ORGANIC LETTERS

2005
Vol. 7, No. 2
215−218

Stereoselective Enol Tosylation: Preparation of Trisubstituted α,β-Unsaturated Esters

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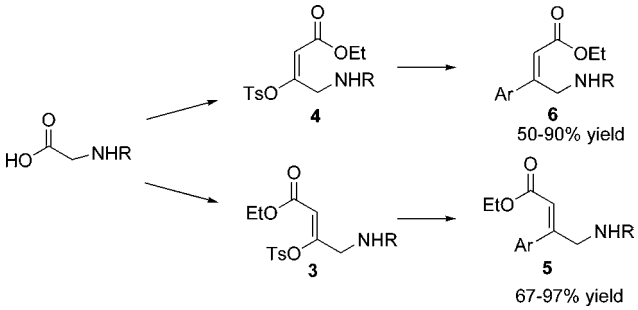
Received October 18, 2004

ABSTRACT



The stereoselective preparation of (*E*)- or (*Z*)-trisubstituted α,β-unsaturated esters in three steps from N-protected glycine is presented. The key step in the synthesis is the highly selective enol tosylation of γ-amino β-keto esters. The enol tosylates are stable, crystalline compounds that undergo smooth and effective Suzuki–Miyaura coupling reaction with a variety of aryl boronic acids.

γ-Aminobutyric acid (GABA) analogues have received considerable attention as important target molecules in the pharmaceutical industry due to their profound effects on the various central nervous system functions. GABA analogues have been used as antispastic agents, mood enhancement agents, and tranquilizers. The common structural motif of these biologically active molecules is the γ-amino carbonyl group. In this context, the selective formation of γ-amino α,β-unsaturated esters is of significant interest. [1,2] Similarly, the trisubstituted α,β-unsaturated ester core is also a useful synthetic building block given the relatively straightforward method to incorporate it in a given synthesis, as well as the ability to perform asymmetric reductions of the double bond.[3,4] The reduction of the ester to afford a valuable difunctionalized allylic fragment has also been reported.[5]

We recently required access to both geometric isomers of a γ-amino α,β-unsaturated ester. There are no general methods for accessing both the (*Z*)- and (*E*)-esters of this type. Consequently, our interests centered on developing an efficient and highly selective route for the formation of compounds of the general structure **5** and **6**. Intermediates lacking the key amino functionality have been prepared by utilizing Horner−Emmons chemistry[6] or a Reformatsky reaction/elimination protocol.[7] These transformations usually involve multiple steps and poor selectivity and result in low overall yields. Other methods include the addition of

(1) Becht, J.; Meyer, O.; Helmchen, G. *Synthesis* **2003**, *18*, 2805−2810. Allan, R. D.; Bates, M. C.; Drew, C. A.; Duke, R. K.; Hambley, T. W.; Johnston, G. A. R.; Mewett, K. N.; Spence, I. *Tetrahedron* **1990**, *46*, 2511−2524. Silverman, R. B.; Invergo, B. J.; Levy, M. A.; Andrew, C. R. *J. Bio. Chem*. **1987**, *262*, 3192−3195. Karla, R.; Ebert, B.; Thorkildsen, C.; Herdeis, C.; Johansen, T. N.; Nielsen, B.; Krogsgaard-Larsen, P. *J. Med. Chem*. **1999**, *42*, 2053−2059 and references therein.

(2) Hjeds, H.; Honoré, T. *Acta Chem. Scand. B* **1978**, *32*, 187−192.

(3) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem., Int. Ed*. **2003**, *42*, 943−946.

(4) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 9473−9474.

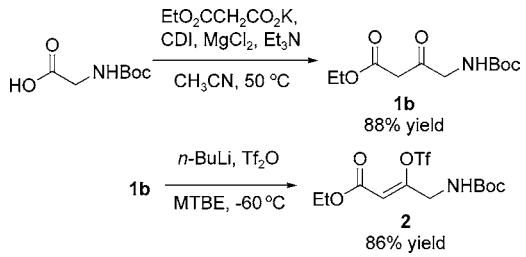
(5) Zahn, T. J.; Weinbaum, C.; Gibbs, R. A. *Bio. Med. Chem. Lett*. **2000**, *10*, 1763−1766. Martin, R.; Islas, G.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron* **2001**, *57*, 6367−6374. Mu, Y.; Gibbs, R. A. *Tetrahedron Lett*. **1995**, *36*, 5669−5672. Srikrishna, A.; Reddy, T. J.; Kumar, P. P.; Vijaykumar, D. *Synlett* **1996**, *1*, 67−68.

10.1021/ol047854z CCC: $30.25
Published on Web 12/17/2004

organocuprates to alkynes,[8] asymmetric addition of aryl boronic acids to unsaturated esters,[9] and Heck coupling of aryl halides with acrylates.[10] The alkyne substrates can be difficult to prepare, and both other methods provide access to only the (*E*)-isomer.

Although it was known that the selectivity of β-keto ester enolization could be controlled by the choice of base and/or solvent,[11,12] to our knowledge there are no reports of the selective enolization of γ-amino β-keto esters.[13] It was uncertain what effect, if any, an adjacent NH group would have on the selectivity of the enolization step. Herein, we describe the stereoselective formation of both the (*Z*)- and (*E*)-γ-amino α,β-unsaturated esters in three steps from N-protected glycine derivatives. In this letter, we also highlight the use of enol tosylates as a practical alternative to enol triflates.

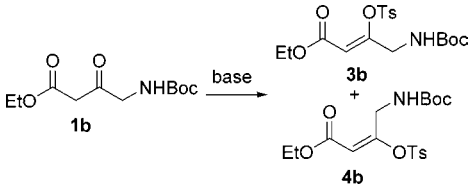
Scheme 1



The requisite β-keto esters were prepared from N-protected glycine derivatives via a Masamune homologation protocol in good yield.[2,14] Our initial focus was on the development of an enolization process for the stereoselective preparation of enol triflates and the subsequent cross-coupling of these substrates to aryl boronic acids. The selective formation of the (*Z*)-enol triflate[15] from the β-keto ester was achieved in 86% isolated yield with 1.1 equiv of *n*-BuLi in MTBE at −60 °C. Investigation of the subsequent Suzuki−Miyaura coupling step indicated that the enol triflate was unstable to the reaction conditions. Substrate decomposition was reduced in the presence of LiBr and LiCl,[16] but the yields were typically less than 50% and difficult to reproduce. Other research groups have circumvented stability issues of triflates by preparing the nonaflate equivalents; however, these compounds were used in cross-coupling reactions with organozinc reagents[17] or under Stille coupling conditions.[13] We desired a process that did not require a separate transmetalation step or involve the use of tin reagents. Therefore, we turned our attention toward the stereoselective preparation of enol tosylates and their potential use as cross-coupling partners with readily available aryl boronic acids. While cross-coupling reactions of enol tosylates are much less developed and under-utilized relative to enol triflates, there has been much recent interest in the transition metal-catalyzed cross-coupling reactions of aryl and vinyl tosylates.[18]

Although the (*Z*)-enol tosylate **3** is selectively formed under kinetic conditions and Ts_2O is much less reactive than Tf_2O, treatment of **1b** with LHMDS followed by Ts_2O addition afforded ~20:1 ratio of the (*Z*)-:(*E*)-isomers and a 67% assay yield.[19] An optimization study identified LDA as the ideal base for deprotonation of **1b**, while *n*-BuLi is optimal for **1a** (20:1, 80% assay yield). Use of NaHMDS degrades the selectivity for formation of (*Z*)-isomer, while KHMDS reverses the selectivity, resulting in the formation of the (*E*)-isomer as the major product (Table 1). If KHMDS is used as the base in the presence of 1 equiv of LiBr, good selectivity for the formation of the (*Z*)-isomer is maintained, but the yield is diminished. These results are consistent with a substantial counterion effect on the reaction. We were also interested in preparing the (*E*)-enol tosylate isomer. Although literature reports describe the use of a strong base in polar

Table 1. Examination of Various Bases on the Formation of Enol Tosylates from β-Keto Ester **1b**



base	solvent	**3b**:**4b**	% assay yield[a]
LHMDS[b]	THF	24:1	63
LHMDS[b]	THF/30 mol % DMF	7:1	23
n-BuLi[b]	THF	30:1	65
LDA[b]	THF	12:1	93
NaHMDS[b]	THF	2:1	52
KHMDS[b]	THF	1:7	72
KHMDS[b,c]	THF	16:1	46
Et_3N[d]	CH_2Cl_2	1:25	83

[a] Assay yield determined by HPLC analysis of the reaction mixture with comparison to a purified standard. [b] Reaction conditions: keto ester **1b** (200 mg, 0.85 mmol) was dissolved in 5 mL of THF cooled to −50 °C; the reaction was aged for 3 h after base (1.1 equiv) addition, and then Ts_2O (1.1 equiv) was added and the reaction allowed to warm to room temperature. [c] LiBr (1 equiv) was added. [d] Reaction conditions: keto ester **1b** (7.88 g, 32.1 mmol) and Ts_2O (1.02 equiv) in 100 mL CH_2Cl_2 at 0 °C were added followed by Et_3N, and the reaction was allowed to warm to room temperature.

(6) Song, Y.; Clizbe, L.; Bhakta, C.; Teng, W.; Li, W.; Wu, Y.; Jia, Z. J.; Zhang, P.; Wang, L. Doughan, B.; Su, T.; Kanter, J.; Woolfrey, J.; Wong, P.; Huang, B.; Tran, K.; Sinha, U.; Park, G.; Reed, A.; Malinowski, J.; Hollenbach, S.; Scarborough, R. M.; Zhu, B. *Bio. Med. Chem. Lett.* **2002**, *12*, 1511−1515.

(7) Thakur, V. V.; Nikalje, M. D.; Sudalai, A. *Tetrahedron: Asymmetry* **2003**, *14*, 581−586.

(8) Dieter, R. K.; Lu, K. *J. Org. Chem.* **2002**, *67*, 847−855. Dieter, R. K.; Lu, K.; Velu, S. E. *J. Org. Chem.* **2000**, *65*, 8715−8724.

(9) Meyer, O.; Becht, J.; Helmchen, G. *Synlett* **2003**, *10*, 1539−1541.

(10) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000.

(11) Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1984**, *25*, 1333−1336. Gebauer, O.; Brückner, R. *Synthesis* **2000**, *4*, 588−602.

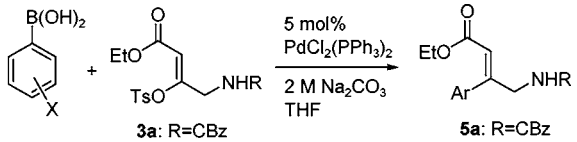
(12) Shao, Y.; Eummer, J. T.; Gibbs, R. A. *Org. Lett.* **1999**, *1*, 627−630.

(13) Example of selective enolization of a trisubstituted amino keto ester: Bösche, U.; Nubbemeyer, U. *Tetrahedron* **1999**, *55*, 6883−6904.

(14) Jones, R. C. F.; Bhalay, G.; Carter, P. A.; Duller, K. A. M.; Dunn, S. H. *J. Chem. Soc., Perkin Trans. 1* **1999**, *7*, 765−776.

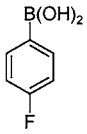
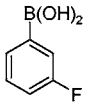
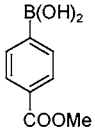
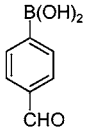
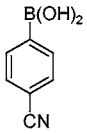
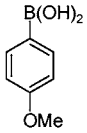
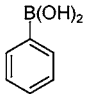
(15) Geometry was assigned on the basis of NOE studies, and the (*E*)-isomer was not observed by HPLC in the reaction mixture.

Table 2. Suzuki−Miyaura Cross-Coupling of (*Z*)-Enol Tosylates with Aryl Boronic Acids



3a: R=CBz
3b: R=Boc

5a: R=CBz
5b: R=Boc

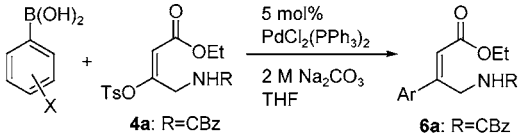
Entry	Boronic Acid	% yield 5a	% yield 5b
1		76	91
2		72	95
3		76	81
4		80	76
5		67	97
6		86	87
7		--	93
8		72	90

aprotic solvents (KHMDS in DMF)[20] to afford the (*E*)-isomer,[12] a much simpler procedure was developed using Et_3N in CH_2Cl_2.[21] This protocol affords both **4a** and **4b** in good yield and purity. An important property of these enol tosylates is that they are stable crystalline solids that may be readily purified by crystallization. Also, unlike Tf_2O, a liquid that is readily hydrolyzed to triflic acid, Ts_2O is a stable solid that can be easily weighed on the benchtop.

(16) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201−2208 and references therein.

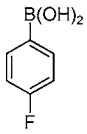
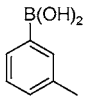
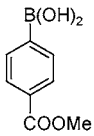
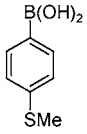
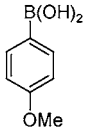
(17) Bellina, F.; Ciucci, D.; Rossi, R.; Vergamini, P. *Tetrahedron* **1999**, *55*, 2103−2112. Romero, D. L.; Manninen, P. R.; Han, F.; Romero, A. G. *J. Org. Chem.* **1999**, *64*, 4980−84.

Table 3. Suzuki−Miyaura Cross-Coupling of (*E*)-Enol Tosylates with Aryl Boronic Acids



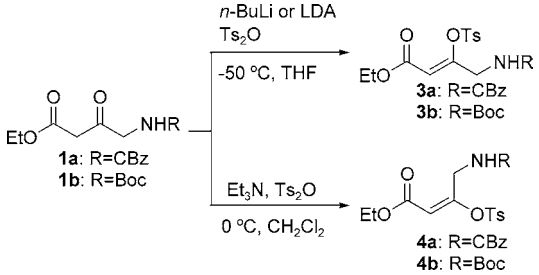
4a: R=CBz
4b: R=Boc

6a: R=CBz
6b: R=Boc

Entry	Boronic Acid	% yield 6a	% yield 6b
1		72	61
2		50	81
3		74	84
4		75	86
5		73	72
6		70	65
7		75	90

With access to both stereodefined enol tosylates, we began to investigate the coupling of these intermediates with a variety of aryl boronic acids. Results from optimization studies show catalytic $PdCl_2(PPh_3)_2$ with aqueous Na_2CO_3

Scheme 2



in THF to be the best reaction conditions for cross-coupling of both enol tosylate isomers. Cross-coupling works efficiently for aryl boronic acids containing electron-withdrawing groups (Table 2, entries 1−3, 5, and 6) and electron-neutral groups (entry 8). Aryl boronic acids containing an electron-donating group are also tolerated (entries 4 and 7), as is an ortho-substituted aryl boronic acid. Control experiments performed in the absence of Pd catalyst show no starting material conversion, thereby ruling out an addition/elimination pathway. In addition, the fact that the reactions provide pure geometrical isomers also argues against an addition/elimination pathway.[22] The (*E*)-enol tosylates also undergo cross-coupling reactions with a range of aryl boronic acids. As shown in Table 3, electron-withdrawing groups are still tolerated in the reaction, although lower yields are observed with some of the N-CBz derivatives (entry 2). The reaction works effectively with a variety of electron-donating substituents (entries 4−6), and once again, an ortho substituent on the aryl boronic acid is tolerated. In general, lower yields are obtained with the (*E*)-enol tosylate than with the (*Z*)-isomer in these cross-coupling reactions.[23]

In conclusion, a rapid and highly selective approach for the preparation of aromatic trisubstituted α,β-unsaturated esters from readily available glycine derivatives has been achieved. This approach is highlighted by the selective enolization of keto esters **1a**,**b** and formation of the corresponding enol tosylates. Both geometric enol tosylate derivatives undergo efficient cross-coupling reactions with electronically diverse aryl boronic acids to afford a wide variety of aromatic trisubstituted α,β-unsaturated esters. We anticipate that these esters will be useful synthetic derivatives and that enol tosylates will continue to emerge as viable synthetic alternatives to enol triflates.

Acknowledgment. We thank Robert Reamer and Dr. Peter Dormer for assistance in NMR interpretation.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047854Z

(18) Huffman, M. A.; Yasuda, N. *Synlett* **1999**, *4*, 471−473. Lakshman, M. K.; Thomson, P. F.; Nuqui, M. A.; Hilmer, J. H.; Sevova, N.; Boggess, B. *Org. Lett.* **2002**, *4*, 1479−1482. Wu, J.; Zhu, Q.; Wang, L.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 670−673. Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818−11819. Lakshman, M.; Thomson, P.; Nuqui, M.; Hilmer, J.; Sevova, N.; Boggess, B. *Org. Lett.* **2002**, *4*, 1479−1482. Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049−3051. Percec, V.; Golding, G. M.; Smidrkal, J. Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447−3452.

(19) Assignment of (*E*)- and (*Z*)-isomers was made on the basis of NMR and NOE studies. (*E*)-Enol tosylate geometry confirmed by X-ray crystallography.

(20) From Table 1, the presence of 30 mol % DMF in THF with LHMDS results in a degradation of the *Z*/*E* ratio. However, there are multiple products and low yields of enol tosylates.

(21) Crisp, G. T.; Meyer, A. G. *J. Org. Chem.* **1992**, *57*, 6972−6975.

(22) From Table 3, entry 2a gives 5% isomerization and entry 1a gives 3% isomerization. In all other examples, <3% isomerization is observed. Control experiments: **4a**, phenyl boronic acid and Na_2CO_3 solution were heated for 12 h at 40 °C; **4b**, 4-thiomethyl phenyl boronic acid and Na_2CO_3 were heated for 12 h at 40 °C. In both cases, no conversion to product was observed by HPLC.

(23) The major byproduct for some of these reactions is the homocoupled biaryl product, which is consistent with competitive decomposition of the boronic acid. However, some of the lower yielding reactions contain multiple byproducts that were not characterized.