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Stereoselective Synthesis of Acetoacetate-Derived Enol Triflates

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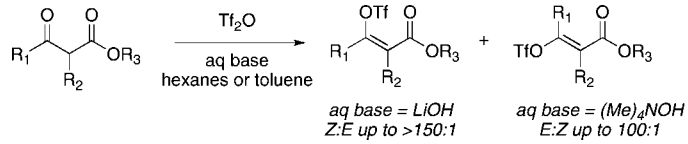
ABSTRACT

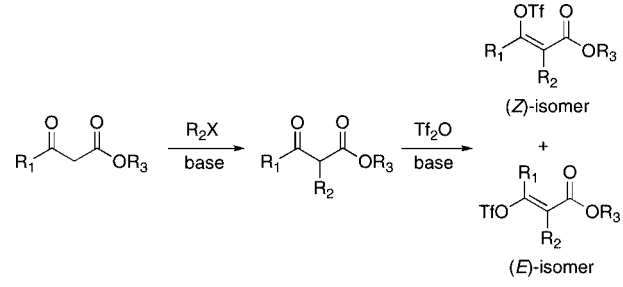


A highly stereoselective method for preparing (*Z*)- and (*E*)-enol triflates derived from substituted acetoacetate derivatives is described. The salient feature of this methodology is the use of Schotten−Baumann-type conditions to control enolate geometry using either aqueous LiOH (*Z*-selective) or aqueous $(Me)_4NOH$ (*E*-selective) in combination with triflic anhydride to provide a practical and predictable approach to these valuable substrates.

Enol triflates have served as strategic precursors to a number of elegant syntheses toward important target molecules including isoprenoids,[1] α,β-butenolides,[2] carbapenems,[3] phormoidrides,[4] leptofuranin D,[5] agelasimines,[6] the latrunculin macrolides,[7] and angiotensin II receptor antagonists.[8] In addition, they continue to serve as indispensable substrates toward the development of new cross-coupling methodologies[9] and more recently in carbon−carbon bond fragmentation reactions.[10]

We have been interested in utilizing enol triflates as valuable precursors in our own methodology development. In particular, we were most eager to utilize enol triflates derived from acetoacetate derivatives since the starting materials are obtainable in bulk quantities and easy to functionalize through standard alkylation chemistry en route to fully substituted substrates (Scheme 1). We assumed (as others have)[11] that we could readily obtain in a stereoselective fashion both (*Z*)- and (*E*)-enol triflates derived from various acyclic β-keto esters with relative ease and in high yields given their aforementioned historical precedence. However, we were surprised after a thorough survey of the literature that a general and practical method to stereoselec-

Scheme 1



(1) (a) Shao, Y.; Eummer, J. T.; Gibbs, R. A. *Org. Lett.* **1999**, *1*, 627. (b) Mu, Y.; Gibbs, R. A. *Tetrahedron Lett.* **1995**, *36*, 5669. (c) Gibbs, R. A.; Krishnan, U.; Dolence, J. M.; Poulter, C. D. *J. Org. Chem.* **1995**, *60*, 7821.

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(4) (a) Leighton, J. L.; Bio, M. M. *J. Org. Chem.* **2003**, *68*, 1693. (b) Bio, M. M.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 2905. (c) Bio, M. M.; Leighton, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 890.

(5) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2003**, *68*, 7428.

(6) Ohba, M.; Kawase, N.; Fujii, T. *J. Am. Chem. Soc.* **1996**, *118*, 8250.

(7) (a) Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Jensen, J. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 5358. (b) Fürstner, A.; De Souza, D.; Turet, L.; Fenster, M. D. B.; Parra-Rapado, L.; Wirtz, C.; Mynott, R.; Lehmann, C. W. *Chem.−Eur. J.* **2007**, *13*, 115.

(8) Keenan, R. M.; Weinstock, J.; Finkelstein, J. A.; Franz, R. G.; Gaitanopoulos, D. E.; Girard, G. R.; Hill, D. T.; Morgan, T. M.; Samanen, J. M.; Hempel, J.; Eggleston, D. S.; Aiyar, N.; Griffin, E.; Ohlstein, E. H.; Stack, E. J.; Weidley, E. F.; Edwards, R. *J. Med. Chem.* **1992**, *35*, 3858.

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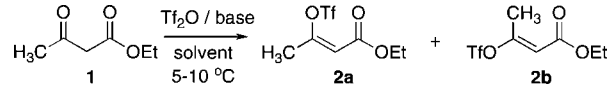
tively synthesize both geometric isomers on a broad range of acyclic acetoacetate derivatives has yet to fully emerge. We did come across sporadic reports on methods to selectively generate both enolate isomers on isolated examples.[12] Nonetheless, these methods appear to be optimized specifically for those substrates and have not been demonstrated on a range of substituted acetoacetates. As a consequence, many are left to employ processes that are poorly selective or, in the worse case scenario, selective for the undesired isomer.

The synthetic utility of new methodology should be gauged not only by the products that are produced but also by the availability of the starting materials that feed into it. It is not surprising that if starting materials are neither commercially available nor accessible in a few short, practical steps the methodology will suffer limited application. Thus, we realized that any methodology we develop which employs enol triflates as entry points will be of little value if we cannot first practically access these substrates with high stereoselectivity and yields. In this Letter, we wish to report our findings toward achieving this goal.

Given the precedence of successfully using triflic anhydride to synthesize aryl triflates under Schotten−Baumann-type conditions,[13] our efforts initially focused on using various aqueous bases as a means of controlling enolate geometry by judicious choice of the counterion. A summary of our most encouraging results from our screening efforts using ethyl acetoacetate (**1**) is presented in Table 1. We quickly identified the combination of hydrocarbon-based solvents and saturated aqueous LiOH (∼5 N) as a convenient route to the (*Z*)-isomer **2a** with high selectivity (>150:1) and assay yield (94% in hexanes). In constrast, aqueous solutions of tetraalkylammonium hydroxides were highly *E*-selective. We found that $(Me)_4NOH$ (15 wt % in water) was superior providing the (*E*)-enol triflate **2b** with good *E*-selectivity (24:1) and assay yield (84% in hexanes).[14]

Table 1. Screening of Various Bases and Solvents for the Stereoselective Formation of (*Z*)- and (*E*)-Enol Triflates from Ethyl Acetoacetate[a]



aqueous base	solvent	**2a**:**2b**[b]	assay yield[c]
2 N NaOH	THF	N/A	<5%
2 N NaOH	MTBE	N/A	<5%
2 N NaOH	toluene	1:2.6	35%
2 N KOH	toluene	1:9.5	63%
2 N CsOH	toluene	1:6.1	76%
2 N LiOH	toluene	34:1	81%
sat. LiOH[d]	toluene	>150:1	91%
	hexanes	**>150:1**	**94%**
$(Bu)_4NOH$[e]	toluene	1:39	30%
$(Me)_3BnNOH$[e]	toluene	1:20	61%
$(Me)_4NOH$[f]	hexanes	1:23	79%
$(Me)_4NOH$[g]	toluene	1:18	82%
	hexanes	**1:24**	**84%**

[a] Reaction conditions: ethyl acetoacetate (260 mg, 2.0 mmol) was dissolved in 10 mL of solvent and cooled to 5 °C; aqueous base (5 equiv) was then added, and the biphasic mixture was stirred for 5 min. Then triflic anhydride (2.5 equiv) was added dropwise to maintain the internal reaction temperature < 10 °C. [b] Isomeric ratios determined by HPLC analysis. [c] Assay yield determined by HPLC analysis of the reaction mixture using a purified standard of each isomer. [d] ∼5.0 N. [e] 40 wt % solution in water. [f] 25 wt % solution. [g] 15 wt % solution.

With two predictable methods in hand to selectively access either the (*Z*)-enol triflate (via aqueous LiOH) or the (*E*)-enol triflate (via aqueous $(Me)_4NOH$), we set out to challenge the methodology on a range of acetoacetate derivatives (Table 2). From our results, some general comments can be made. First, the stereoselectivities and yields are consistently higher for (*Z*)-enol triflates than the corresponding (*E*)-enol triflates. Second, in many cases, the crude enol triflates are obtained in >98% purity by simply removing the aqueous phase from the reaction followed by concentration of the organic phase. Finally, increasing substitution at the 4-position has a dramatic impact on obtaining the (*E*)-enol triflates selectively and significantly reduces the overall conversion. The most dramatic example is seen with ethyl benzoylacetate where the (*Z*)-enol triflate **8a** is the sole isomer isolated regardless of the base employed.[15]

We next set out to explore the scope on a selected series of 2-substituted acetoacetate derivatives in an attempt to access fully substituted β-keto enol triflates in a stereoselective fashion.[16] The results are summarized in Table 3.

(9) For a general review of enol triflate coupling reactions, see: (a) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47. (b) For recent examples, see: Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943. (c) Wallace, D. J.; Klauber, D. J.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749. (d) Li, S.; Dieter, K. *J. Org. Chem.* **2003**, *68*, 969. (e) Dillinger, S.; Bertus, P.; Pale, P. *Org. Lett.* **2001**, *3*, 1661. (f) Movassaghi, M.; Ondrus, A. E. *J. Org. Chem.* **2005**, *70*, 8638.

(10) (a) Tummatorn, J.; Dudley, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 5050. (b) Kamijo, S.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 175. (c) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028.

(11) Although many methods that utilized enol triflates make reference to the ease of accessibility of both acyclic stereoisomers, most substrate tables in these reports are filled with cyclic examples providing evidence to the contrary.

(12) (a) Baxter, J. M.; Steinhuebel, D.; Palucki, M.; Davies, I. W. *Org. Lett.* **2005**, *7*, 215. (b) Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1984**, *25*, 1333. (c) Gebauer, O.; Brückner, R. *Synthesis* **2000**, *4*, 588. See also ref 1a.

(13) Frantz, D. E.; Weaver, D. G.; Carey, J. P.; Kress, M. H.; Dolling, U. H. *Org. Lett.* **2002**, *4*, 4717.

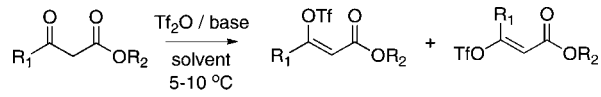
(14) Although the results in Table 1 suggest hexanes is the preferred solvent in both cases, toluene provides a suitable alternative for substrates with limited solubility in hexanes.

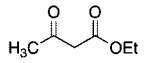
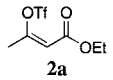
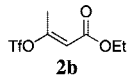
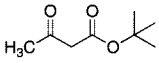
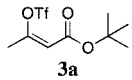
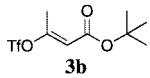
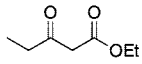
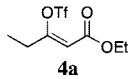
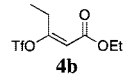
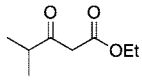
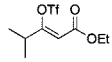
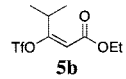
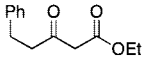
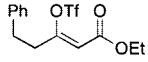
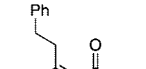
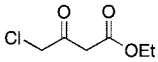
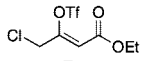
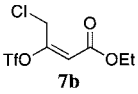
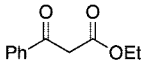
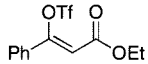
(15) We surveyed a number of different conditions (both published and unpublished) in an attempt to obtain the (*E*)-enol triflate derived from ethyl benzoylacetate under basic conditions. In every experiment, we could only obtain the (*Z*)-isomer. For a report on obtaining the (*E*)-isomer under acidic conditions, see: (a) Vasilyev, A. V.; Walspurger, S.; Chassaing, S.; Pale, P.; Sommer, J. *Eur. J. Org. Chem.* **2007**, 5470.

(16) Reports of gaining access to both enol triflates stereoisomers stereoselectively on 2-substituted derivatives are scarce. See ref 2. Other selected examples: (a) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770. (b) Lipshutz, B. H.; Alami, M. *Tetrahedron Lett.* **1993**, *34*, 1433. (c) Yao, M.-L.; Deng, M.-Z. *Tetrahedron Lett.* **2000**, *41*, 9083. (d) Ide, M.; Nakata, M. *Synlett* **2001**, 1511. (e) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393. (f) Bobeck, D. R.; Warner, D. L.; Vedejs, E. *J. Org. Chem.* **2007**, *72*, 8506.

(17) The (*E*)-isomer (**12b**) derived from ethyl 2-phenylacetoacetate was a notable exception. Multiple attempts at achieving complete conversion by increasing the amounts of either base and/or Tf_2O did not provide any improvements. In addition, regardless of the conditions we tried, we could not separate the enol triflate isomers away from the unreacted starting material via column chromatography.

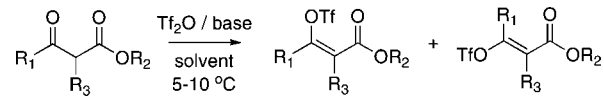
Table 2. Stereoselective Synthesis of Enol Triflates Derived from Acetoacetate Derivatives[a]

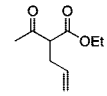
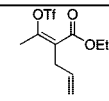
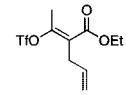
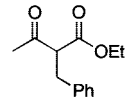
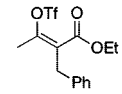
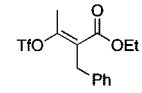
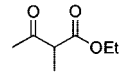
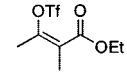
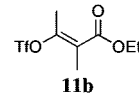
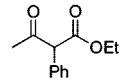
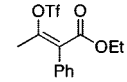
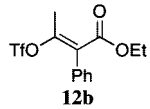
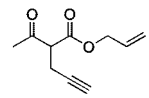
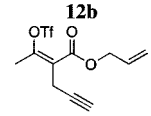
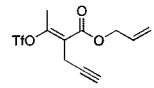


substrate	base solvent	product[b]	*Z* : *E* ratio[c]	yield[d]
	LiOH toluene	 **2a**	>150:1	85%[e]
	$(Me)_4NOH$ hexanes	 **2b**	1:24	70%[e]
	LiOH hexanes	 **3a**	>150:1	93%[e]
	$(Me)_4NOH$ hexanes	 **3b**	1:22	95%[e]
	LiOH toluene	 **4a**	98:1	95%[e]
	$(Me)_4NOH$ hexanes	 **4b**	1:8.3	73%
	LiOH toluene	 **5a**	>150:1	93%[e]
	$(Me)_4NOH$ hexanes	 **5b**	1:1.9	30%
	LiOH toluene	 **6a**	>150:1	94%[e]
	$(Me)_4NOH$ hexanes	 **6b**	1:4.2	55%
	LiOH hexanes	 **7a**	105:1	85%[e]
	$(Me)_4NOH$ hexanes	 **7b**	1:6.6	29%
	LiOH toluene	 **8a**	>150:1	98%[e]
	$(Me)_4NOH$ toluene	**8a**	>150:1	25%

[a] All reactions were performed with 2.5 equiv of Tf_2O and either 7.5 equiv of sat. LiOH or 5.0 equiv of 15 wt % $(Me)_4NOH$ in water in an open-air flask. [b] Stereochemistry assigned by comparison with literature values or by NOE studies. [c] Ratios determined by ^1H NMR analysis of the crude reaction mixture. [d] Isolated yields. [e] No purification required.

Table 3. Stereoselective Synthesis of Enol Triflates Derived from 2-Substituted Acetoacetate Derivatives[a]



substrate	base solvent	product[b]	*Z* : *E* ratio[c]	yield[d]
	LiOH hexanes	 **9a**	>150:1	92%[e]
	$(Me)_4NOH$ hexanes	 **9b**	1:28	87%[e]
	LiOH hexanes	 **10a**	>150:1	98%[e]
	$(Me)_4NOH$ hexanes	 **10b**	1:32	94%[e]
	LiOH toluene	 **11a**	36:1	67%[e]
	$(Me)_4NOH$ hexanes	 **11b**	1:50	83%[e]
	LiOH toluene	 **12a**	>150:1	93%[e]
	$(Me)_4NOH$ hexanes	 **12b**	1:4.1	63%[f]
	LiOH hexanes	 **13a**	>150:1	76%
	$(Me)_4NOH$ hexanes	 **13b**	1:100	94%[e]

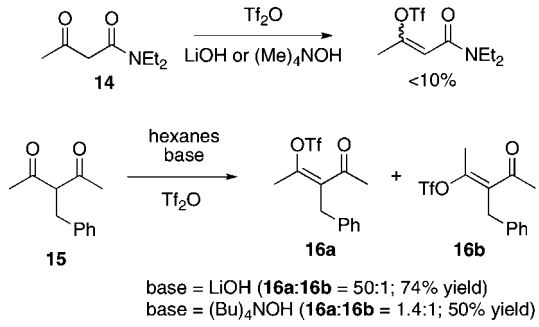
[a] All reactions were performed with 2.5 equiv of Tf_2O and either 7.5 equiv of sat. LiOH or 5.0 equiv of 15 wt % $(Me)_4NOH$ in water in an open-air flask. [b] Stereochemistry assigned by comparison with literature values or by NOE studies. [c] Ratios determined by ^1H NMR analysis of the crude reaction mixture. [d] Isolated yields. [e] No purification required. [f] Isomers could not be separated by column chromatography. Contaminated with ~10% unreacted starting material.

Again, some general comments can be made based on the results we observed. The same trend was observed as before where we routinely obtain the (*Z*)-enol triflates with much higher selectivities than the corresponding (*E*)-enol triflates. The only exception is ethyl 2-methylacetoacetate where we see slightly higher selectivity for the (*E*)-enol triflate (**11b**) compared to the corresponding (*Z*)-isomer (**11a**). Again, most of the products are obtained in >98% purity by a simple extractive workup followed by concentration.[17]

In its current state of development, there are several limitations that we would like to mention. We noticed in some cases that viscous and/or heterogeneous solutions were obtained

during the course of these reactions. This does not appear to impact yields on a small scale (<10 mmol) with vigorous magnetic stirring. Nonetheless, on a larger scale we recommend using mechanical overhead stirring to ensure proper mixing. In addition, all attempts to access either enol triflate isomer from β-keto amide **14** failed to give acceptable yields (<10%). Finally, we found that although the 1,3-diketone **15** serves as a viable substrate to (*Z*)-enol triflate **16a** with high selectivity (50:1) and good yield (74%) we were unable to obtain the (*E*)-enol triflate **16b** selectively even when $(Bu)_4NOH$ was employed as the base (Scheme 2).

Scheme 2



In conclusion, we have developed a practical process to stereoselectively obtain both (*Z*)- and (*E*)-enol triflates from substituted acetoacetate derivatives. The salient feature of this methodology is the use of Schotten−Baumann-type conditions to dictate enolate geometry either by using LiOH (*Z*-selective) or $(Me)_4NOH$ (*E*-selective) in combination with triflic anhydride and hydrocarbon-based solvents. The reactions do not require an inert atmosphere, and more notably in many cases the crude products are isolated in >98% purity obviating the need for chromatographic purification. The ease of accessing both enol triflate isomers in a stereoselective and predictable fashion on a broad range of substrates should significantly increase the utility of prior methodologies and inspire new methods toward stereodefined olefinic products.

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Supporting Information Available: General experimental procedures and characterization data (^1H and ^{13}C NMR, ESI-MS) for all products reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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