ORGANIC LETTERS

2001
Vol. 3, No. 20
3177−3180

Solid-Phase Synthesis of β-Amino Ketones and Six-Ring Carbamates via Immobilized α-Alkoxycarbonylamino Sulfones

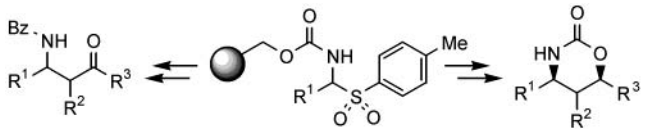
Stefan Schunk and Dieter Enders*

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule, Professor-Pirlet-Strasse 1, 52074 Aachen, Germany

enders@rwth-aachen.de

Received July 24, 2001

ABSTRACT



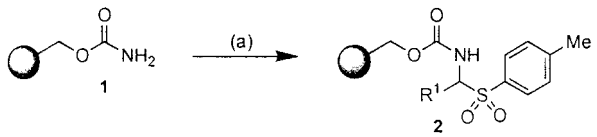
***β*-Amino ketones and substituted 1,3-oxazinan-2-ones have been synthesized utilizing polymer-bound and carbamate-linked α-alkoxycarbonylamino sulfones. Key steps in the synthesis are the immobilization of the *N*-acylimine precursor, the Mannich-type addition of various nucleophiles, and the diastereoselective reduction of the resin-bound ketone.**

The Mannich reaction is an effective carbon−carbon bond-forming reaction that has been applied to solid-phase organic synthesis (SPOS) by immobilizing a variety of amines,[1] imines,[2] and iminium species,[3] yielding piperazine derivatives,[1] amino esters,[2a] pyrazolone derivatives,[2b] α-amino acids,[2c] pyrrolidines,[3c] and homoallylic amines.[3d] Handling and preparation of resin-bound *N*-acyliminium ions is difficult due to their high reactivity and instability.[3a,b] The use of also very reactive but uncharged *N*-acylimines, which can easily be prepared from stable precursors, provides an attractive alternative. These acylimines, generated in situ from α-amino sulfones, are known to react with a wide variety of nucleophiles[4] (e.g., ketone enolates,[4a] Reformatsky reagents,[4b] nitromethane anion,[4c] vinylmagnesium bromide,[4d] and 1-alkynyllithiums[4d]). This versatility is of great importance for SPOS as it provides access to diverse compounds from a common intermediate.

We herein report the immobilization of *N*-acylimines by utilizing an α-amino sulfone precursor[5] and its application in a Mannich-type reaction for the solid-phase synthesis of *β*-amino ketones and six-ring carbamates. The reaction of this precursor with an ester enolate, an aryl Grignard reagent, and allylzinc bromide is also demonstrated.

Scheme 1 illustrates the preparation of the *N*-acylimine precursor. The carbamate resin **1**[3d] was synthesized from commercially available benzyl alcohol resin. We decided to use this resin instead of Wang resin in order to avoid

Scheme 1[a]



[a] (a) 6 equiv of R^1CHO, 3 equiv of *p*-toluene-sodiumsulfinate, 6 equiv of TFA, CH_2Cl_2, 60 °C, 1 h.

(1) Schlienger, N.; Bryce, M. R.; Hansen, T. K. *Tetrahedron* **2000**, *56*, 10023−10030.

(2) For imines: (a) Kobayashi, S.; Aoki, Y. *Tetrahedron Lett.* **1998**, *39*, 7345−7348. For acylhydrazones: (b) Kobayashi, S.; Furuta, T.; Sugita, K.; Okitsu, O.; Oyamada, H. *Tetrahedron Lett.* **1999**, *40*, 1341−1344. For α-imino acetates: (c) Kobayashi, S.; Akiyama, R.; Kitagawa, H. *J. Comb. Chem.* **2000**, *2*, 438−440.

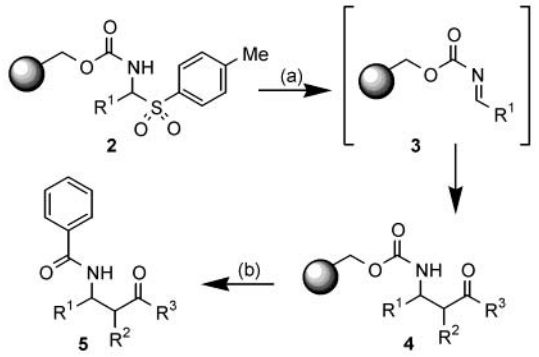
(3) For acyliminium ions: (a) Vanier, C.; Wagner, A.; Mioskowski, C. *Chem. Eur. J.* **2001**, *7*, 2318−2323. (b) van Maarseveen, J. H.; Meester, W. J. N.; Veerman, J. J. N.; Kruse, C. G.; Hermkens, P. H. H.; Rutjes, F. P. J. T.; Hiemstra, H. J. *Chem. Soc., Perkin Trans. 1* **2001**, 994−1001. (c) Veerman, J. J. N.; Rutjes, F. P. J. T.; van Maarseveen, J. H.; Hiemstra, H. *Tetrahedron Lett.* **1999**, *40*, 6079−6082. (d) Meester, W. J. N.; Rutjes, F. P. J. T.; Hermkens, P. H. H.; Hiemstra, H. *Tetrahedron Lett.* **1999**, *40*, 1601−1604.

10.1021/ol016487d CCC: $20.00
Published on Web 09/12/2001

premature cleavage of the linking system during the TFA-promoted synthesis of the α-*N*-carbamato-sulfone resin **2**.[6]

p-Nitrobenzaldehyde was chosen as the aldehyde component to optimize the reaction conditions, since it provides a basis for CHN combustion analysis. The loading of resin **2** for $R^1 = p\text{-}NO_2Ph$ was determined to be 81% (based on the loading of resin **1**). Evidence for a successful synthesis of resins **2** are the C−H out of plane vibrations of the para-substituted aromatic ring in the IR spectrum at $\tilde{\nu} \approx 850\ cm^{-1}$. To study the suitability of different resins **2** for the preparation of β-amino ketones, we had to investigate their reaction with ketone enolates (Scheme 2). An excess of basic

Scheme 2[a]



[a] (a) 4 equiv of $R^2CH{=}C(OLi)R^3$, THF, −78 °C, 2 h then rt, 30 min; (b) Cleavage A: (i) $BF_3{\cdot}Et_2O$, Me_2S, CH_2Cl_2, rt, 14 h. (ii) benzoyl chloride, NEt_3, 30 min. Cleavage B: (i) $ZnBr_2$, benzoyl chloride, CH_2Cl_2, rt, 14 h. (ii) NEt_3, 30 min.

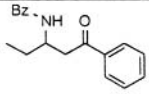
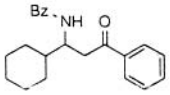
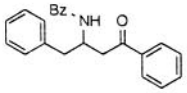
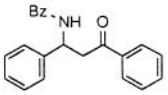
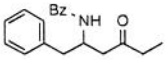
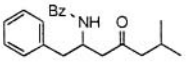
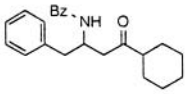
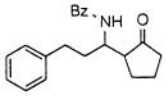
nucleophile leads, after carbamate deprotonation and elimination of lithium *p*-toluolsulfinate, to the desired, immobilized *N*-acylimines **3**. These react with the remaining ketone enolate to yield the resin-bound amino ketones **4**.

Several cleavage protocols for carbamate linkers are known which usually require strongly acidic conditions.[7] We first applied a dimethyl sulfide promoted $BF_3{\cdot}Et_2O$ cleavage[8] (cleavage A, Table 1), which only allowed for the cleavage of aromatic amino ketone resins **4** (R^3 = Ph), yielding benzoyl (Bz) protected β-amino ketones **5a**−**d**.

Failure of this procedure in the case of aliphatic ketone components (R^3 = alkyl) is probably due to a Lewis acid catalyzed dimerization of amino ketones, yielding imines. Therefore, milder cleavage conditions should give the desired amino ketones **5e**−**h**, which were isolated after $ZnBr_2$/benzoyl chloride cleavage[9] (cleavage B) and chromatography in lower yields.

(4) (a) Palomo, C.; Oiarbide, M.; González-Rego, C.; Sharma, A. K.; García, J. M.; González, A.; Landa, C.; Linden, A. *Angew. Chem.* **2000**, *112*, 1105−1107; *Angew. Chem., Int. Ed.* **2000**, *39*, 1063−1065. (b) Mecozzi, T.; Petrini, M. *Tetrahedron Lett.* **2000**, *41*, 2709−2712. (c) Ballini, R.; Petrini, M. *Tetrahedron Lett.* **1999**, *40*, 4449−4452. (d) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970−8972. (e) Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238−1240. (f) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622−2636. (g) Kinoshita, H.; Hayashi, Y.; Murata, Y.; Inomata, K. *Chem. Lett.* **1993**, *8*, 1437−1440. (h) Morton, J.; Rahim, A.; Walker, E. R. H. *Tetrahedron Lett.* **1982**, *23*, 4123−4126.

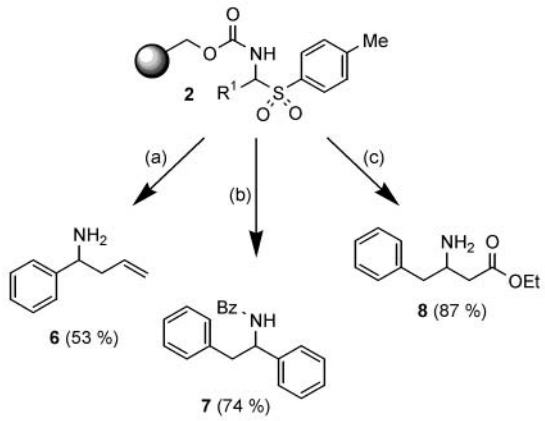
Table 1. Yields of Bz-Protected β-Amino Ketones **5**

5 [a]	β-amino ketone	cleavage	yield [%] [b]
a		A	80
b		A	54
c		A	50
d		A	44
e		B	40
f		B	31
g		B	23
h		B	35

[a] Compounds **5** were characterized by $^1H/^{13}C$ NMR spectroscopy and MS experiments after chromatography (SiO_2; Et_2O/pentane 1:1). [b] Yields of amino ketones **5** after four steps based on loading of resin **1**.

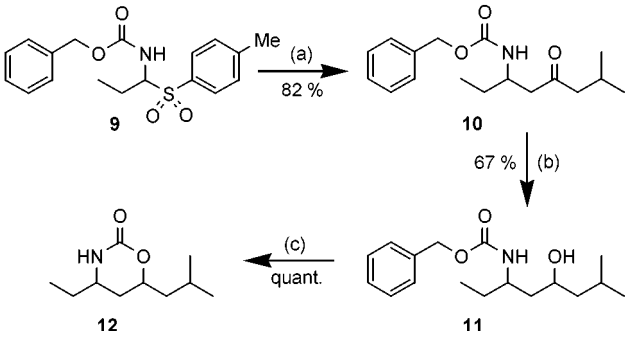
A brief investigation of further nucleophiles in the reported addition−cleavage procedure showed that we could successfully add allylzinc bromide, an ester enolate, and an aryl Gringard reagent to yield the expected homoallylic amine **6**, secondary amine **7**, and β-amino acid ester **8**, respectively (Scheme 3).

Scheme 3[a]



[a] (a) (i) 4 equiv of allylzinc bromide, (ii) $BF_3{\cdot}Et_2O$, Me_2S, CH_2Cl_2, rt, 14 h; aqueous acid/base workup; (b) (i) 4 equiv of PhMgCl, (ii) Cleavage A; (c) (i) 4 equiv of ethyl acetate enolate, (ii) $BF_3{\cdot}Et_2O$, Me_2S, CH_2Cl_2, rt, 14 h; aqueous acid/base workup.

Scheme 4[a]



[a] (a) 4 equiv of $H_2C{=}C(OLi)CH_2(CH_3)_2$, THF, −78 °C, 15 min; (b) 3 equiv of $LiAl[OC(CH_3)_3]_3H$, THF, −78 °C, 1 h then 0 °C to rt, 14 h; (c) 1 equiv of LiHMDS, THF, rt, 30 min.

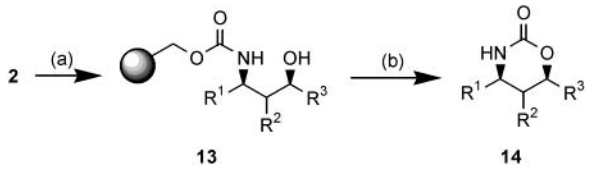
Because of the continuously high interest in solid-supported heterocycle synthesis,[10] we decided to utilize the immobilized amino ketones for the synthesis of 1,3-oxazinan-2-ones via a cyclization−cleavage strategy.

Preliminary investigations concerning the optimization of the reduction and cyclization procedures were conducted on a solution-phase model compound (Scheme 4). Lithium tri-*tert*-butoxyaluminohydride gave the best results in the reduction of the amino ketone **10** (de = 71% of *syn*-diastereomer) obtained via a Mannich-type reaction with excess ketone enolate (R^2 = H, R^3 = *i*-Bu) from **9**. NMR experiments showed that both diastereomers of **11** cyclized upon treatment with LiHMDS within 30 min at room temperature to give 4-ethyl-6-isobutyl-1,3-oxazinan-2-one **12**.[11] A diastereoselective cyclization−cleavage of resin-bound amino alcohols **13** can therefore be ruled out.

The reaction conditions used in liquid phase could easily be transferred to solid phase (Scheme 5).

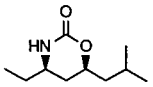
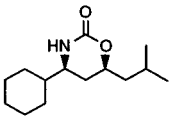
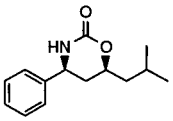
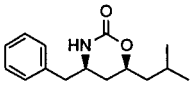
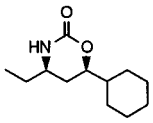
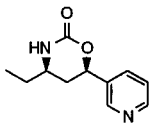
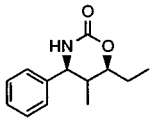
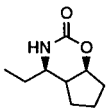
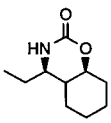
The addition of 4-methylpentane-2-one enolate to different resins **2** gave after reduction and cyclization of **13** excellent results concerning the purity and diastereomeric excess of the final products **14a**−**d**. Addition of different ketones to immobilized propanalaldehyde acylimine equivalents (**14e**, **14f**) gave also good results. Diethyl ketone, cyclopentanone, and cyclohexanone as ketone components in this synthesis yielded diastereomeric mixtures of 4,5,6-substituted 1,3-oxazinan-2-ones (**14g**) or bicyclic 1,3-oxazinan-2-ones (**14h**, **14i**). The relative configuration of the carbamates was established as cis via NMR analysis. The two major diastereomers of trisubstituted carbamates **14g**−**i** are as expected cis concerning positions 4 and 6, with no preference at position 5 (Table 2).

Scheme 5[a]



[a] (a) (i) 4 equiv of $R^2CH{=}C(OLi)R^3$, THF, −78 °C, 2 h then rt, 30 min, (ii) 3 equiv of $LiAl[OC(CH_3)_3]_3H$, THF, −78 °C, 1 h then 0 °C to rt, 14 h; (b) 1 equiv of LiHMDS, THF, −78 °C, 15 min then rt, 2 h.

Table 2. Purities, de/dr Values and Yields of Six-Ring Carbamates **14**

14 [a]	carbamate	purity [b] [%]	*de* [%] or *dr* [c]	yield [d] [%]
a		96	94	86
b		96	≥ 96	79
c		95	≥ 96	58
d		95	≥ 96	72
e		88	≥ 96	45
f		95	≥ 96	50
g		98	0.1 : 1.0 : 1.8	65
h		93	0.3 : 1.0 : 1.7	70
i		98	0 : 1.0 : 1.4	52

[a] Compounds were characterized by $^1H/^{13}C$ NMR spectroscopy and GC-MS measurements. [b] Purities determined after filtration by GC. [c] de and dr determined by ^{13}C NMR spectroscopy. [d] Yields of carbamates **14** after four steps based on loading of resin **1**.

(5) (a) Engberts, J. B. F. N.; Olijnsma, T.; Strating, J. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 1211−1222. (b) Engberts, J. B. F. N.; Strating, J. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 942−950.

(6) For premature cleavage problems of Wang carbamates caused by $BF_3{\cdot}Et_2O$, see ref 3c.

(7) Dörwald, F. Z. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, 2000; Chapter 3.

(8) Sánchez, I. H.; López, F. J.; Soria, J. J.; Larraza, M. I.; Flores, H. J. *J. Am. Chem. Soc.* **1983**, *105*, 7460−7643.

(9) Li, W.; Lin, Y.; Yo, Y. *Tetrahedron Lett.* **2000**, *41*, 6619−6622.

(10) Recent Review: Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195−214.

(11) Compund **12** was not isolated from byproducts.

In conclusion, we have demonstrated the use of immobilized *N*-acylimines, which were generated from stable α-amino sulfone precursors, for the synthesis of benzoyl-protected *β*-amino ketones and the synthesis of mono- and bicyclic 1,3-oxazinan-2-ones. Furthermore, the preparation of homoallylic amines, secondary arylamines, and *β*-amino acid esters has also been exemplified.

Acknowledgment. We especially thank N. Fricke for excellent experimental support and Dr. J. Runsink for NMR measurements and carrying out NOE investigations. This work was supported by the Fonds der Chemischen Industrie and by the Deutsche Forschungsgemeinschaft (SFB 380, Graduiertenkolleg 440, Stipend to S.S.). We thank Degussa AG, BASF AG, and Bayer AG for the donation of chemicals.

Supporting Information Available: Experimental procedures and characterizations for compounds **5a**, **5e**, **14b**, and **14c**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016487D