Pergamon

Tetrahedron Letters 43 (2002) 7495–7498

TETRAHEDRON LETTERS

Combined solid phase and solution synthesis of a library of α,α-disubstituted-α-acylaminoketones

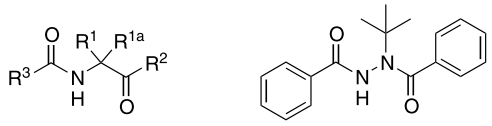
Javier Garcia,[a,b] Ernesto Nicolàs,[a] Fernando Albericio,[a,*] Enrique L. Michelotti[b,*,†] and Colin M. Tice[c]

[a]*Department of Organic Chemistry, University of Barcelona, 08028 Barcelona, Spain*
[b]*Rohm and Haas Company, PO Box 904, 727 Norristown Road, Spring House, PA 19477-0904, USA*
[c]*RHeoGene Inc., PO Box 949, 727 Norristown Road, Spring House, PA 19477-0949, USA*

Received 12 August 2002; revised 23 August 2002; accepted 26 August 2002

Abstract—Preparation of a demonstration library of α,α-disubstituted-α-acylaminoketones, of interest as ecdysone agonists, is described. The five-step synthetic sequence employed α,α-disubstituted amino acids, Grignard reagents and carboxylic acids as building blocks in a strategic combination of solid phase and solution steps.

α,α-Disubstituted-α-acylaminoketones of general structure **1** have been reported as antibiotics,[1] fungicides[2,3] and pesticides.[4] We became interested in this class of compounds, particularly those in which R^1 and R^{1a} are alkyl groups and R^2 and R^3 are aromatic rings, as potential bioisosteres of diacylhydrazine ecdysone agonists e.g. **2**[5] (Fig. 1). In the preceding paper, we reported on a solid phase approach in which the intermediates were linked to the resin via a Weinreb amide.[6] This approach afforded the desired products **1** in certain cases but was of limited utility due to a lack of generality in the building blocks that could be used and poor product purity. In an attempt to access a broader range of target compounds **1**, we explored the alternative approaches described here and achieved success with a combined solid phase and solution route.



1 **2**

Figure 1. α,α-Disubstituted-α-acylaminoketones **1** and diacylhydrazine **2**

Initially we explored a purely solution strategy starting with Boc-Aib-OH (**3a**) (Fig. 2) which was coupled with *N*,*O*-dimethylhydroxylamine using DCC to afford Boc protected Weinreb amide **4a** (Scheme 1). Treatment of **4a** with excess ethylmagnesium bromide (**5a**) in solution at room temperature under an inert atmosphere did not give the expected Boc protected α-aminoketone **6** but rather a mixture of the α-aminoketone **7a** and the symmetrical α-acylaminoketone **8**. Presumably **7a** and **8** arise from nucleophilic addition of the Grignard reagent to the carbonyl of the Boc group of **6**, followed by loss of either the anion of **7a** or *t*-butoxide anion to afford **8**.

Although α-aminoketones **7** can readily be acylated to afford the desired α-acylaminoketones **1**, the need to purify every intermediate at this stage was unattractive. In addition, we anticipated that when higher molecular weight substituted aromatic Grignard reagents were employed, the crude α-aminoketones **7** would be even less pure due to the presence of biphenyls that are often a byproduct of aromatic Grignard preparation and of non-volatile aromatic compounds from quenching the excess Grignard reagent. Performing the Grignard reaction on an intermediate that remained bound to a solid support would allow removal of these impurities by simple filtration and we thus chose to explore attachment of the Weinreb amide intermediate to a solid

Abbreviations: Aib, α-aminoisobutyric acid; Boc, *tert*-butoxycarbonyl; DCC, *N*,*N*′-dicyclohexylcarbodiimide; DIC, *N*,*N*′-diisopropylcarbodiimide; DMAP, 4-(dimethylamino)pyridine; DMF, *N*,*N*-dimethylformamide; HOAc, acetic acid; *i*-Pr_2NEt, *N*,*N*-diisopropylethylamine; NMM, *N*-methylmorpholine; NMP, *N*-methylpyrrolidin-2-one; PAS-FTIR, photoacoustic Fourier transform infrared spectroscopy; TFA, trifluoroacetic acid.

* Corresponding authors.
† Current address: Locus Discovery Inc., Four Valley Square, 512 Township Line Road, Blue Bell, PA 19422, USA.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01804-X

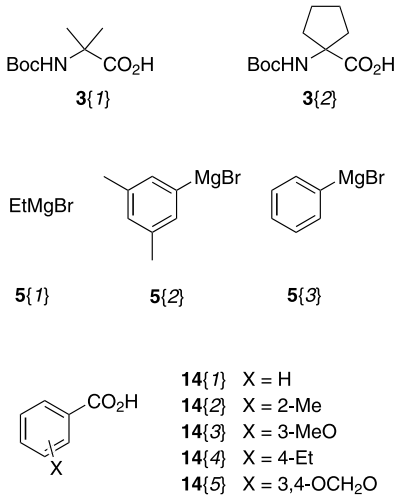
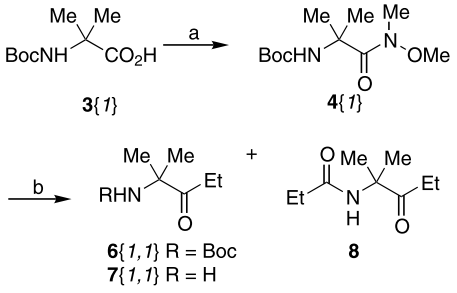


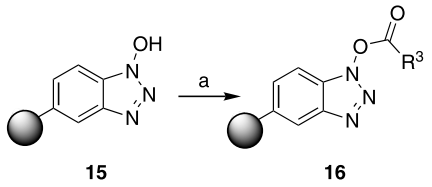
Figure 2. Reagents **3**, **5** and **14** used for production of demonstration library.



Scheme 1. (a) MeNHOMe·HCl (1.2 equiv.), DMAP (1.2 equiv.), *i*-Pr_2NEt (1.2 equiv.), DCC (1.2 equiv.), CH_2Cl_2, 25°C, 5 days; (b) EtMgBr **5a** (5 equiv.), THF, 25°C, 5 h.

support via its amino group,[7] and posterior acylation in solution after cleavage of the free aminoketone from the resin.

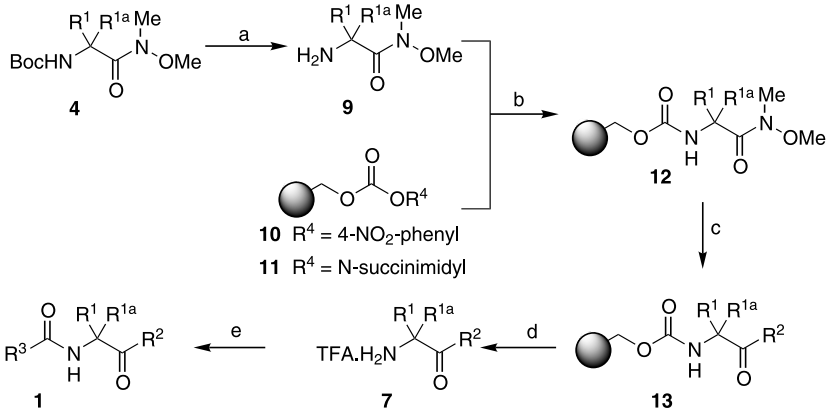
Thus, Boc protected Weinreb amide **4a** was deprotected with TFA to provide α-aminoamide **9a** as its TFA salt in 80% yield (Scheme 2). Wang resin was treated with *p*-nitrophenyl chloroformate and NMM in CH_2Cl_2 to produce the activated *p*-nitrophenyl carbonate resin



Scheme 3. (a) R^3CO_2H (**14**, 5 equiv.), DIC (5 equiv.), DMAP (1 equiv.), DMF/CH_2Cl_2 (1:1).

10,[8] which was incubated with excess **9a** in NMP at 60°C in the presence of *i*-Pr_2NEt to afford resin bound Weinreb amide **12a**. Alternatively **12a** could be prepared by reaction of **9a** with (*N*-succinimidyl)carbonate resin **11** at room temperature.[9] Treatment of resin **12a** with a large excess of ethylmagnesium bromide (**5a**) in dry THF afforded resin bound ketone **13a**. In contrast to the analogous solution phase reaction of **4a** with **5a**, the reaction of **12a** proceeded without disruption of the carbamate linker. Resin bound intermediates **10**, **12a** and **13a** were characterized by PAS-FTIR. The resonances in the carbonyl region were diagnostic. Cleavage of **13a** with wet TFA gave α-aminoketone **7a** as its TFA salt in 82% yield based on the initial functionalization of polymeric support **11**. The purity of **7a** was estimated at 85% based on ^1H NMR. The major impurity was **9a** which presumably resulted from cleavage of unreacted **12a** from the resin. To facilitate the purification of the products obtained in final coupling step, the polymer supported active ester **16a** was prepared from benzoic acid **14a**, supported HOBt and DIC (Scheme 3).[10] Thus, excess DIC, the corresponding urea and unreacted benzoic acid were removed by simple filtration and washings. The final conversion of **7a** to **1a** was accomplished using 1.5 equiv. of resin **16a**. LC MS indicated that the main impurities in the crude product were aminoketone **7a** and carboxylic acid **14a**. These were readily removed by treatment of the crude product with a weakly basic ion exchange resin followed by passage through a short column of silica gel to afford **1a**[11] in 87% yield and 83% purity by HPLC.[12]

Encouraged by these results, we embarked on production of the remaining members of a 25-compound



Scheme 2. (a) TFA/CH_2Cl_2 (1:1), 25°C, 20 min; (b) **9** (5 equiv.), *i*-Pr_2NEt (15 equiv.), NMP, 60°C, 16 h; (c) R^2MgBr (**5**, 15 equiv.), THF, 25°C, 4 h followed by HOAc/CH_2Cl_2 (9:1); (d) TFA/H_2O (95:5); (e) **16** (1.5 equiv.), *i*-Pr_2NEt (1.5 equiv.), CH_2Cl_2.

demonstration library using the reagents shown in Fig. 2. Firstly, resin bound Weinreb amide **12a** was reacted with 3,5-dimethylphenylmagnesium bromide to afford a second α-aminoketone **7b** after cleavage. Secondly, cyclic amino acid **3b** was converted to resin bound Weinreb amide **12b** which was successfully reacted with the three Grignard reagents **5a**–**c** to afford the expected α-aminoketones **7c**–**e**. The yields and purities of all five α-aminoketone intermediates are shown in Table 1. Finally, the four additional library members **1b**–**e** were prepared from aminoketone **7a** by reaction with activated carboxylic acid resins **16b**–**e** and the completely enumerated library of the 20 compounds **1f**–**y** derived from reaction of **7b**–**e** with the resins **16a**–**e** was prepared. All library compounds were characterized by ^{1}H NMR and LC MS. The yields and purities of the library compounds are shown in Table 2. The yields ranged from 61 to 92%. On average the yields were better when the aromatic Grignard reagents **5b** and **5c** were employed and when the benzoic acid **14** did not have an *ortho* substituent. Purities ranged between 82 and 97% with no obvious trends correlated with the reagents employed.

In conclusion, we have described the synthesis of a demonstration library of 25 α-acylamino-α,α-disubstituted ketones **1** taking strategic advantage of the features of solid phase chemistry and solution chemistry in conjunction with polymer bound reagents.

Table 1. Yields and purities of α-aminoketones **7**[a]

Cmpd	R^1, R^{1a}	R^2	Yield[b]	Purity of **7** (% recovered **9**)[c]
7a	Me, Me	Et	82	85 (9)
7b	Me, Me	3,5-diMe-Ph	76	89[d] (9)
7c	–$(CH_2)_4$–	Et	80	80 (12)
7d	–$(CH_2)_4$–	3,5-diMe-Ph	86	94[d] (5)
7e	–$(CH_2)_4$–	Ph	94	92[d] (3)

[a] Isolated as trifluoroacetate salts.
[b] Yield was calculated based on the initial functionalization of the resin.
[c] Purity was calculated by integration of appropriate peaks in the ^{1}H NMR.
[d] Purity confirmed by integration of the HPLC trace at 220 nm.

References

1. JP 4,8018,222 (*Chem. Abstr.* 79:78590).
2. US 5,304,572 (*Chem. Abstr.* 121:76155).
3. Young, D. H.; Slawecki, R. A. *Pestic. Biochem. Physiol.* **2001**, *69*, 100–111.
4. WO 2001/60783 (*Chem. Abstr.* 135:195424).
5. Wing, K. D.; Slawecki, R. A.; Carlson, G. R. *Science* **1988**, *241*, 470–472.
6. Tice, C. M.; Michelotti, E. L.; Mata, E.; Nicolàs, E.; Garcia, J.; Albericio, F. *Tetrahedron Lett.* **2002**, *43*, 7491–7494.
7. Porco, J. A., Jr.; Deegan, T.; Devenport, W.; Gooding, O. W.; Heisler, K.; Labadie, J. W.; Newcomb, B.; Nguyen, C.; van Eikeren, P.; Wong, J.; Wright, P. *Mol. Diversity* **1997**, *2*, 197–206.
8. Dixit, D. M.; Smith, H.; Leznoff, C. C. *J. Chem. Soc., Chem. Commun.* **1977**, 798–799.
9. Alsina, J.; Rabanal, F.; Chiva, C.; Giralt, E.; Albericio, F. *Tetrahedron* **1998**, *54*, 10125–10152.
10. Pop, I. E.; Déprez, B. P.; Tartar, A. L. *J. Org. Chem.* **1997**, *62*, 2594–2603.
11. Granger, R.; Técher, H.; Massiau, A. *C.R. Hebd. Seances Acad. Sci.* **1960**, *250*, 4378–4380.
12. The following experimental procedure is representative. **Preparation of 9a**. To a stirred mixture of Boc-Aib-OH (**3a**, 5 g, 24.61 mmol, 1 equiv.), MeNHOMe·HCl (2.88 g, 29.53 mmol, 1.2 equiv.), DMAP (3.61 g, 29.53 mmol, 1.2 equiv.), *i*-Pr_2NEt (5.02 mL, 29.53 mmol, 1.2 equiv.) and CH_2Cl_2 (100 mL) was added DCC (6.09 g, 29.53 mmol, 1.2 equiv.). The mixture was stirred at room temperature for 5 days. The mixture was filtered to remove precipitated *N*,*N*′-dicyclohexylurea and the filtrate was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL), washed with 10% aqueous citric acid (3×200 mL), 10% aqueous $NaHCO_3$ (3×200 mL) and saturated aqueous sodium chloride (3×200 mL), and dried over $MgSO_4$. Removal of solvent gave the crude product which was purified by column chromatography (hexane/ethyl acetate 60:40) to afford **4a** (4.85 g, 80%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 6H), 1.58 (s, 9H), 3.22 (s, 3H), 3.69 (s, 3H), 6.95 (bs, 1H). MS (ESI, +ve ion): m/z 247.2 $(M+1)^+$. The Boc protected Weinreb amide **4a** (1.1 g, 4.47 mmol) was taken up in TFA/CH_2Cl_2 (1:1, 50 mL) and stirred for 20 min. Removal of the solvent left **9a** (1.15 g, 99%, quantitative yield) as its TFA salt. ^{1}H NMR (200 MHz, CD_3OD): δ 1.63 (s, 6H), 3.25 (s, 3H), 3.78 (s, 3H). MS (ESI, positive

Table 2. Yields and purities of library compounds of general structure **1**

α-Aminoketone used[a]	R^3 = Ph **14a**[b]	R^3 = 2-Me-Ph **14b**	R^3 = 3-MeO-Ph **14c**	R^3 = 4-Et-Ph **14d**	R^3 = 3,4-OCH_2O-Ph **14e**
7a	**1a**[c] 87[d] (83)[e]	**1b** 61 (82)	**1c** 78 (89)	**1d** 76 (82)	**1e** 83 (91)
7b	**1f** 90 (95)	**1g** 76 (90)	**1h** 80 (85)	**1i** 92 (92)	**1j** 81 (86)
7c	**1k** 82 (96)	**1l** 65 (87)	**1m** 70 (88)	**1n** 69 (92)	**1o** 73 (87)
7d	**1p** 89 (94)	**1q** 80 (92)	**1r** 87 (95)	**1s** 88 (96)	**1t** 84 (97)
7e	**1u** 76 (95)	**1v** 74 (92)	**1w** 83 (92)	**1x** 84 (84)	**1y** 77 (82)

[a] See Table 1 for R^1, R^{1a} and R^2 substituent definitions.
[b] Carboxylic acid building block used. See Fig. 2 and Scheme 3.
[c] Product compound number.
[d] Yields were calculated based on starting α-aminoketone TFA salt.
[e] Purities were calculated based on integration of the HPLC trace at 220 nm.

ion): m/z 147.3 $(M+1)^+$. **Preparation of 12a**. To a suspension of resin **10** (1 g, 0.86 mmol) in i-Pr_2NEt (2.2 mL, 12.9 mmol, 15 equiv.) and NMP (5 mL) was added **9a** (1.15 g, 4.42 mmol, 5 equiv.). The mixture was heated at 60°C for 16 h, cooled and washed with NMP (5×10 mL), DMF (5×10 mL), CH_2Cl_2 (5×10 mL), and dried in vacuo overnight to leave **12a**. PAS-FTIR carbamate C=O stretch: 1727 cm^{-1}, amide C=O stretch: 1646 cm^{-1}. **Preparation of 7a**. To a suspension of **12a** (0.86 mmol) in dry THF (5 mL) under argon was added ethylmagnesium bromide solution (1 M in THF, 12.9 mL, 12.9 mmol, 15 equiv.). The mixture was stirred for 4 h and the resin was washed with THF (5×10 mL), DMF/H_2O (5×10 mL), CH_2Cl_2 (5×10 mL), followed by HOAc/CH_2Cl_2 (9:1), and CH_2Cl_2 (5×10 mL) to afford **13a**. PAS-FTIR carbamate C=O stretch: 1734 cm^{-1}, ketone C=O stretch: 1718 cm^{-1}. The resin was treated with 5 mL of TFA/H_2O (90:10) for 2 h. The mixture was filtered and the filtrate was evaporated to afford **7a** (0.19 g, 82%) as its TFA salt. ^1H NMR (200 MHz, $(CD_3)_2CO$): δ 1.04 (t, $J=6.8$ Hz, 3H), 1.71 (s, 6H), 2.77 (q, $J=7$ Hz, 2H), 8.97 (bs, 1H). MS (ESI, positive ion): m/z 115.89 $(M+1)^+$. **Preparation of 1a**. Hydroxybenzotriazole resin **15** (0.107 g, 0.196 mmol) was treated with benzoic acid (0.12 g, 0.982 mmol, 5 equiv.), DIC (0.152 mL, 0.982 mmol, 5 equiv.) and DMAP (0.024 g, 0.196 mmol, 1 equiv.) in DMF/CH_2Cl_2 (1:1) and shaken for 5 h. The mixture was filtered and the resin was washed with DMF (10×5 mL) and CH_2Cl_2 (10×5 mL) to give **16a**. To a suspension of **16a** (0.196 mmol, 1.5 equiv.) in CH_2Cl_2 (2 mL) were added i-Pr_2NEt (0.033 mL, 0.196 mmol, 1.5 equiv.) and **7a** (0.03 g, 0.131 mmol, 1 equiv.). The mixture was agitated for 16 h and filtered. The filtrate was shaken for with a weakly basic ion exchange resin Amberlite IRA-95 (1 g, 4.7 mmol g^{-1}, 25 equiv.) for 16 h to remove benzoic acid present in the solution and filtered. The filtrate was eluted through a short column of silica gel (hexane/ethyl acetate 50:50) to remove the unreacted amine. The organic solvent was evaporated to leave **1a** (0.03 g, 87%) as a white solid. ^1H NMR (200 MHz, $CDCl_3$): δ 1.14 (t, $J=7.2$ Hz, 3H), 1.57 (s, 6H), 2.63 (q, $J=7$ Hz, 2H), 7.21 (bs, 1H), 7.38–7.56 (aromatic H's, 3H), 7.79 (dd, $J=8$, 1.8 Hz, 2H). MS (ESI, positive ion): m/z 220.2 $(M+1)^+$.