63 mmol/g). The mixture was shaken at room temperature for 3 days and drained. The resin was washed with DMF (10×5 mL), and CH_2Cl_2 (10×5 mL) to afford **14**. PAS-FTIR Fmoc carbamate C=O stretch: 1726 cm^{-1}, amide C=O stretch 1632 cm^{-1}, resin amide C=O stretch 1678 cm^{-1}. The conversion was 66% determined by PAS-FTIR. Resin **14** (0.3 g, 0.189 mmol, 0.63 mmol/g) was suspended in 20% piperidine in DMF (7 mL), and the reaction mixture was stirred for 20 min. The solution was drained, and the resin was washed thoroughly with DMF (5×5 mL), and CH_2Cl_2 (5×5 mL) to leave **15**. To the obtained resin **15** was added benzoic acid (0.231 g, 1.89 mmol, 10 equiv.), HOAt (0.257 g, 1.89 mmol, 10 equiv.), and DIC (0.293 mL, 1.89 mmol, 10 equiv.) in 3 mL of DMF. The reaction was shaken for 5 h and drained. The resin was washed with DMF (5×5 mL) and CH_2Cl_2 (5×5 mL) to afford **16**. PAS-FTIR resin amide C=O stretch 1678 cm^{-1}, amide bound to the solid support C=O stretch: 1631 cm^{-1}, benzamide C=O stretch 1653 cm^{-1}. **Preparation of 1b.** To a suspension of **16** (0.1 g, 0.063 mmol, 0.63 mmol/g), in anhydrous THF (2 mL) under an atmosphere of argon was added a 1 M solution of phenylmagnesium bromide in THF (**4b**, 0.63 mL, 0.63 mmol, 10 equiv.). The reaction mixture was shaken for 18 h and quenched by addition of 1 M HCl:THF (1:1). The pH of the resulting solution was $\sim$3. The mixture was stirred for 30 min. The solution was drained into a vial, and the resin was washed with THF (3×2 mL). The combined filtrates were evaporated to dryness, and the residue was dissolved in THF. The solution was applied to a silica gel solid phase extraction cartridge which was eluted with CH_2Cl_2 (2×2 mL). The eluate was concentrated to leave a crude product (21 mg) containing 38% of **1b** and 46% of biphenyl. The crude product was subjected to flash chromatography using hexane:ethyl acetate (1:1), and the appropriate fractions were pooled and evaporated to give **1b** (6 mg, 36%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (s, 6H), 6.84 (bs, 1H), 7.30–7.57 (aromatic H's, 8H), 7.88 (dd, J=8, 1.6 Hz, 2H). MS (ESI, positive ion): m/z 268.3 $(M+1)^+$. In addition biphenyl (10 mg) was isolated. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25–7.45 (aromatic H's, 6H), 7.64 (dd, J=7.6, 1.2 Hz, 4H).