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General, Robust, and Stereocomplementary Preparation of β-Ketoester Enol Tosylates as Cross-Coupling Partners Utilizing TsCl−*N*-Methylimidazole Agents

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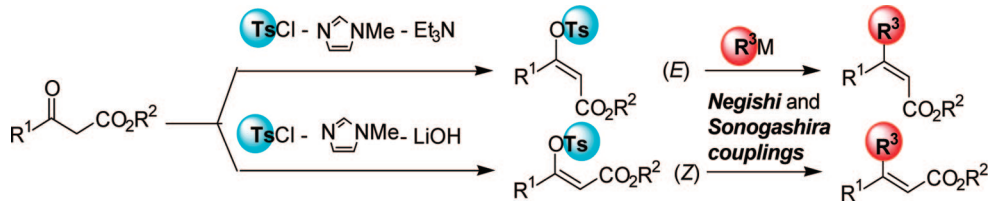
ABSTRACT



We have developed a general, robust, and cost-effective method for the (*E*)- or (*Z*)-stereocomplementary enol tosylation of β-ketoesters using TsCl−*N*-methylimidazole (NMI)−Et_3N or LiOH. TsCl coupled with NMI formed a highly reactive *N*-sulfonylammonium intermediate. Stereocongested secondary alcohols were smoothly sulfonylated using Ts(Ms)Cl−NMI−Et_3N. β-Ketoesters underwent (*E*)-selective tosylation using TsCl−NMI−Et_3N and (*Z*)-selective tosylation using TsCl−NMI−LiOH (total of 23 examples; 60%−99% yield). Stereoretentive Negishi and Sonogashira couplings using enol tosylates proceeded successfully to give trisubstituted α,β-unsaturated esters.

Tosylation and mesylation of alcohols are well-recognized fundamental processes in various fields of organic synthesis.[1] In our continuing study of mild, practical, and cost-effective condensation reactions, we reported four pyridine-free methods that utilized TsCl and a sterically uncongested amine system.[2] This protocol was applied in natural product synthesis and process chemistry, for example, vinblastine,[3] fluorescent amino acid derivatives,[4] and flumioxadine.[5] We present herein highly efficient (*E*)- and (*Z*)-stereocomplementary enol tosylations of β-ketoesters utilizing TsCl−*N*-methylimidazole (NMI)−Et_3N or LiOH (Scheme 1).

NMI is an efficient promoter of the condensation reactions, *O*-, *N*-, and *S*-acylations, esterification, amide formation, and thioesterification,[6] as well as *C*-acylation (crossed Ti−Claisen condensation).[7]

With this information taken into account, the fundamental tosylation reactivity was monitored using 3-octanol with a TsCl−NMI−Et_3N (most available tertiary amine) reagent

(1) Smith, M. T.; March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley: New York, 2001; p 576.

(2) (a) Tanabe, Y.; Yamamoto, H.; Yoshida, Y.; Miyawaki, T.; Utsumi, N *Bull. Chem. Soc. Jpn.* **1995**, *68*, 297. (K_2CO_3−cat. Et_3N−cat. Me_3N·HCl). (b) Yoshida, Y.; Sakakura, Y.; Aso, N.; Okada, S.; Tanabe, T. *Tetrahedron,* **1999**, *55*, 2183. (Et_3N−cat. Me_3N·HCl). (c) Yoshida, Y.; Shimonishi, K.; Sakakura, Y.; Okada, S.; Aso, N.; Tanabe, Y. *Synthesis* **1999**, 1633. [$(Me_2N(CH_2)_nNMe_2)$]. (d) Morita, J; Nakatsuji, H.; Misaki, T.; Tanabe, Y. *Green Chem.* **2005**, *7*, 711. [cat. $BnNMe_2$ ($BuNMe_2$)/H_2O/pH ∼10].

(3) (a) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137. (b) Miyazaki, T.; Yokoshima, S.; Simizu, S.; Osada, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 4737.

(4) Hudgins, R. P.; Huang, F.; Gramlich, G.; Nau, W. M. *J. Am. Chem. Soc.* **2002**, *124*, 556.

(5) Yoshida, R.; Sakai, M.; Sato, R.; Haga, T.; Nagano, E.; Oshio, H.; Kamoshita, K. *Proceedings of the Brighton Crop Protection Conference−Weeds*; BCPC: Hampshire, U.K., 1991; p 69.

(6) Wakasugi, K.; Iida, A.; Misaki, T.; Nishii, Y.; Tanabe, Y. *Adv. Synth. Catal.* **2003**, *345*, 1209.

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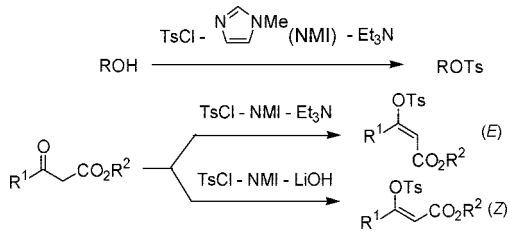
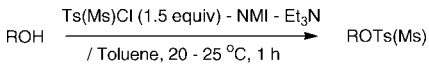
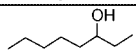
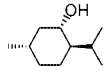
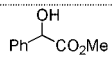
Scheme 1. Tosylations of Alcohols and β-Ketoesters Using a TsCl−*N*-Methylimidazole (NMI)−Et_3N or LiOH System



(Table 1). The combination of NMI and Et_3N exhibited a remarkable synergistic effect (entries 1−4).[8] In contrast, the use of DMAP, a super acylation catalyst, instead of Et_3N resulted in no reaction (entry 5). Stereocongested secondary alcohols, such as *l*-menthol, methyl mandelate, and 3,3-dimethyl-2-butanol, underwent the present reaction to give the desired tosylates (entries 7, 9, 11). Relevant mesylations also proceeded more smoothly (entries 8, 10, 12). This might be the most powerful and fastest method among the reported amine-promoted sulfonylations (entry 11).

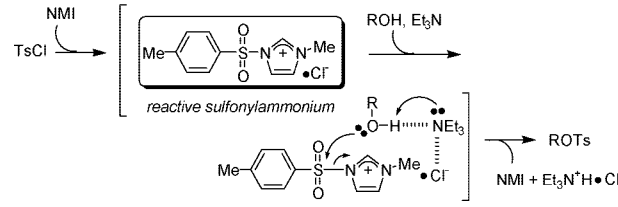
Table 1. Powerful Sulfonylation of Alcohols



entry	ROH	NMI / equiv	Et_3N / equiv		yield / %
1		none	1.5	Ts	NR
2		1.5	none		24
3		3.0	none		24
4		1.5	1.5		94
5		1.5 (DMAP)	1.5		NR
6				Ms	98
7		1.5	1.5	Ts	93
8				Ms	99
9		1.5	0.1	Ts	96
10				Ms	95
11		1.5	1.5	Ts	90[a] (36[a, b])
12				Ms	99[a]

[a] Chlorobenzene (C_6H_5Cl) was used instead of toluene. [b] Et_3N−Me_3N•HCl[2a] was used instead of NMI−Et_3N.

Scheme 2. Plausible Mechanism for NMI-Promoted Sulfonylation of Alcohol



A plausible mechanism for this observation is as follows (Scheme 2). The NMI reagent captures TsCl to form a highly reactive *N*-sulfonylammonium intermediate, which in turn condenses with an alcohol to produce a tosylate assisted by Et_3N, while releasing Et_3N•HCl. Careful ^1H NMR (300 MHz) monitoring of a mixture of TsCl and NMI in CD_3CN rationally supported the present hypothesis; the generation of a *N*-sulfonylammonium intermediate was unambiguously detected.[9] The apparent downfield chemical shift of NMI moieties in the intermediate is related to the higher sulfonylation reactivity of the present system in accordance with a relevant discussion.[8a] This successful result prompted us to investigate stereoselective enol tosylation of β-ketoesters.

(*E*)- or (*Z*)-Stereofixed enol sulfonates are recognized as useful cross-coupling partners. Enol triflates are generally used for this purpose,[10] but they have two drawbacks particularly for process chemistry: instability and high cost. Despite its high demand, there have been few investigation of enol tosylation. Recently, the Merck process group disclosed a notable stereocomplementary tosylation method for a sole specific γ-amino-β-ketoester using Ts_2O and Et_3N or LDA.[11] They rationally point out the advantage over enol triflates with regard to stability and benchtop handling procedures, etc. Expensive reagents (Ts_2O and LDA) and low temperature (−50 °C) for 3 h were, however, required.[12]

Our initial investigation was guided by the tosylation of methyl acetoacetate using TsCl−NMI−Et_3N or other bases (Table 2). The use of Et_3N successfully promoted the (*E*)-selective tosylation (entry 1), which is consistent with the reported reaction using Ts_2O and Et_3N.[11]

Lithium reagents (^{n}BuLi, LDA, LiHMDS, ^{t}BuOLi) promoted the (*Z*)-selective tosylation (entries 3−5, 8), whereas the use of KHMDS and NaHMDS decreased the selectivity (entries 6 and 7). More practical and robust LiOH exhibited

(7) (a) Misaki, T.; Nagase, R.; Matsumoto, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2005**, *127*, 2854. (b) Iida, A.; Nakazawa, S.; Okabayashi, T.; Horii, A.; Misaki, T.; Tanabe, Y. *Org. Lett.* **2006**, *8*, 5215. (c) Iida, A.; Nakazawa, S.; Nakatsuji, H.; Misaki, T.; Tanabe, Y. *Chem. Lett.* **2007**, *36*, 48. We have been pointing out that NMI is superior to DMAP for acylation reactions with regard to reactivity, cost, and toxicity [NMI (rat LD_{50}, oral, 1130 mg/kg) and DMAP (56 mg/kg)]

(8) This observation resembles the precedent reports of esterification and amide formations promoted by combined bases NMI and TMEDA. (a) Nakatsuji, H.; Morita, J.; Misaki, T.; Tanabe, Y *Adv. Synth. Catal.* **2006**, *348*, 2057. (b) Nakatsuji, H.; Morimoto, M.; Misaki, T.; Tanabe, Y. *Tetrahedron* **2007**, *50*, 12071.

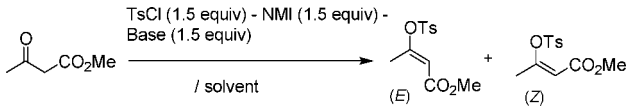
(9) NMI [δ 3.63 (s, 3H), 6.89 (s, 1H), 6.95 (s, 1H), 7.38 (s, 1H)] and **A** [δ 2.39 (s, 3H), 3.93 (s, 3H), 7.46−7.48(m, 2H), 7.70. (s, 1H), 8.02 (s, 1H), 8.12−8.15 (m, 2H), 11.05 (s, 1H)]. A chart was described in ESI.

(10) For a recent example Hansen, A. L.; Skrydstrup, T. *J. Org. Chem.* **2005**, *70*, 5997.

(11) Baxter, J. M.; Steinhuebel, D.; Palucki, M.; Davies, I. W. *Org. Lett.* **2005**, *7*, 215.

(12) Klapars, A.; Campos, K. R.; Chen, C-y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185. TsCl is ca. 1/10 more inexpensive than Ts_2O. It was commented that the use of TsCl caused α-chlorination as a side reaction.

Table 2. Tosylation of Methyl Acetoacetate Using TsCl−NMI−Bases



entry	base	temp / °C	solvent	yield / %[a]	*E* / *Z*[a]
1	Et_3N	20−25	C_6H_5Cl	92	98/2
2				trace[a]	
3	^nBuLi	−50 to −45	THF	80	3/97
4	LDA			70	8/92
5	LiHMDS			39	10/90
6	KHMDS			23	35/65
7	NaHMDS			69	39/61
8	^tBuOLi	0 → 20−25	C_6H_5Cl	68	7/93
9	Li_2CO_3			NR	
10	LiCl			NR	
11	LiOH			86	4/96
12				trace[b]	

[a] Determined by ^1H NMR of the crude products. [b] In the absence of NMI.

markedly higher reactivity and (*Z*)-selectivity (entry 11). The absence of NMI resulted in no reaction (entries 2 and 12).

The proposed mechanism is illustrated in Scheme 3. In Method A using Et_3N, the reaction does not proceed via chelation to give (*E*)-products, whereas in Method B using LiOH, the reaction proceeds via a Li-chelation pathway to give (*Z*)-products.

Scheme 3. Proposed Mechanism of the Stereoselective Enol Tosylation

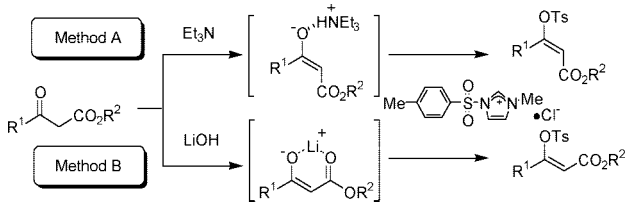
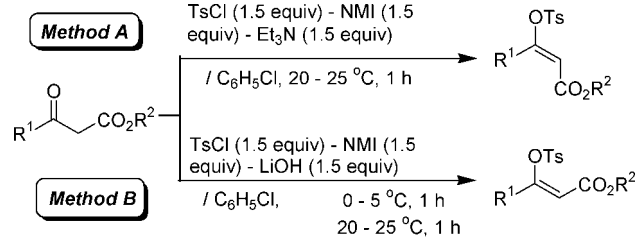


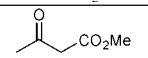
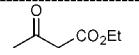
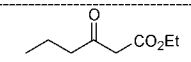
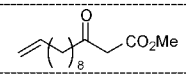
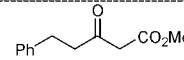
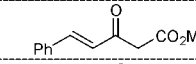
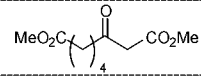
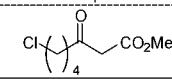
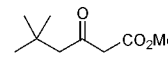
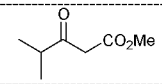
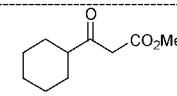
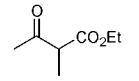
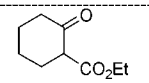
Table 3 lists the substrate-generality of the present enol tosylation. The salient features are as follows: (i) All substrates examined produced good to excellent results in yield and (*E*)- and (*Z*)-stereoselectivity. (ii) Double bonds, ω-chloro, and methyl ester functionalities were tolerated (entries 9−14). (iii) Sterically congested β-ketoesters and α-substituted β-ketoesters could also be applied (entries 15−23).

To demonstrate the present method, we focused our attention on the stereoretentive cross-coupling of enol tosylates. Table 4 lists the Negishi cross-coupling[13] of various enol tosylates. The present reaction proceeded under milder conditions than for the corresponding Suzuki−Miyaura coupling.[10]

(13) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.

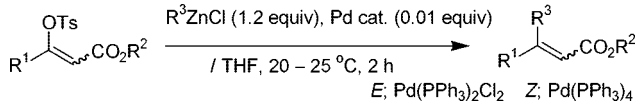
Table 3. Enol Tosylation of β-Keto Esters by TsCl−NMI−Bases

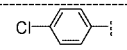
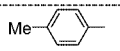
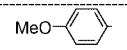
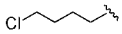


entry	$R^1CO_2R^2$	method[a]	product	yield / %	*E* / *Z*[b]
1		A	**1a**	92	98 / 2
2		B	**1b**	86	4 / 96
1		A	**2a**	92	98 / 2
2		B	**2b**	81	2 / 98
3		A	**3a**	99	95 / 5
4		B	**3b**	74	1 / 99
5		A	**4a**	92	98 / 2
6		B	**4b**	81	1 / 99
7		A	**5a**	91	98 / 2
8		B	**5b**	84	3/ 97
9		A	**6a**	97	95 / 5
10		B	**6b**	87	5 / 95
11		A	**7a**	95	96 / 4
12		B	**7b**	89	2/ 98
13		A	**8a**	80	95 / 5
14		B	**8b**	72	3 / 97
15		A	**9a**	97	96 / 4
16		B	**9b**	85	4 / 96
17		A	**10a**	89	97 / 3
18		B	**10b**	66	2 / 98
19		A	**11a**	73	94 / 6
20		B	**11b**	60	1 / 99
21		A	**12a**	86[c,d]	>99 / 1
22		B	**12b**	84[c]	<1 / 99
23		B	**13**	91[c]	–

[a] **General Procedure. [Method A]** TsCl (1.50 mmol) in chlorobenzene (1.0 mL) was added to a stirred solution of a β-ketoester (1.00 mmol), NMI (1.50 mmol), and Et_3N (1.5 mmol) in C_6H_5Cl (1.0 mL) at 20−25 °C and the mixture was stirred for 1 h. Water was added to the stirred mixture, which was extracted with EtOAc. The organic phase was washed with 1 M HCl and brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2column chromatography (hexane−AcOEt = 20:1−5:1) to give the desired product. **[Method B]** TsCl (1.50 mmol) in chlorobenzene (1.0 mL) was added to the stirred solution of a β-ketoester (1.00 mmol), NMI (1.50 mmol), and LiOH (1.5 mmol) in C_6H_5Cl (1.0 mL) at 0−5 °C under an Ar atomosphere, and the mixture was stirred at 20−25 °C for 1 h. Similar workup as for Method A gave the desired products. [b] Determined by ^1H NMR of the crude products. [c] In CH_2Cl_2. [d] TMEDA was used instead of Et_3N.

Table 4. Stereoretentive Negishi Coupling of Enol Tosylates



entry	R^1	R^2	R^3		product	yield / %[a]
1	Me	Me	Ph	(*E*)	**14a**	84
2				(*Z*)	**14b**	94
3	Me	Me		(*E*)	**15a**	83
4				(*Z*)	**15b**	81
5	Me	Me		(*E*)	**16a**	85
6				(*Z*)	**16b**	87
7	Me	Me		(*E*)	**17a**	84
8				(*Z*)	**17b**	84
9	Me	Me		(*E*)	**18a**	81
10				(*Z*)	**18b**	95
11	Pr	Et	Ph	(*E*)	**19a**	87
12				(*Z*)	**19b**	90
13		Me	Ph	(*E*)	**20a**	81
14				(*Z*)	**20b**	84
15		Me	Ph	(*E*)	**21a**	87
16				(*Z*)	**21b**	84
17		Me	Ph	(*E*)	**22a**	92[b,c]
18				(*Z*)	**22b**	74[c]
19		Me	Ph	(*E*)	**23a**	75
20				(*Z*)	**23b**	83

[a] R^3MgBr (1.20 mmol) in THF (1.0 mL) was added to a stirred solution of $ZnCl_2$ (1.20 mmol) in THF (1.0 mL) at 0−5 °C under an Ar atomosphere, and the mixture was stirred for 30 min. To the mixture was successively added an (*E*)- or (*Z*)-enol tosylate (1.00 mmol) in THF (1.0 mL) and $Pd(PPh_3)_2Cl_2$ (0.01 mmnol), followed by stirring at 20−25 °C for 1 h. [b] $Pd(PPh_3)_4$ was used instead of $Pd(PPh_3)_2Cl_2$. [c] 15 h.

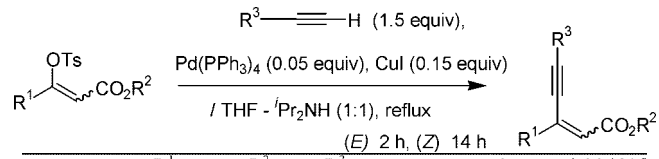
Table 5 lists the application to the Sonogashira coupling.[14] The reaction using (*E*)-substrates proceeded within 2 h using $Pd(PPh_3)_2Cl_2$ catalyst, whereas (*Z*)-substrates required 14 h using $Pd(PPh_3)_4$catalyst.

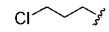
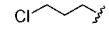
All reactions examined (Tables 4 and 5) were successfully performed in good to excellent yield with nearly complete stereoretention.

In conclusion, we developed a general, robust, and (*E*)- and (*Z*)-enol tosylation of β-ketoesters promoted by

(14) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467.

Table 5. Stereoretentive Sonogashira Coupling of Enol Tosylates



entry	R^1	R^2	R^3		product	yield / %[a]
1	Me	Me	Ph	(*E*)	**24a**	91[b]
2				(*Z*)	**24b**	84[b]
3	Me	Me	TBS	(*E*)	**25a**	97
4				(*Z*)	**25b**	89
5	Pr	Et	Ph	(*E*)	**26a**	86
6				(*Z*)	**26b**	83
7	Pr	Et	TBS	(*E*)	**27a**	95
8				(*Z*)	**27b**	83
9		Me	Ph	(*E*)	**28a**	84
10				(*Z*)	**28b**	70
11		Me	TBS	(*E*)	**29a**	93
12				(*Z*)	**29b**	80
13		Me	Ph	(*E*)	**30a**	88
14				(*Z*)	**30b**	76
15		Me	TBS	(*E*)	**31a**	94
16				(*Z*)	**31b**	96

[a] An alkyne (1.50 mmol) in THF (0.5 mL) and $^iPr_2NH$ (1.0 mL) was added to a stirred solution of (*E*)- *or* (*Z*)-enol tosylate (1.00 mmol), CuI (0.15 mmol), and $Pd((PPh_3)_4$ (0.05 mmol) in THF (1.0 mL) at 20 − 25 °C under an Ar atomosphere. [b] $^iPr_2NEt$ was used instead of $^iPr_2NH$.

TsCl−NMI−Et_3N or LiOH. Cross-coupling reactions (Negishi and Sonogashira) were successfully performed to give stereoretentive trisubstituted α,β-unsaturated esters. The present method provides a new avenue for practical and stereocontrolled preparation of trisubstituted olefins.

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Supporting Information Available: Experimental procedure and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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