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Three-Component Coupling Reaction and Cyclization of *N*-Tosylimines and TMS-Substituted Propiolate Mediated by DABCO

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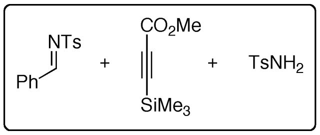
Received October 1, 2007



A new three-component coupling reaction of methyl 3-trimethylsilylpropiolate, *N*-tosylimine, and tosylamide mediated by DABCO was developed. This reaction was based on the consecutive α- and *β*-activation method of propiolate involving intramolecular silyl migration previously developed by our group. On the basis of these results, a new cyclization reaction was designed to find a chromene-forming reaction utilizing salicyl *N*-tosylimine as a bifunctional substrate.

Development of domino-type reactions has been one of the most significant research areas of organic chemistry because of the high efficiency and the applicability for concise syntheses of complex molecules.[1] We have recently explored a new function of alkynes conjugated with a carbonyl group and reported that methyl 3-trimethylsilylpropiolate can act as a versatile synthetic tool which participates in a successive carbon−carbon bond-forming reaction with aldehydes mediated by suitable tertiary amines.[2] Activation of alkynes and subsequent reaction with various reagents have been widely studied and reported in recent years, including phosphine catalysts,[3] metal complex formation,[4] and Morita−Baylis−Hillman-type reactions.[5] Acetylene dicarboxylates have also been reported to be a good substrate for amine-catalyzed reactions.[6] In this context, we have discovered a new type of reaction between methyl 3-trimethylsilylpropiolate and *N*-tosylimines.[7] In this paper, we describe a three-component coupling reaction of propiolates, *N*-tosylimines, and sulfonamides mediated by DABCO[8] and the application for chromene-forming reaction.

First, we examined the reaction of methyl 3-trimethylsilylpropiolate with phenyl *N*-tosylimine (**1**) in the presence of tertiary amine such as DABCO and DBU. These examinations ended in failure, and considerable amounts of the starting materials were recovered unchanged, unlike the case using aldehydes as an electrophile.[2] During a search for suitable reaction conditions, however, we have noticed that a small amount of new product can be detected by TLC in some cases. Isolation and structure analysis revealed that the product had a highly functionalized olefin structure **2** in which new C−C and C−N bonds were formed at α- and *β*-positions of the propiolate, respectively (∼10% yield). The formation of **2** was unexpected because the latter nitrogen unit was most likely incorporated by the action of tosylamide, which was accidentally generated by hydrolytic decomposition of *N*-tosylimine by ambient moisture. This finding brought by mere chance led us to investigate the three-component coupling reaction for practical use. Thus, phenyl *N*-tosylimine (**1**) was allowed to react with equimolar amounts of methyl 3-trimethylsilylpropiolate and tosylamide in the presence of tertiary amine as a trigger nucleophile in refluxing THF for 20 h, and the results are shown in Scheme 1. As expected, the intended coupling reaction proceeded to afford the olefin **2** with up to 47% yield when using DABCO.[9]

As summarized in Table 1, this coupling reaction was applicable for variously substituted *N*-tosylimines. In every case, the functionalized olefins **2a**−**j** were obtained in moderate yields.[10] These reactions showed exclusive *E*-selectivity on the olefin geometry, which was confirmed by NOE observation between the methine proton on the α-position and the tosylamide N−H proton on the *β*-position. Because the reaction of the isolated **2a** with sodium methoxide in refluxing methanol resulted in no change of the olefin geometry, *E*-olefin is likely to be a thermodynamically more stable form.

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(7) For the reaction of *N*-tosylimines catalyzed by tertiary amines, see: (a) Li, C.-Q.; Shi, M. *Org. Lett*. **2003**, *5*, 4273. (b) Zhao, G.-L.; Huang, J.-W.; Shi, M. *Org. Lett*. **2003**, *5*, 4737.

(8) For three-component coupling reaction based on Morita−Baylis−Hillman reaction, see: (a) Evans, C. A.; Miller, S. J. *J. Am. Chem. Soc*. **2003**, *125*, 12394. For nickel-catalyzed three-component coupling of alkynes and imines, see: (b) Patel, S.; Jamison, T. F. *Angew. Chem., Int. Ed*. **2003**, *42*, 1364.

(9) We have thoroughly explored optimal reaction conditions using various solvents, tertiary amines, time and temperature, and equivalents of the reagents. However, an improved result over a 47% yield could not be obtained. Details of these examinations are described in Supporting Information.

(10) Besides the desired olefin products **2**, unreacted imines were detected in the reaction mixture, which were hydrolyzed during a workup process.

10.1021/jo702649q CCC: $40.75

SCHEME 1

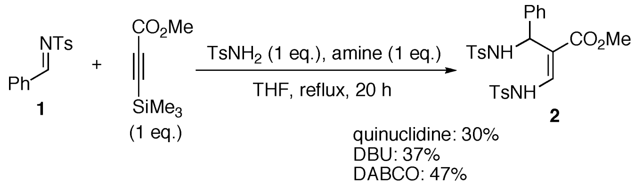
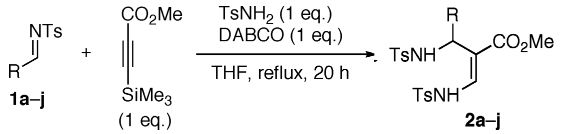
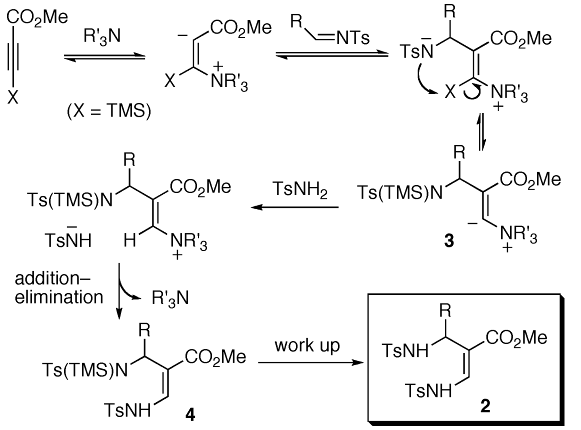


TABLE 1. Reaction of *N*-Tosylimines with Propiolate and Tosylamide in the Presence of DABCO



entry		R	yield (%)
1	**a**	Ph	47
2	**b**	$4\text{-NO}_2\text{-C}_6\text{H}_4$	46
3	**c**	$4\text{-Cl-C}_6\text{H}_4$	34
4	**d**	$2\text{-Me-C}_6\text{H}_4$	39
5	**e**	$4\text{-Me-C}_6\text{H}_4$	30
6	**f**	$2\text{-MeO-C}_6\text{H}_4$	49
7	**g**	$4\text{-MeO-C}_6\text{H}_4$	42
8	**h**	$2,6\text{-Me}_2\text{C}_6\text{H}_3$	34
9	**i**	1-naphthyl	45
10	**j**	*tert*-Bu	34

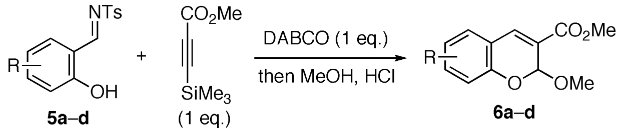
SCHEME 2



We suppose the mechanism of the present reaction partially involves the consecutive activation pathway of the propiolate including intramolecular TMS migration, as previously described (Scheme 2).[2] Ammonium ylide intermediate **3** may be able to abstract the acidic proton of tosylamide. Subsequent addition−elimination process regenerates DABCO and gives the compound **4**, which finally affords the observed products **2** by cleavage of the weak N−Si bond during acid workup. This reaction mechanism agrees with the facts that (1) when using deuterated tosylamide ($TsND_2$), the deuterium was incorporated onto the β-carbon of the acrylate product **2**; (2) the trimethylsilyl group was not retained in the product **2**, indicating this group moved onto the nitrogen atom at least before workup.

The three-component coupling reaction mentioned above gives a hint that *N*-tosylimines containing acidic hydrogen comparable to that of tosylamide can be utilized for a new cyclization reaction with 3-trimethylsilylpropiolate. With this purpose in mind, we chose salicyl *N*-tosylimines (**5**) as such a bifunctional substrate. The envisaged cyclization occurred when the compound **5a** was reacted with the propiolate, mediated by DABCO in refluxing THF, to give methyl 2-methoxy-2*H*-chromene-3-carboxylate (**6a**) in 49% yield after acidic MeOH workup (Table 2, entry 1).[11] The reaction yield was finally improved to 81% when using benzene as a solvent,[12] although heating was required (entries 2−4). Several other substrates (**5b**−**d**) were also examined for the cyclization reaction and found to afford the corresponding chromene derivatives, except for the highly electron-deficient substrate **5d** (entries 5−7). This nitro-substituted imine was rather unstable, probably due to susceptibility to nucleophilic species, to give a complex mixture under the reaction conditions.

TABLE 2. Reaction of Salicyl *N*-Tosylimines (5) with Propiolate in the Presence of DABCO



entry		R	solvent	condition	yield (%)
1	**a**	H	THF	reflux, 1.5 h	49
2	**a**	H	DCE[a]	reflux, 1.5 h	40
3	**a**	H	benzene	rt, 24 h	trace
4	**a**	H	benzene	reflux, 1.5 h	81
5	**b**	5,6-benzo[b]	benzene	reflux, 4 h	75[c]
6	**c**	5-Cl	benzene	reflux, 4 h	58
7	**d**	5-NO_2	benzene	reflux, 2 h	0[d]

[a] 1,2-Dichloroethane. [b] The numbering on the aromatic ring starts from the carbon bearing the imine group and proceeds clockwise. [c] Based on the recovered imine (37%). [d] Afforded a complex mixture.

The next experiments (Scheme 3) suggested that the 4*H*-chromene derivative **8** possessing a tosylamino group was likely to be the first cyclized product because the compound **7** could be trapped by careful workup without acid treatment. This compound obviously arises from the intermediate **8** via thermal N-migration. In addition, purely isolated **7** could be easily transformed into the compound **6a** in acidic MeOH solution.[13,14] The compound **7** was rather labile under acidic conditions and probably converted to a benzopyrylium cation, having high reactivity for various nucleophiles,[15] by exclusion of the

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[11] For recent examples of organocatalyzed syntheses of the chromene-type skeleton from salicyl aldehydes, see: (a) Sunden, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Cordova, A. *Chem.—Eur. J.* **2007**, *13*, 574. (b) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun.* **2007**, 507. (c) Govender, T.; Hojabri, L.; Moghaddam, F. M.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1763. (d) Zhao, G.-L.; Shi, Y.-L.; Shi, M. *Org. Lett.* **2005**, *7*, 4527. (e) Lesch, B.; Bräse, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 115. (f) Kaye, P. T.; Musa, M. A.; Nocada, X. W.; Robinson, R. S. *Org. Biomol. Chem.* **2003**, *1*, 1133.

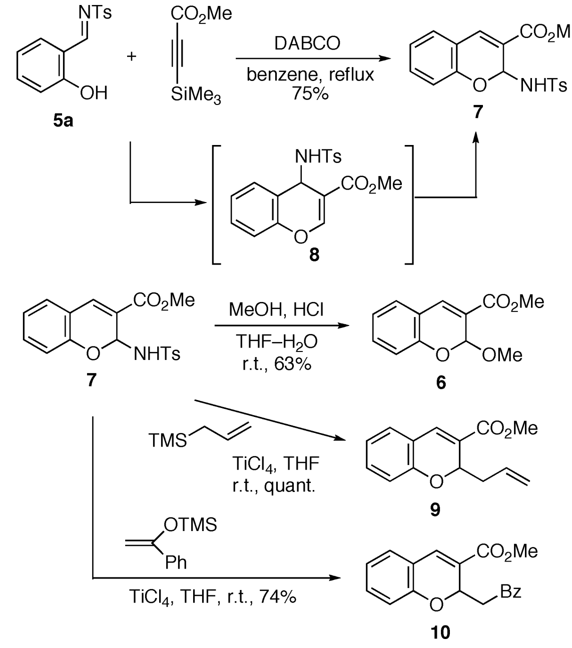
[12] Considering harmfulness of benzene, the reaction of **5a** was investigated using toluene as an alternative solvent, providing a comparable result (110 °C, 3 h, 72% yield) with the case of benzene.

[13] We suppose that the mechanism of the cyclization reaction (formation of **8**) follows the same pathway as depicted in Scheme 2 in an intramolecular fashion because the same reaction in the presence of CD_3-OD (this deuterium ought to be exchanged for the phenolic hydrogen of **5**) gave the product **6** in which the deuterium was incorporated at the 2-position (as well as the methoxy hydrogens).

[14] For recent reports on chromene-forming reaction of salicyl *N*-tosylimine and conjugated alkynes or allenic esters, relating to our reaction systems but via a different reaction pathway, see: (a) Shi, Y.-L.; Shi, M. *Org. Lett.* **2005**, *7*, 3057. (b) Guo, Y.-W.; Shi, Y.-L.; Li, H.-B.; Shi, M. *Tetrahedron* **2006**, *62*, 5875. (c) Shi, Y.-L.; Shi, M. *Chem.—Eur. J.* **2006**, *12*, 3374.

[15] Ohkata, K.; Akiba, K. *Adv. Heterocycl. Chem.* **1996**, *65*, 283.

SCHEME 3



tosylamino group. Therefore, the compound **7** can be a versatile intermediate for the syntheses of variously functionalized chromene derivatives. For example, the reaction of **7** with allyltrimethylsilane or acetophenone silyl enol ether in the presence of titanium chloride gave rise to the formation of 2-substituted chromenes **9** and **10** in high yields, respectively (Scheme 3).[16]

In summary, we have developed a new three-component coupling reaction utilizing a consecutive activation protocol of conjugated alkynes mediated by DABCO, providing unique nitrogen-containing olefin compounds. This methodology was successfully applied for a new chromene-forming reaction, which can be a new efficient access to variously functionalized chromene derivatives. Efforts to explore further applications are currently in progress in our laboratory.

Experimental Section

General Remarks. All nonaqueous reactions were carried out under an Ar atmosphere. Reagents were purchased from commercial sources and used as received. Anhydrous solvents were prepared by distillation over CaH_2 or purchased from commercial sources. *N*-Tosylimines **1a**−**j** and **5a**−**d** were prepared according to the reported method.[17]

General Procedure for the Reaction of *N*-Tosylimines with Methyl 3-Trimethylsilylpropiolate and Tosylamide in the Presence of DABCO. A solution of methyl 3-trimethylsilylpropiolate (156 mg, 1 mmol), *N*-tosylimine (**1a**−**j**, 1 mmol), *p*-toluenesulfonamide (171 mg, 1 mmol), and DABCO (112 mg, 1 mmol) in anhydrous THF (1 mL) was refluxed for 20 h. The mixture was cooled to room temperature and diluted with CH_2Cl_2 (20 mL). This solution was washed with 10% HCl and brine successively and dried over $MgSO_4$. After evaporation of the solvent, the residue was subjected to silica gel column chromatography to afford the products **2a**−**j** in the yields listed in Table 1. Spectral data for the compounds **2b**−**j** are provided in Supporting Information.

Methyl (*E*)-2-[Phenyl-(*p*-tolylsulfonylamino)methyl]-3-(*p*-tolylsulfonylamino)prop-2-enoate (2a): Colorless powder (from hexane); mp 174−176 °C; ^{1}H NMR ($CDCl_3$) $\delta = 2.37$ (s, 3H), 2.43 (s, 3H), 3.50 (s, 3H), 5.48 (d, $J = 9.0$ Hz, 1H), 6.18 (d, $J = 9.0$ Hz, 1H), 7.05−7.16 (m, 7H), 7.31 (d, $J = 7.7$ Hz, 2H), 7.39 (d, $J = 12$ Hz, 1H), 7.46 (d, $J = 8.1$ Hz, 2H), 7.80 (d, $J = 8.1$ Hz, 2H), 8.72 (d, $J = 12$ Hz, 1H); ^{13}C NMR ($CDCl_3$) $\delta = 21.8$, 21.9, 51.8, 53.5, 109.2, 126.0, 126.9, 127.1, 127.7, 128.6, 129.6, 130.1, 136.4, 136.7, 136.8, 138.1, 143.7, 144.6, 166.5; IR (KBr) 3246, 1688, 1599 cm^{-1}; MS *m/z* 514 (M^+). Anal. Calcd for $C_{25}H_{26}N_2O_6S_2$: C, 58.35; H, 5.09; N, 5.44. Found: C, 58.39; H, 5.03; N, 5.47.

Reaction of Methyl 3-Trimethylsilylpropiolate with Salicyl *N*-Tosylimine (5a): Formation of the Chromene Derivatives 6a and 7. A solution of methyl 3-trimethylsilylpropiolate (156 mg, 1 mmol), salicyl *N*-tosylimine (**5a**, 275 mg, 1 mmol), MS3Å (100 mg), anhydrous methanol (32 mg, 1 mmol), and DABCO (112 mg, 1 mmol) in anhydrous benzene (1.5 mL) was refluxed for 1.5 h. The mixture was cooled to room temperature and diluted with CH_2Cl_2 (20 mL). This solution was washed with 10% HCl and brine successively and dried over $MgSO_4$. After evaporation of the solvent, the residue was subjected to silica gel column chromatography to afford **6a** (179 mg, 81%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) $\delta = 3.55$ (s, 3H), 3.85 (s, 3H), 5.95 (s, 1H), 7.01−7.09 (m, 2H), 7.29−7.38 (m, 2H), 7.70 (s, 1H); ^{13}C NMR ($CDCl_3$) $\delta = 51.9$, 55.8, 95.2, 116.9, 119.4, 121.2, 121.9, 129.0, 131.9, 134.2, 152.0, 164.8; IR (neat) 2952, 1714 cm^{-1}; MS *m/z* 220 (M^+). Exact mass calcd for $C_{12}H_{12}O_4$: 220.0736. Found: 220.0736.

The same reaction as above was carried out in the absence of methanol, and the mixture was concentrated in vacuo and directly subjected to silica gel column chromatography to afford **7** (270 mg, 75%) as a pale yellow solid: mp 161−163 °C; ^{1}H NMR ($CDCl_3$) $\delta = 2.50$ (s, 3H), 3.77 (s, 3H), 5.88 (d, $J = 9.6$ Hz, 1H), 6.36 (d, $J = 8.2$ Hz, 1H), 6.58 (d, $J = 9.6$ Hz, 1H), 6.97−7.02 (m, 1H), 7.18−7.31 (m, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.67 (s, 1H), 7.79 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$) $\delta = 21.7$, 52.3, 117.3, 119.2, 120.5, 122.5, 126.3, 127.3, 128.9, 129.1, 129.3, 129.5, 132.2, 134.7, 138.3, 143.4, 150.7, 163.8; IR (KBr) 3285, 2958, 1687, 1433 cm^{-1}; MS *m/z* 359 (M^+). Exact mass calcd for $C_{18}H_{17}NO_5S$: 359.0827. Found: 359.0852.

The other substituted salicyl *N*-tosylimines (**5b** and **5c**) were also reacted with methyl 3-trimethylsilylpropiolate according to the above procedure (reflux, 4 h) to afford the chromene derivatives **6b** and **6c**, respectively (yields are indicated in Table 2). Spectral data for these compounds are provided in Supporting Information.

Reaction of the Chromene Derivative 7 with Silyl Reagents: Formation of Substituted Chromene Derivatives 9 and 10. To a stirred solution of the compound **7** (36 mg, 0.1 mmol) and allyltrimethylsilane (11 mg, 0.1 mmol) in anhydrous THF (1 mL) was added $TiCl_4$ (1.0 M toluene solution, 0.1 mL, 0.1 mmol), and the mixture was stirred at room temperature for 3 h. After addition of saturated $NaHCO_3$ solution, the aqueous mixture was extracted with Et_2O and then dried over $MgSO_4$. Evaporation of the solvent left a residue, which was chromatographed on silica gel to afford the allylated product **9** (23 mg, quant.) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) $\delta = 2.29$−2.38 (m, 1H), 2.47−2.58 (m, 1H), 3.82 (s, 3H), 5.00−5.09 (m, 2H), 5.26−5.30 (m, 1H), 5.80−5.94 (m, 1H), 6.84−6.95 (m, 2H), 7.15 (dd, $J = 1.7$, 7.4 Hz, 1H), 7.23−7.27 (m, 1H), 7.46 (s, 1H); ^{13}C NMR ($CDCl_3$) $\delta = 38.2$, 51.9, 73.5, 116.9, 117.8, 120.5, 121.4, 125.3, 128.7, 132.0, 132.9, 133.2, 153.2, 165.1; IR (neat) 2952, 1712 cm^{-1}; MS *m/z* 230 (M^+). Exact mass calcd for $C_{14}H_{14}O_3$: 230.0943. Found: 230.0921.

Similarly using acetophenone silyl enol ether instead of allyltrimethylsilane as a reagent, the compound **7** afforded the compound **10** (74%) as a pale yellow solid: mp 104−105 °C; ^{1}H NMR ($CDCl_3$) $\delta = 3.34$ (dd, $J = 6.9$, 14 Hz, 1H), 3.37 (dd, $J = 4.4$, 14

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(16) For reports on allylation of benzopyrylium derivatives, see: (a) Lee, Y. G.; Ishimaru, K.; Iwasaki, H.; Ohkata, K.; Akiba, K. *J. Org. Chem.* **1991**, *56*, 2058. (b) Ohkata, K.; Ishimaru, K.; Lee, Y. G.; Akiba, K. *Chem. Lett.* **1990**, 1725.

(17) McKay, W. R.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2435.

Hz, 1H), 3.75 (s, 3H), 4.53 (dd, $J = 4.4, 6.9$ Hz, 1H), 6.98−7.05 (m, 2H), 7.13−7.22 (m, 2H), 7.40−7.45 (m, 2H), 7.50−7.56 (m, 1H), 7.75 (s, 1H), 7.91−7.94 (m, 2H); ^{13}C NMR ($CDCl_3$) $\delta = 29.7$, 47.3, 51.5, 108.9, 116.3, 123.6, 124.7, 127.7, 127.9, 128.3, 129.0, 132.8, 136.7, 149.8, 151.7, 166.5, 197.5; IR (KBr) 2925, 1709, 1680, 1649 cm^{-1}; MS *m*/*z* 308 (M^+). Exact mass calcd for $C_{19}H_{16}O_4$: 308.1049. Found: 308.1046.

Supporting Information Available: Details of investigations of optimal conditions for the three-component coupling reaction, characterization data for the compounds **2b**−**j**, **6b**, and **6c**, and ^{1}H and ^{13}C NMR spectra of the compounds **2a**−**j**, **6a**−**c**, **7**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702649Q