Tetrahedron Letters 51 (2010) 5238–5241

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of pyrrolidin-2-ones via tandem reactions of vinyl sulfonium salts under mild conditions

Chunsong Xie [a], Deyu Han [b], Yue Hu [b], Jinhua Liu [a,*], Tian Xie [a,*]

[a] Research Center of Biomedicine and Health, Hangzhou Normal University, Hangzhou 310012, PR China
[b] College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 310012, PR China

ARTICLE INFO

Article history:
Received 28 May 2010
Revised 15 July 2010
Accepted 20 July 2010
Available online 24 July 2010

ABSTRACT

A novel and efficient synthesis of pyrrolidin-2-ones through the tandem reactions of vinyl sulfonium salts with malonyl amides under very mild conditions is reported. The reaction demonstrates a wide tolerance toward various aryls, acyl, sulfonyl, and benzyl while aliphatic groups delivering the tetrahydro-2-oxofuran product.

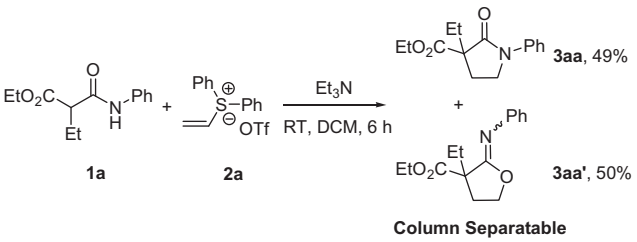
Introduction

Pyrrolidin-2-ones (also γ-lactams) are structurally ubiquitous motifs in many natural products[1] and pharmaceuticals.[2] During the past few years, many patented pharmaceutical ingredients based on these units have been approved for their potential treatment toward many common diseases such as hepatitis, diabetes, and cancers.[3] The SAR studies have shown that they are structural necessities in many biologically active molecules since they play important roles in the binding with receptor proteins.[4] Besides these, pyrrolidin-2-ones have also been widely used as monomers for many functional polymer materials.[5] The utilization of them in organic synthesis has also attracted wide attention[6] and many pyrrolidines[7] as well as γ-amino acids[8] have been efficiently accessed from them.

As a result, the synthesis of pyrrolidin-2-ones has been widely studied and many promising methods have been developed.[9] For example, the direct amination of either dihydrofuran-2(3*H*)-ones[2b] or 1,4-dicarbonyl compounds (also their acetals)[10] has been frequently used. However, both methods have proven to be defective because they are always performed under acidic conditions and/or at high temperatures. In the latest years, many novel cyclization protocols such as the intramolecular cyclization of β,γ-unsaturated amides,[11] the thermal ring-closure of oxirane-containing enamides,[12] the cascades of imines with 3-nitropropanoate,[13] as well as the transition-metal promoted multi-component assembly involving imines, β-halo allylic alcohols, and CO,[14] have been proposed for the synthesis of various pyrrolidin-2-ones. Although these procedures have been well documented, they still suffer from the drawbacks that elevated temperatures and/or the use of contaminative metals are needed. Accordingly, the development of efficient, mild, and general reactions for the synthesis of pyrrolidin-2-ones from readily accessible materials is still highly desirable and of much significance.

In the past few years, vinyl sulfonium salts have exhibited great utilizations in organic synthesis, and many heterocyclic motifs have been efficiently accessed by the tandem assemblies of these reactive electrophiles.[15] During our continuous explorations on the heterocycle synthesis by the domino reactions of vinyl sulfonium salts,[16] we excitedly found that the pyrrolidin-2-one frameworks could be synthesized straightforwardly via the reactions of vinyl sulfonium salts with malonyl amides in high efficiency and under very mild conditions. In view of the easy availability of these two reactants[15b,17] and the mild conditions involved, as well as the cleavability of the ester group in the products, this novel synthesis represents a good complement to the existing preparation methods for pyrrolidin-2-ones.

We started our researches by choosing the reaction between ethyl 2-(phenylcarbamoyl)butanoate **1a** and diphenyl vinyl sulfonium triflate **2a** as the model (Scheme 1). To our delight, in the presence of TEA, after being conducted in DCM at room temperature for 6 h, the reaction indeed took place and delivered pyrrolidin-2-one **3aa** in 49% yield. However, in addition to the formation of **3aa**, an isomeric tetrahydro-2-iminofuran product **3aa′** was also formed in 50% yield.

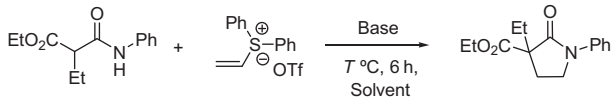


Scheme 1. Initial experiment.

* Corresponding authors. Tel.: +86 571 28862281; fax: +86 571 28865630 (J.L.).
E-mail addresses: ljh@hznu.edu.cn (J. Liu), tianxie@hznu.edu.cn (T. Xie).

0040-4039/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2010.07.108

Table 1
Optimization of the conditions [a]



1a 2a 3aa

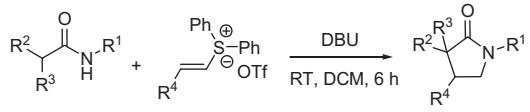
Entry	Base	Solvent	T [b] (°C)	Yields[c] (%)
1	DBU	DCM	rt	93
2	NaH	DCM	rt	47
3	No	DCM	rt	0
4	DBU	DCM	45	88
5	DBU	DCM	0	86
6	DBU	THF	rt	90

[a] *Reaction conditions:* **1a** (235 mg, 1.0 mmol), **2a** (543 mg, 1.5 mmol), base (2.0 mmol), solvents (5.0 mL).
[b] Bath temperature.
[c] Isolated yields.

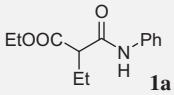
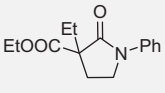
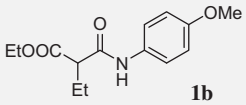
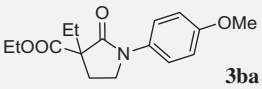
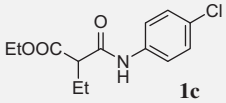
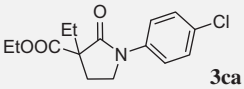
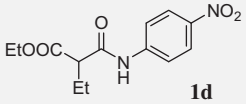
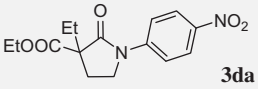
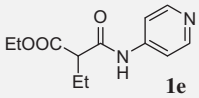
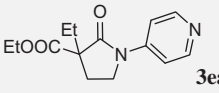
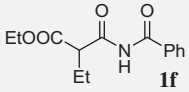
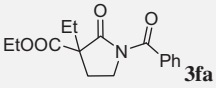
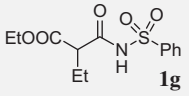
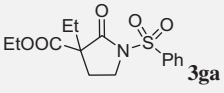
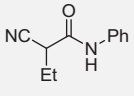
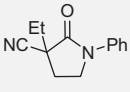
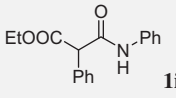
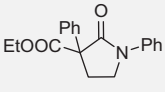
To improve the selectivity as well as the efficiency of the reaction, we next performed an optimization on the reaction conditions (Table 1). Changing the base to be a stronger one such as DBU and NaH had proven to be positive to the selectivity and the efficiency of the tandem reaction (Table 1, entries 1–2). When the reaction was conducted in the presence of DBU as the base, a high yield (93%, Table 1, entry 1) of the pyrrolidin-2-one **3aa** was exclusively formed. Similarly, in the case of NaH, a completely selective formation of **3aa** and **3aa′** could also be observed albeit with a moderate yield (47%, Table 1, entry 2). A control experiment revealed that the base was very crucial and the reaction could not work in the absence of a base (Table 1, entry 3). On the other hand, the screening of the reaction temperature showed that the room temperature was optimal and a slightly lower yield (88% and 86%, respectively) was afforded when the tandem reaction was performed either at 45 °C or in an ice-water bath (Table 1, entries 4–5). However, solvents seemed to have little influence on the reaction. When conducted in THF at the same temperature, the reaction could give a comparable yield (90%) with that in DCM (Table 1, entry 6).

With the optimal conditions in hand, we next studied the scope of the reaction and the results are summarized in Table 2. Various *N*-aryl malonyl amides like ethyl 2-(4-methoxylphenylcarbamoyl)butanoate **1b** and ethyl 2-(4-chlorophenylcarbamoyl)butanoate **1c** as well as ethyl 2-(4-nitrophenylcarbamoyl)butanoate

Table 2
Scope of the reaction[a]

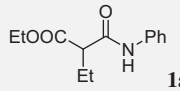
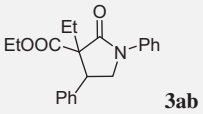
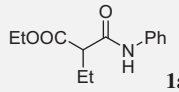
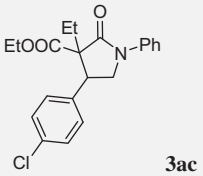
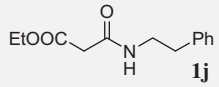
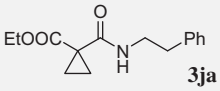
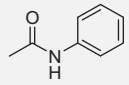
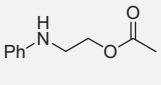


1 2 3

Entry	1	R^4	Products	Yield[b] (%)
1	 **1a**	H **2a**	 **3aa**	93
2	 **1b**	H **2a**	 **3ba**	98
3	 **1c**	H **2a**	 **3ca**	93
4	 **1d**	H **2a**	 **3da**	83
5	 **1e**	H **2a**	 **3ea**	77
6	 **1f**	H **2a**	 **3fa**	74
7	 **1g**	H **2a**	 **3ga**	88
8	 **1h**	H **2a**	 **3ha**	85
9	 **1i**	H **2a**	 **3ia**	79

(*continued on next page*)

Table 2 (*continued*)

Entry	1	R^4	Products	Yield[b] (%)
10	 **1a**	Ph **2b**	 **3ab**	41
11	 **1a**	4-Cl–C_6H_4 **2c**	 **3ac**	63
12	 **1j**	H **2a**	 **3ja**	77[c]
13	 **1k**	H **2a**	 **3ka**	32

[a] *Reaction conditions:* amides (1.0 mmol), vinyl sulfoniums (1.5 mmol), DBU (2.0 mmol), DCM (5.0 mL), room temperature, 6 h.
[b] Isolated yield based on amides.
[c] The reaction was performed on a 0.5 mmol scale.

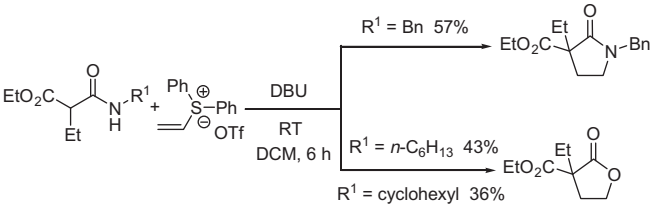
1d had proven to be the reliable reaction partners with vinyl sulfonium, leading to *N*-aryl pyrrolidin-2-ones in high yields (Table 2, entries 2–4). In addition, *N*-heteroaryl malonyl amide like ethyl 2-(pyridin-4-ylcarbamoyl)butanoate **1e** also reacted smoothly with vinyl sulfonium resulting in pyrrolidin-2-one **3ea** bearing 4-pyridyl in 77% yield (Table 2, entry 5). When using the malonyl amides bearing an acyl and sulfonyl as the substrates, the reaction could also proceed efficiently leading to the overwhelming formation of *N*-acyl and *N*-sulfonyl pyrrolidin-2-one in 74% and 88% yield, respectively (Table 2, entries 6 and 7). This is of particular importance that these removable groups will allow the preparation of diversely N-substituted pyrrolidin-2-ones feasible.

Besides these substrates bearing substituents at the nitrogens, 2-cyano-*N*-phenylbutanamide **1h** was also found to be able to undergo the tandem reaction efficiently, affording the desired pyrrolidin-2-one **3ha** bearing a cyano at the 3-position in 85% yield (Table 2, entry 8). Analogously, ethyl 2-(phenylcarbamoyl)-2-phenylacetate **1i** could also be used in the tandem reaction and produce the pyrrolidin-2-one **3ia** in 79% yield (Table 2, entry 9).

On the other hand, substituted vinyl sulfonium salts such as diphenyl styryl sulfonium triflate **2b** and diphenyl 4-chlorostyryl sulfonium triflate **2c** had also been used for the tandem reaction and yielded 4-substituted pyrrolidin-2-ones **3ab** and **3ac** in moderate yield (Table 2, entries 10 and 11). These reactions were of much importance since they implied the assemblies of the pyrrolidin-2-ones bearing substituents at 4-positions were viable. Meanwhile, the regioselectivity revealed that the reactivity of the methines was superior to the amides in the malonyl amides, and the reaction was initiated by the nucleophilic attack of the active methines to the vinyl sulfoniums. The same conclusion could also be drawn by the exclusive formation of the cyclopropane derivative **3ja** from the reaction of ethyl 2-(phenethylcarbamoyl)acetate **1j** with vinyl sulfonium (Table 2, entry 12).

In order to explore the reactions of the vinyl sulfoniums with simple acetamides, we next performed the reaction of *N*-phenylacetamide **1k** with vinyl sulfonium under the standard conditions. To our astonishment, this reaction did not produce the anticipated pyrrolidin-2-one product and, instead, an ester of aminoethanol **3ka** was isolated in 32% yield (Table 2, entry 13).[18]

Lastly, the reactions between vinyl sulfonium salts and *N*-alkyl malonyl amides had also been studied (Scheme 2). *N*-Benzyl amide was found to be able to work with diphenyl vinyl sulfonium triflate

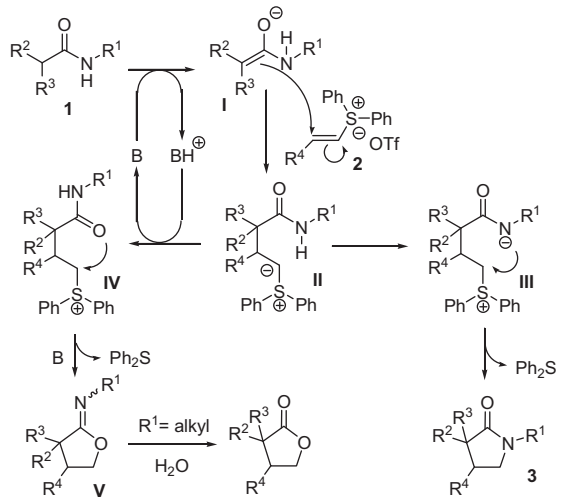


Scheme 2. The reactions of *N*-alkyl amides.

giving the corresponding pyrrolidin-2-one in 57% yield. However, other *N*-alkyl amides such as ethyl 2-(hexylcarbamoyl)butanoate and ethyl 2-(cyclohexylcarbamoyl)butanoate exclusively led to the same γ-lactone product ethyl 3-ethyl-tetrahydro-2-oxofuran-3-carboxylate in variable yields (43% and 36%). It was evident that the tetrahydro-2-oxofuran product was produced by the hydrolysis of the corresponding tetrahydro-2-iminofuran intermediates due to the instability of this kind of *N*-alkyl tetrahydro-2-iminofuran products. These indicated that the N-substitution also had a dramatic impact on the product distribution possibly due to the fact that it would affect the acidity of the N–H bonds of the amide moieties.

Based upon these results, we proposed a plausible mechanism for the pyrrolidin-2-one synthesis which was illustrated in Scheme 3. As we mentioned above, under the promotion of the bases, the assemblies were possibly initiated by the nucleophilic addition of the enolates **I** to the electrophilic vinyl sulfonium salts and generated the sulfur ylids **II**. Then depending on the N-substitution and the bases, the reaction would proceed toward two directions, namely the intramolecular proton transfer to form the imino anion-containing sulfoniums **III** and the intermolecular protonation to produce the sulfoniums **IV**. Under the circumstances of **III**, the nitrogens of the imino anion moieties would attack the sulfoniums, leading to the formation of pyrrolidin-2-ones **3**. On the contrary, the carbonyl oxygens of the amide parts would attack the sulfoniums, yielding the tetrahydro-2-iminofurans **V** which would be further hydrolyzed to give the tetrahydro-2-oxofuran product when R^1 were aliphatic groups.

In conclusion, we have developed an expeditious efficient synthesis of pyrrolidin-2-ones by the assemblies of vinyl sulfonium salts and malonyl amides under very mild conditions. Various substituents such as aryl, acyl, sulfonyl, and benzyl can be tolerated



Scheme 3. Proposed mechanism.

but the other aliphatic groups affording the tetrahydro-2-oxofuran product. A plausible mechanism has been proposed in which an anion relay sequence has been included. Further investigations of the reaction mechanism as well as the applications of the pyrrodin-2-one synthesis are currently ongoing in our laboratory.

Experimental

Typical procedure for the tandem reactions

Ethyl 2-(phenylcarbamoyl)butanoate **1a** (235 mg, 1.0 mmol), DBU (304 mg, 2.0 mmol), and DCM (2 mL) were charged into an oven-dried flask. The solution of diphenyl vinyl sulfonium triflate **2a** (543 mg, 1.5 mmol) in DCM (3 mL) was added dropwise into the above solution at room temperature. The reaction mixture was then allowed to react at the same temperature for 6 h. After the completion of reaction, the solvent was removed in vacuum. The residue was then separated on a silica gel column by using petroleum ether/EtOAc = 12:1 as an eluent and the final products were obtained as colorless oil (243 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.64 (d, J = 8.4 Hz, 2H), 7.37 (t, J = 7.8 Hz, 2H), 7.16 (t, J = 7.4 Hz, 1H), 4.21 (m, 2H), 3.96 (q, J = 9.2 Hz, 1H), 3.76 (t, J = 9.2 Hz, 1H), 2.65 (m, 1H), 2.18 (m, 1H), 2.10 (m, 1H), 1.88 (m, 1H), 1.27 (t, J = 7.6 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 171.3, 139.3, 128.8, 124.8, 120.0, 61.5, 57.7, 46.2, 27.3, 27.1, 14.1, 8.9. HRMS (EI) Calcd for $C_{15}H_{19}NO_3$: $[M]^+$ 261.1365. Found, 261.1381.

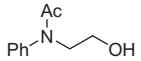
Acknowledgments

The authors gratefully thank the grant support from the National Natural Science Foundation of China (20675022) and the Zhejiang Provincial Major Project of China (2007C01004-2). The financial support from the Zhejiang Provincial Natural Science Foundation of China (Y4090408) and the Hangzhou City Research Project (20090331N04) as well as the Hangzhou Normal University Research Program (YS05203121) are simultaneously acknowledged by Dr. C.S.X.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.108.

References and notes

1. Duan, X. J.; Li, X. M.; Wang, B. G. *J. Nat. Prod.* **2007**, *70*, 1210.
2. (a) Donohue, S. R.; Krushinski, J. H.; Pike, V. W.; Chernet, E.; Phebus, L.; Chesterfield, A. K.; Felder, C. C.; Halldin, C.; Schaus, J. M. *J. Med. Chem.* **2008**, *51*, 5833; (b) Kulig, K.; Sapa, J.; Nowaczyk, A.; Filipek, B.; Malawska, B. *Eur. J. Med. Chem.* **2009**, *44*, 3994.
3. (a) Chang, T.; Hattori, M.; Sheu, C. PCT Int. Appl. WO2009094807-A1.; (b) Ngo, V. X.; Old, D. W. PCT Int. Appl. WO2009055289-A2.; (c) Hook, D.; Ruch, T.; Riss, B.; Wietfeld, B.; Sedelmeier, G.; Napp, M.; Baenziger, M.; Hawker, S.; Ciszewski, L.; Waykole, L. M. PCT Int. Appl. WO2008083967-A2.; (d) Bush, J. K.; Hansen, M. M.; Li, R.; Mabry, T. E.; Snyder, N. J.; Wallace, O. B.; Xu, Y. PCT Int. Appl. WO2007127688-A2.; (e) Kenda, B.; Quesnel, Y.; Ates, A.; Michel, P.; Turet, L.; Mercier, J. PCT Int. Appl. WO2006128692-A2.
4. Young, R. J.; Campbell, M.; Borthwick, A. D.; Brown, D.; Burns-Kurtis, C. L.; Chan, C.; Convery, M. A.; Crowe, M. C.; Dayal, S.; Diallo, H.; Kelly, H. A.; King, N. P.; Kleanthous, S.; Mason, A. M.; Mordaunt, J. E.; Patel, C.; Pateman, A. J.; Senger, S.; Shah, G. P.; Smith, P. W.; Watson, N. S.; Westona, H. E.; Zhou, P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5953.
5. Bencini, M.; Ranucci, E.; Ferruti, P.; Manfredi, A. *Macromol. Rapid Commun.* **2006**, *27*, 1060.
6. (a) Reymond, S.; Cossy, J. *Chem. Rev.* **2008**, *108*, 5359; (b) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632; (c) Torssell, S.; Wanngren, E.; Somfai, P. *J. Org. Chem.* **2007**, *72*, 4246; (d) Rege, P. D.; Johnson, F. *J. Org. Chem.* **2003**, *68*, 6133; (e) Sibi, M. P.; Liu, M. *Org. Lett.* **2000**, *2*, 3393; (f) Olive, G.; Moigne, F. L.; Mercier, A.; Rockenbauer, A.; Tordo, P. *J. Org. Chem.* **1998**, *63*, 9095.
7. (a) Zhu, Q. M.; Huang, H. M.; Shi, D. J.; Shen, Z. Q.; Xia, C. G. *Org. Lett.* **2009**, *11*, 4536; (b) Breman, A. C.; Dijkink, J.; Maarseveen, J. H.; Kinderman, S. S.; Hiemstra, H. *J. Org. Chem.* **2009**, *74*, 6327.
8. (a) Castelhano, A. L.; Krantz, A. *J. Am. Chem. Soc.* **1984**, *106*, 1877; (b) Banziger, M.; McGarrity, J. F.; Meul, T. *J. Org. Chem.* **1993**, *58*, 4010; (c) Huang, P. Q.; Wang, S. L.; Ye, J. L.; Ruan, Y. P.; Huang, Y. Q.; Zheng, H.; Gao, J. X. *Tetrahedron* **1998**, *54*, 12547; (d) Gheorghe, A.; Schulte, M.; Reiser, O. *J. Org. Chem.* **2006**, *71*, 2173; (e) Crucianelli, E.; Martelli, G.; Orena, M.; Rinaldi, S.; Sgolastra, F. *Tetrahedron: Asymmetry* **2009**, *20*, 1824.
9. (a) Candeias, N. R.; Branco, L. C.; Gois, P. M. P.; Afonso, C. A. M.; Trindade, A. F. *Chem. Rev.* **2009**, *109*, 2703; (b) Wei, Z. Y.; Knaus, E. E. *Tetrahedron Lett.* **1993**, *34*, 4439; (c) Brown, G. R.; Foubister, A. J.; Wright, B. *J. Chem. Soc., Chem. Commun.* **1984**, 1373; (d) Vedejs, E.; Meier, G. P. *Tetrahedron Lett.* **1979**, *20*, 4185.
10. (a) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656; (b) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F.; Williard, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 7429; (c) Katritzky, A. R.; Mehta, S.; He, H. Y.; Cui, X. L. *J. Org. Chem.* **2000**, *65*, 4364.
11. (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127; (b) Liu, X. Y.; Li, C. H.; Che, C. M. *Org. Lett.* **2006**, *8*, 2707.
12. Yang, L.; Zheng, Q. Y.; Wang, D. X.; Huang, Z. T.; Wang, M. X. *Org. Lett.* **2008**, *10*, 2461.
13. Pelletier, S. M. C.; Ray, P. C.; Dixon, D. J. *Org. Lett.* **2009**, *11*, 4512.
14. Umemura, S.; McLaughlin, M.; Micalizio, G. C. *Org. Lett.* **2009**, *11*, 5402.
15. (a) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 257; (b) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3784; (c) Unthank, M. G.; Tavassoli, B.; Aggarwal, V. K. *Org. Lett.* **2008**, *10*, 1501; (d) Unthank, M. G.; Hussain, N.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7066; (e) Yamanaka, H.; Yamane, Y.; Mukaiyama, T. *Heterocycles* **2004**, *63*, 2813; (f) Matsuo, J.; Yamanaka, H.; Kawana, A.; Mukaiyama, T. *Chem. Lett.* **2003**, *32*, 392; (g) Kim, K. H.; Jimenez, L. S. *Tetrahedron: Asymmetry* **2001**, *12*, 999; (h) Wang, Y. F.; Zhang, W. H.; Colandrea, V. J.; Jimenez, L. S. *Tetrahedron* **1999**, *55*, 10659.
16. Xie, C. S.; Han, D. Y.; Liu, J. H.; Xie, T. *Synlett* **2009**, 3155.
17. Franzén, J.; Fisher, A. *Angew. Chem., Int. Ed.* **2009**, *47*, 1351.
18. Another possible structure of **3ka** was  (CAS 28358-86-3). However, after the comparison of the spectroscopic data we obtained and the reference (H. Firouzabadi, N. Iranpoor, F. Nowrouzi, K. Amani, *Chem. Commun.* **2003**, 764–765) reported, we finally assigned the structure of **3ka** to be the ester of the aminoethanol as described in Table 2. A possible pathway for the formation of **3ka** was as follows: