Pergamon

Tetrahedron Letters 42 (2001) 3525–3527

TETRAHEDRON LETTERS

Synthesis of β-amino arylketones through the addition of ArLi derivatives to β-aminoesters

Paulo G. Lima,[a,b] Lucia C. Sequeira[b] and Paulo R. R. Costa[a,*]

[a]*Laboratório de Química Bioorgânica (LQB), Núcleo de Pesquisas de Produtos Naturais, Centro de Ciências da Saúde, bloco H, Ilha da Cidade Universitária, Universidade Federal do Rio de Janeiro (UFRJ), 21941-590 Rio de Janeiro, Brazil*
[b]*Instituto de Química, Universidade Federal do Rio de Janeiro (UFRJ), 21941-590 Rio de Janeiro, Brazil*

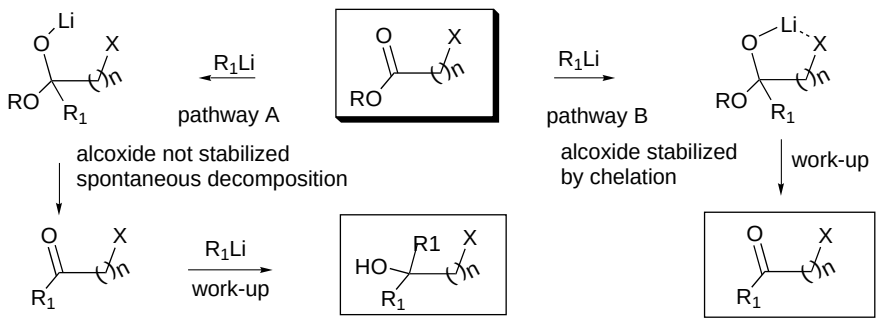
Received 25 October 2000; revised 26 February 2001; accepted 1 March 2001

Abstract—2-Lithiumthiophene and 2-lithiumpyridine were allowed to react with *N*-substituted β-aminoesters. Only β-amino arylketones were obtained from *N*-BOC, *N*-H derivatives, while arylenoates were formed (retro-conjugate addition) from those substrates bearing *N*-Bn, *N*-H substituents, despite the aryllithium used. When the nitrogen is disubstituted (BOC and Bn), the product distribution depended on the nucleophile, leading to tertiary alcohols for 2-lithiumthiophene or ketones for 2-lithiumpyridine. Tertiary alcohols were also formed when PhLi was used as a nucleophile.

While carboxylic acids[1] and amides[2] react with organolithium compounds to give preferentially ketones, tertiary alcohols are usually obtained when esters are used as substrates,[3] due to the decomposition of the tetrahedral lithium alkoxide intermediate, followed by the reaction of the resulting ketone, which is more reactive than the corresponding ester, with another equivalent of the nucleophile before the work-up (Scheme 1, pathway A). However, the presence of polar groups at the α-position can stabilize the alcoxide intermediate by an inductive effect or formation of five membered chelated species (Scheme 1, X = O or N, $n = 1$), leading preferentially to ketones (pathway B).[4] On the other hand, we did not find examples in the literature for this type of stabilization involving β-aminoesters as substrates (Scheme 1, X = N, $n = 2$).[5]

In this letter we disclose the results obtained for the reactions of 2-lithiumthiophene (**5a**)[6] and 2-lithiumpyridine (**5b**)[6] with β-aminoesters **3a**,**b**, **4a**,**b** and **5a**,**b**.

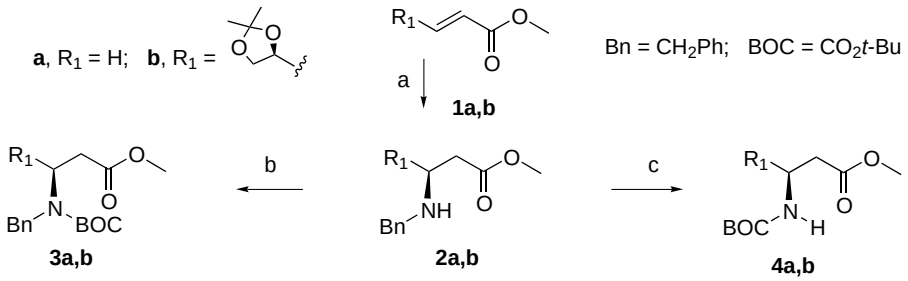
These β-aminoesters were prepared from methyl acrylate (**1a**) or chiral enoate **1b**[7], as shown in Scheme 2. Conjugate addition of benzylamine to **1a** and **1b** led, respectively, to adducts **2a** and *syn*-**2b** in excellent yields. Compound *syn*-**2b** (85% de, crude)[8] could be obtained in an optically pure form, after chromatogra-



Scheme 1. Possible reaction pathway for the addition of R_1Li to α- and β-substituted esters.

* Corresponding author. Tel.: (21)5235938; fax: (21)2702683; e-mail: lqb@nppn.ufrj.br

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00358-6

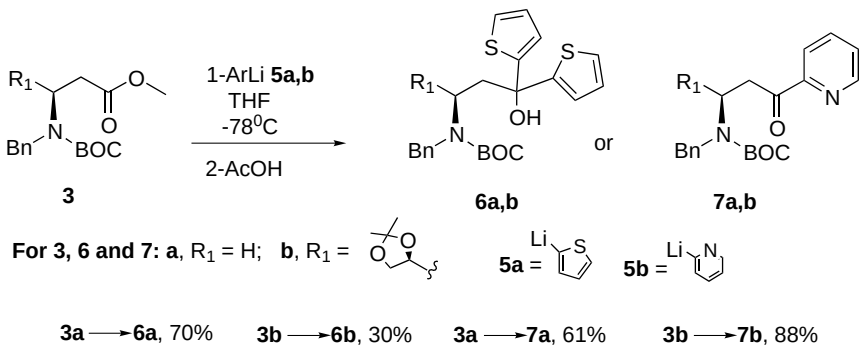


Scheme 2. Preparation of β-aminodiesters **2**–**4** from enoates **1a**,**b**. (a) 3 equiv. $BnNH_2$ neat, –40°C, **2a** (12 h, 100%), **2b** (3 days, 90%); (b) $(Boc)_2O$/MeOH, 100% for **3a**,**b**; (c) H_2 (1 atm), MeOH; $(Boc)_2O$/MeOH, 100% for **4a**,**b**.

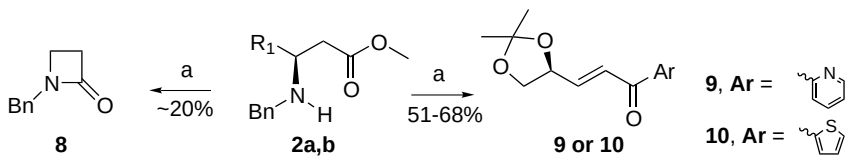
phy. Reaction of **2a**,**b** with $(BOC)_2O$ led to **3a**,**b**, while hydrogenolysis of **2a**,**b** followed by in situ reaction with $(BOC)_2O$, furnished **4a**,**b**.[9]

The reactions involving **3a**,**b** as substrates are shown in Scheme 3. Tertiary alcohols **6a**,**b** were formed when **5a** was used as a nucleophile. In contrast, ketones **7a**,**b** were obtained from the reaction of **3a**,**b** with **5b**.

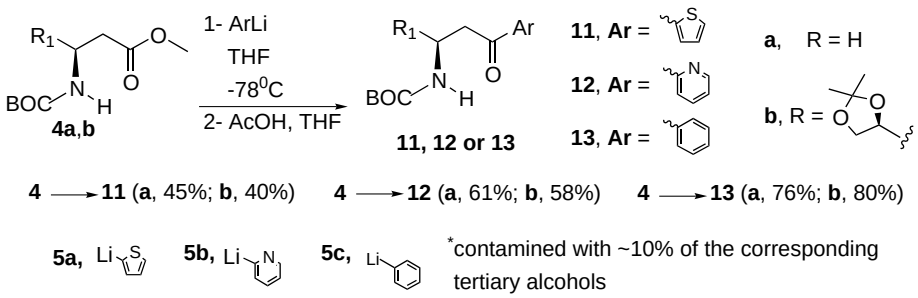
In the next sequence, the reaction of **2a**,**b** with **5a**,**b** was investigated (Scheme 4). In all cases neither ketones nor tertiary alcohols were formed and the reaction pathway



Scheme 3. Reaction of β-aminodiesters **2a**,**b** with phenyllithium derivatives **5a**–**c**.



Scheme 4. Addition of **5a**,**b** to enoates **2a**,**b**. (a) ArLi, THF, –78°C, 30 min; AcOH, THF.



Scheme 5. Preparation of β-aminoketones **11**–**13** from enoates **4a**,**b**.

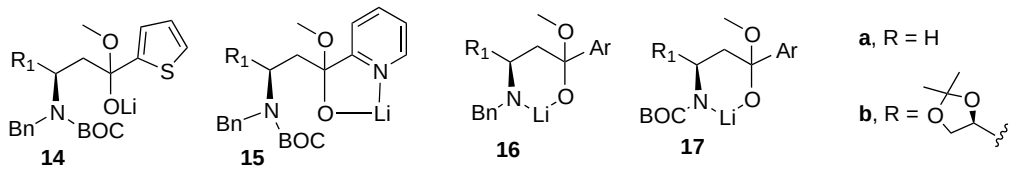


Figure 1. Possible tetrahedral lithium alcoxide intermediates in the additon of **5** to **2**, **3** and **4**.

was shown to be dependent on the structure of the substrate. While **2a** led to the β-lactam **8**, despite the ArLi used, arylenoates **9** and **10** were obtained from **2b**.

In the last set of experiments **4a**,**b** were used as substrates and ArLi **5a**–**c** as nucleophiles (Scheme 5). In all cases, despite the nature of both the β-aminoester and aryllithium employed, β-aminoarylketones were preferentially formed (**11a**,**b**, **12a**,**b** and **13a**,**b**).

Since tertiary alcohols (**6a**,**b**) were exclusively formed in the addition of **5a** to **3a**,**b** (Scheme 3), we propose the intervenience of **14a**,**b** as intermediates of these reactions (Fig. 1). Once the nitrogen atom in **3a**,**b** is not basic and the sulfur atom at the thiophenyl group in the incoming nucleophile has low affinity for the cation lithium, **14a**,**b** is not stabilized and it decomposes in the reaction medium, originating in the corresponding ketones, the precursors of **6a**,**b**. In contrast, the exclusive formation of ketones **7a**,**b** in the additions of **5b** to **3a**,**b** suggest the intervenience of intermediates **15a**,**b**, with the stabilization of the lithium alkoxide intermediate by the nitrogen atom of the incoming nucleophile.

On the other hand, for substrates **2a**,**b** and **4a**,**b**, bearing an acidic N–H bond, the initial formation of a lithium amide is expected. The basic nitrogen atom in these amides could stabilize the lithium alkoxide which originated from the addition of the first equivalent of **5a**,**b**, through the formation of a six membered chelated intermediate, **16a**,**b** and **17a**,**b**, respectively, precluding its decomposition in the reaction medium. However, different reaction courses were observed from **16a**,**b** and **17a**,**b** during the work-up. The decomposition of **16a**,**b** occurs with consecutive elimination of benzylamine, leading to the corresponding arylenoates **9** and **10**, while from **17a**,**b** the expected β-aminoarylketones **12** and **13** are formed.

In conclusion, we report for the first time, that the reaction pathway of the addition of aryllithium derivatives to α,β-aminoesters can be controlled by the nature of the substituents at the nitrogen atom and the nature of the aryl moiety in the nucleophile. The use of this strategy to prepare potencially bioactive 4-keto-4-aryl-homoalanines is on course in our laboratory.

Acknowledgements

This work was supported by grant from PRONEX (No. 41.96.0888.00). P.R.R.C and P.G.L. are recipients of CNPq fellowships.

References

1. (a) Jorgenson, M. J. *Org. React*. **1970**, *18*, 1; (b) Rubottom, G. M.; Kim, C. *J. Org. Chem*. **1983**, *48*, 1550.
2. (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett*. **1981**, *22*, 3815; (b) Betsbrugge, J. V.; Nest, W. V. D.; Verheyden, P.; Tourwe, D. *Tetrahedron* **1998**, *54*, 1753; (c) Berrée, F.; Chang, K.; Cobas, A.; Rapoport, H. *J. Org. Chem*. **1996**, *61*, 715; (d) Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Ricci, A.; Varchi, G. *Synlett* **1998**, 1013; (e) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-F.; Grabowski, E. J. J. *Tetrahedron Lett*. **1995**, *36*, 5461; (f) Myers, A. G.; Yoon, T. *Tetrahedron Lett*. **1995**, *36*, 9429.
3. O'Neill, B. T. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp. 398–399.
4. (a) Barluenga, J.; Pedregal, B.; Concellón, J. M. *Tetrahedron Lett*. **1993**, *34*, 4563; (b) Gassman, P. G.; O'Reilly, N. J. *J. Org. Chem*. **1987**, *52*, 2481; (c) Paleo, M. R.; Sardina, F. J. *Tetrahedron Lett*. **1996**, *37*, 3403; (d) Fermández-Megía, E.; Iglesias-Pintos, J. M.; Sardina, F. J. *J. Org. Chem*. **1997**, *62*, 4770; (e) Seki, M.; Matsumoto, K. *Tetrahedron Lett*. **1996**, *37*, 3165; (f) Draanen, N. A. V.; Arseniyadis, S.; Crimminss, M. T.; Heathcock, C. H. *J. Org. Chem*. **1991**, *56*, 2499.
5. For a similar reaction involving aryltin as nucleophile and palladium as catalyst, see: Salituro, F. G.; McDonald, A. I. *J. Org. Chem*. **1988**, *53*, 6138.
6. 2-Lithiumthiophene was prepared by the reaction of thiophene with *n*-BuLi in THF at 0°C and 2-lithiumpyridine was prepared from 2-bromopyridine by the bromine–lithium exchange with *n*-BuLi at −78°C.
7. Mann, J.; Partlett, N.; Thomas, A. *J. Chem. Res*. **1987**, 369.
8. Matsunaga, H.; Sakamaki, T.; Nagaoka, H.; Yamada, Y. *Tetrahedron Lett*. **1983**, *24*, 3009.
9. Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett*. **1989**, *30*, 837.