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Synthesis of Substituted Chromenes through the DABCO-Catalyzed Reaction of But-3-yn-2-one and Methyl Propiolate with Salicyl *N*-Tosylimines (DABCO = 1,4-diazabicyclo[2.2.2]octane)

Yong-Ling Shi and Min Shi*[a]

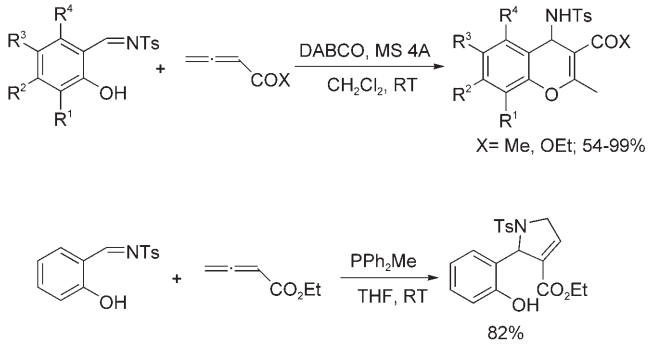
Abstract: The DABCO-catalyzed (DABCO = 1,4-diazabicyclo[2.2.2]octane) reaction of but-3-yn-2-one and methyl propiolate with salicyl *N*-tosylimines yields highly functionalized chromenes and has been thoroughly investigated; the rational mechanism for the reaction has been demonstrated on the basis of ^{1}H NMR spectroscopic investigation.

Keywords: Baylis–Hillman reaction · chromenes · Michael addition · NMR spectroscopy · salicyl *n*-tosylimines

Introduction

Due to their important biological activity and great utility, chromene derivatives have attracted considerable attention from a variety of scientific areas.[1] Different processes for the synthesis of chromenes have been reported during the past few years.[2] More recently, we have communicated an efficient approach to substituted chromenes by amine-catalyzed reaction of allenic esters and ketones with salicyl *N*-tosylimines in 54–99% yields in dichloromethane (Scheme 1).[3] Phosphorus-based catalysts such as PPh_2Me could induce the reaction to give the [3+2] cycloadduct in 82% yield in tetrahydrofuran (THF) (Scheme 1, additional results can be found in Tables S1 and S2 in the Supporting Information).[3]

As an extension of this methodology, we herein report the reaction of but-3-yn-2-one and methyl propiolate with salicyl *N*-tosylimines affording substituted chromenes in the presence of DABCO. In addition, a detailed reaction mechanism is proposed on the basis of an ^{1}H NMR spectroscopic trace of the reaction solution.



Scheme 1. Reaction of allenic esters and ketones with salicyl *N*-tosylimines.

Results and Discussion

Different catalysts were first examined by using the reaction of salicyl *N*-tosylimine (**1a**) with but-3-yn-2-one (**2a**; 1.2 equiv) as a model. The results are summarized in Table 1. Dichloromethane was chosen as the solvent and molecular sieves 4 Å (100 mg for 0.50 mmol of **1a**) was added as a desiccant to prevent the decomposition of imine by ambient moisture. 1,4-Diazabicyclo[2.2.2]octane (DABCO; 10 mol%) was found to be an effective catalyst in this reaction (Table 1, entries 1–5). In the reaction catalyzed by DABCO, imine **1a** was consumed within 1 h, while the yield of **3a** was only 32%. If the reaction time was extended to 10 h, the yield of **3a** could reach 69%. Performing the reaction at lower temperature did not give **3a** in higher yield. The yield of **3a** could be further increased to 71% by extending the reaction time to 24 h. Other nitrogen- and

[a] Y.-L. Shi, Prof. M. Shi
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences, 354 Fenglin Lu
Shanghai 200032 (China)
Fax: (+86) 21-6416-6128
E-mail: mshi@pub.sioc.ac.cn

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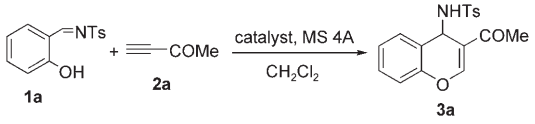
Table 1. Reaction of salicyl *N*-tosylimine **1a** (1.0 equiv) with but-3-yn-2-one **2a** (1.2 equiv) in the presence of 10 mol % of catalyst.



1a 2a 3a

	Catalyst	T [°C]	t [h]	Yield of **3a** [%][a]
1	DABCO	20	1	32
2	DABCO	20	10	69
3	DABCO	−20	10	53
4	DABCO	20	24	71
5	DABCO	−20	1	14
6	Et_3N	20	24	23
7	DMAP	20	29	66
8	DBU	20	13	21
9	PPh_3	20	24	20
10	PPh_2OMe	20	24	trace
11	PPh_2Me	20	24	11
12	$PPhMe_2$	20	24	17
13	PMe_3	20	24	trace
14	PBu_3	20	24	trace
15	iPr$_2$NEt	20	24	no reaction
16	Na_2CO_3	20	24	no reaction
17	$NaHCO_3$	20	24	no reaction
18[b]	DABCO	20	24	63
19[c]	DABCO	20	24	trace

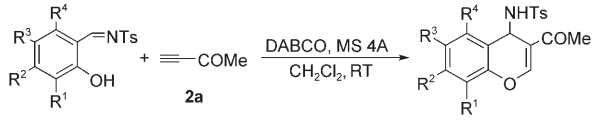
[a] Isolated yields. [b] 1.0 equiv of **2a**. [c] 2.0 equiv of **2a**.

phosphorus-based catalysts were less effective in this reaction (Table 1, entries 6–14). The weak nucleophile ethyldiisopropylamine (iPr$_2$NEt) and inorganic catalysts, such as Na_2CO_3 or $NaHCO_3$, showed no catalytic abilities for this reaction (Table 1, entries 15–17). Reducing the amount of but-3-yn-2-one **2a** to one equivalent and increasing it to two equivalents both afforded **3a** in lower yields under identical conditions (Table 1, entries 18–19). Thus, we established the optimal reaction conditions for this reaction: 1.2 equivalents of **2a**, 10 mol % of DABCO, and performing the reaction at room temperature (20 °C) for 24 h.

Under these optimized reaction conditions, the reaction of several other salicyl *N*-tosylimines **1** with **2a** was also examined. Both electron-withdrawing and electron-donating substituents were tolerated at various positions on the benzene rings in the imines. The corresponding chromenes **3** were obtained in good yields (Table 2, entries 1–7). Even for the sterically hindered substrate *N*-(2-hydroxynaphthalen-1-yl)-methylene-4-methylbenzenesulfonamide, this reaction proceeded smoothly to give the corresponding adduct **3i** in good yield after a prolonged reaction time (Table 2, entry 8).

To test the generality of this methodology, we further subjected methyl propiolate **2b** to the reaction. The results are summarized in Table 3. To our disappointment, the yield of the corresponding chromene **4a** was rather low under these above optimum reaction conditions (Table 3, entry 1). Increasing the amount of the catalyst and extending the reaction time did not give **4a** in satisfactory yield either (Table 3, entry 2). Several other solvents were examined and it was found that performing the reaction in acetonitrile

Table 2. Reaction of other salicyl *N*-tosylimines **1** (1.0 equiv) with but-3-yn-2-one **2a** (1.2 equiv) in the presence of 10 mol % of DABCO.

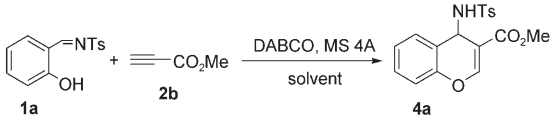


1 2a 3

	R^1	R^2	R^3	R^4	t [h]	Yield of **3** [%][a]
1	OMe	H	H	H	24	**3b**: 84
2	H	OMe	H	H	24	**3c**: 52
3	H	H	OMe	H	24	**3d**: 84
4	H	H	Me	H	24	**3e**: 83
5	H	H	Br	H	24	**3f**: 81
6	Cl	H	Cl	H	24	**3g**: 78
7	H	H	NO_2	H	24	**3h**: 57
8	H	H	−CH=CH−CH=CH−		48	**3i**: 74

[a] Isolated yields.

Table 3. Reaction of salicyl *N*-tosylimine **1a** (1.0 equiv) with methyl propiolate **2b** (1.2 equiv) in the presence of DABCO.



1a 2b 4a

	DABCO [mol %]	Solvent	T [°C]	t [h]	Yield of **4a** [%][a]
1	10	CH_2Cl_2	20	24	11
2	30	CH_2Cl_2	20	48	31
3	30	*tert*-amyl-OH	20	48	13
4	30	DMSO	20	48	38
5	30	CH_3CN	20	48	45
6	25	CH_3CN	80	24	67
7	25	toluene	80	27	27
8	25	*tert*-amyl-OH	80	8	14
9	25	CH_2ClCH_2Cl	80	34	32
10	25	DMSO	80	12	49
11	25	DMF	80	12	69
12[b]	25	CH_3CN	80	8	30
13[b]	25	DMF	80	12	40
14[c]	25	CH_3CN	80	8	70
15[c]	25	DMF	80	12	79

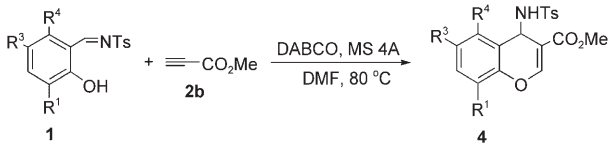
[a] Isolated yields. [b] 2.0 equiv of **2b**. [c] 1.0 equiv of **2b**.

could give a somewhat higher yield (Table 3, entries 3–5). Then the reaction temperature was raised to 80 °C and **4a** was obtained in 67 % yield (Table 3, entry 6). The corresponding reaction conditions were further optimized by varying different solvents in this reaction at 80 °C (Table 3, entries 7–11). Acetonitrile and *N*,*N*-dimethylformamide (DMF) were found to be the solvents of choice. Then the amount of **2b** was also examined in acetonitrile and DMF, respectively at 80 °C (Table 3, entries 12–15). By using one equivalent of **2b** and performing the reaction in DMF, the highest yield of **4a** (Table 3, entry 15) was observed.

Under these optimized reaction conditions, several other salicyl *N*-tosylimines were also examined in the reaction with **2b**. Imines with either electron-withdrawing or electron-donating substituents at various positions on the benzene rings could give the corresponding chromenes **4** in

good yields (Table 4, entries 1–6). For the sterically hindered imine *N*-(2-hydroxynaphthalen-1-yl)-methylene-4-methylbenzenesulfonamide, a prolonged reaction time was also required (Table 4, entry 7).

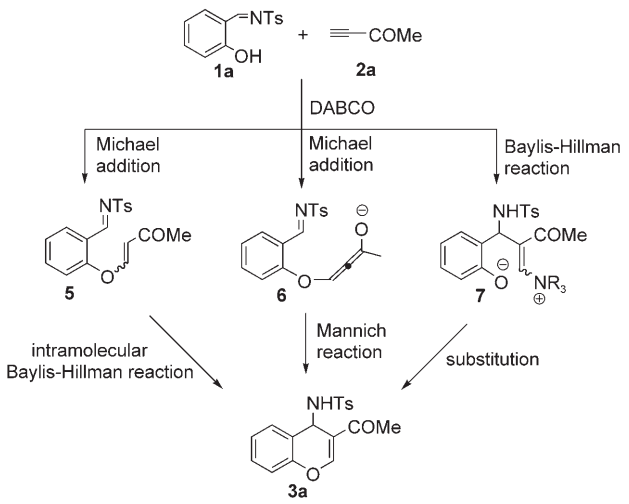
Table 4. Reaction of other salicyl *N*-tosylimines **1** (1.0 equiv) with methyl propiolate **2b** (1.0 equiv) in the presence of 25 mol% of DABCO.



	R^1	R^3	R^4	t [h]	Yield of **4** [%][a]
1	OMe	H	H	12	**4b**: 79
2	H	OMe	H	12	**4c**: 86
3	H	Me	H	12	**4d**: 85
4	H	Br	H	12	**4e**: 83
5	Cl	Cl	H	12	**4f**: 74
6	H	NO_2	H	12	**4g**: 51
7	H	−CH=CH−CH=CH−		21	**4h**: 29

[a] Isolated yields.

Concerning the mechanism for the reaction, there may be three different pathways (Scheme 2).[4–7] The first pathway starts with a Michael addition to form intermediate **5** followed by intramolecular Baylis–Hillman reaction. The second pathway proceeds through tandem Michael addition/Mannich reaction. The third pathway is initiated by Baylis–Hillman reaction and subsequent substitution provides the final product **3a**. Therefore, it is necessary to determine the reaction pathway in the above interesting reaction.



Scheme 2. Possible pathways for the formation of **3a**.

To gain further understanding of the mechanism, we monitored the reaction process of **1a** and **2a** in $CDCl_3$ by ^{1}H NMR spectra. Molecular sieves 4 A was added as well to prevent the decomposition of **1a** during the spectroscopic trace process. Some selected spectra are shown below in Figure 1.

As shown in Figure 1b, when DABCO was added to the solution of **1a** and **2a**, imine **1a** was consumed in five minutes and intermediate **5** was formed (Figure 1b and c). The specific iminium proton and olefinic protons were assigned (see partial enlargement in Figure 1c). Then the corresponding intermediate **5** was gradually converted to the final product **3a** after 24 h (Figure 1d). After 83 h, intermediate **5** completely disappeared and the corresponding product **3a** was obtained (Figure 1e). To clarify that product **3a** was really obtained as shown in Figure 1e, the solution was diluted and some pure compound **3a** was added. As can be seen from Figure 1f, no new peaks occur and only the peaks related to **3a** are enlarged. It should be noted that intermediate **5** was not stable enough for isolation. The attempt to isolate intermediate **5** has not yet proved successful, despite our active endeavors. For the reaction of **1a** and **2b**, a similar intermediate was also observed (Figures S1–S8 in the Supporting Information). The major isomer of intermediate **5** was assigned to be *Z* configuration by comparison the ^3J value (12.3 Hz) of the olefinic protons with that of the intermediate derived from **1a** and **2b** (Figures S1–S8 in the Supporting Information).

Based on these observations, we believe that the reaction was most likely to proceed through the first pathway as shown in Scheme 2. The fact that no reaction occurred when weak nucleophiles served as the catalysts (Table 1, entries 15–17) revealed that DABCO functioned not merely as a base but also as a nucleophile in the Michael addition step. The detailed mechanistic explanation is shown in Scheme 3.

DABCO first reacts with **2a** to generate a zwitterionic intermediate **8**,[7] which abstracts a proton from imine **1a** to release anion **11** and form intermediate **9**,[6a] which might be tautomerized with intermediate **10**. Then Michael addition occurs between the intermediate **11** and **2a** to give intermediate **6**, which subsequently abstracts a proton from **9** yielding intermediate **12**. Consequently, intermediate **12** isomerizes to intermediate **5**, followed by intramolecular Baylis–Hillman reaction catalyzed by DABCO affording product **3a**. The intramolecular Baylis–Hillman reaction is the rate-determining step as indicated by observations of ^{1}H NMR spectra.

Substituents at the terminal alkyne were not tolerated, presumably due to the steric hindrance. The reaction between ethyl 2-butynoate **2c** and imine **1a** did not give the corresponding chromene derivative in satisfactory yield under various reaction conditions (Scheme 4).[3]

In conclusion, we have developed an efficient process for the synthesis of highly functionalized chromenes by reaction of but-3-yn-2-one and methyl propiolate with salicyl *N*-tosylimines. The reaction mechanism has been demonstrated based on the observations of ^{1}H NMR spectra. Efforts are in progress to develop the asymmetric version of this reaction.

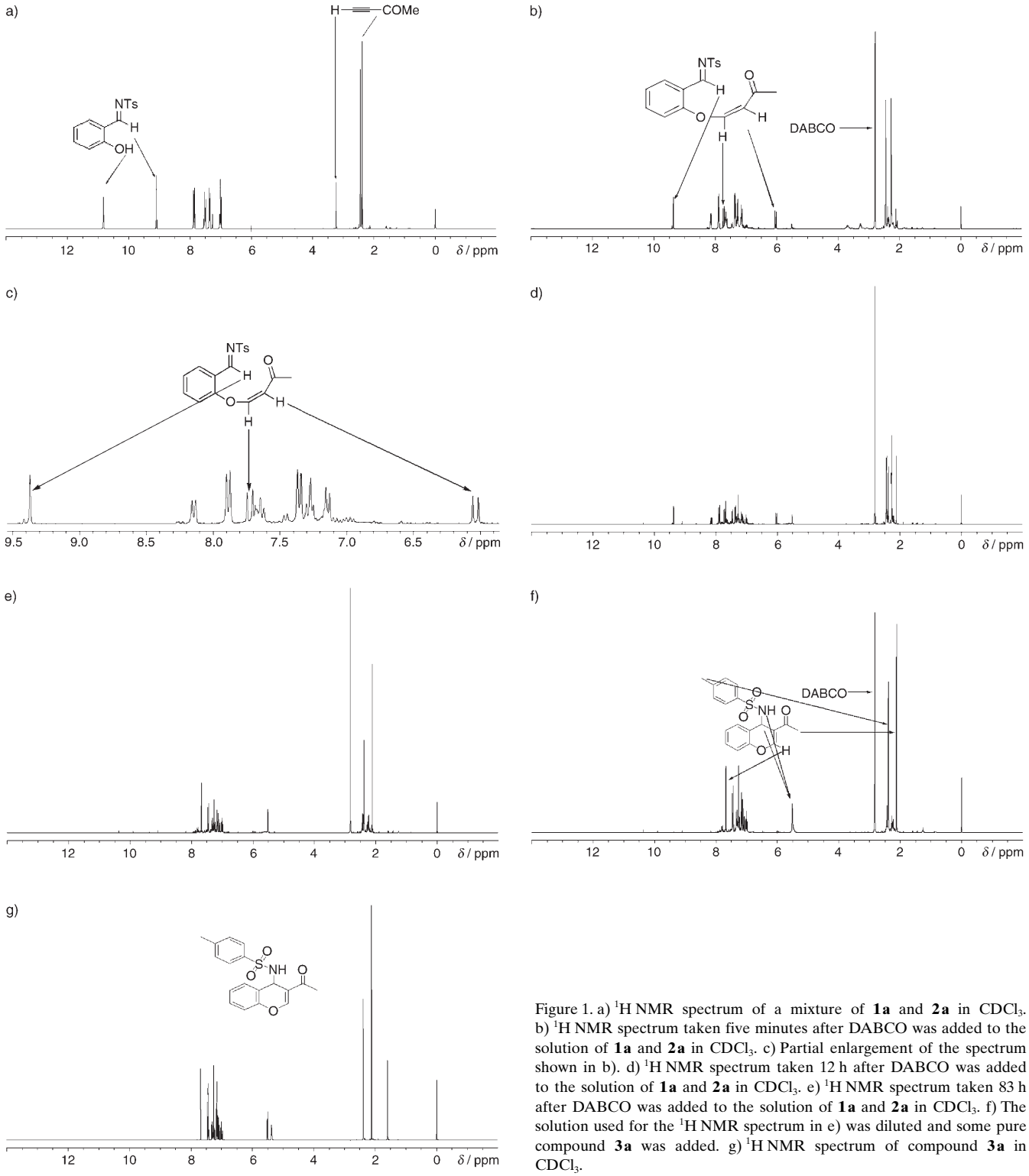
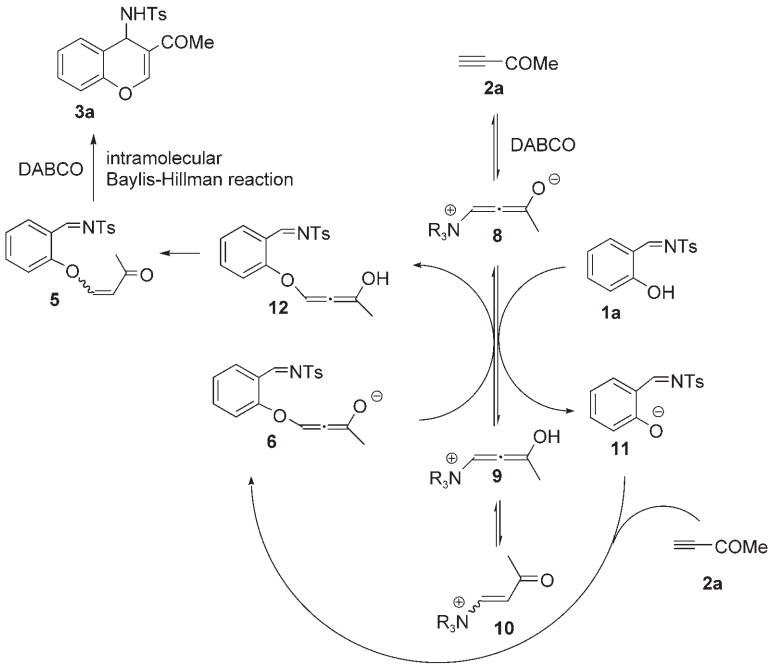


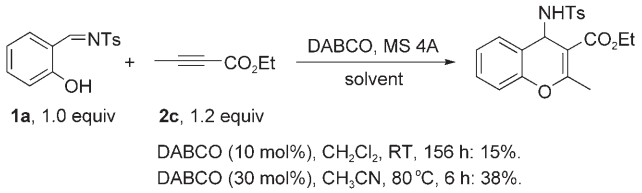
Figure 1. a) ^{1}H NMR spectrum of a mixture of **1a** and **2a** in $CDCl_3$. b) ^{1}H NMR spectrum taken five minutes after DABCO was added to the solution of **1a** and **2a** in $CDCl_3$. c) Partial enlargement of the spectrum shown in b). d) ^{1}H NMR spectrum taken 12 h after DABCO was added to the solution of **1a** and **2a** in $CDCl_3$. e) ^{1}H NMR spectrum taken 83 h after DABCO was added to the solution of **1a** and **2a** in $CDCl_3$. f) The solution used for the ^{1}H NMR spectrum in e) was diluted and some pure compound **3a** was added. g) ^{1}H NMR spectrum of compound **3a** in $CDCl_3$.

Experimental Section

General: Unless otherwise stated, all reactions were carried out under argon atmosphere. All solvents were purified by distillation. Other commercially available reagents were used without further purification. Salicyl *N*-tosylimines[8] and but-3-yn-2-one[9] were prepared according to the literature. All reactions were monitored by TLC. Flash column chromatography was carried out at increased pressure. Infrared spectra were



Scheme 3. Detailed mechanistic explanation for the formation of **3a**.



Scheme 4. Reaction of **1a** with ethyl 2-butynoate **2c**.

measured on a Perkin–Elmer 983 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury vx 300 NMR spectrometer in $CDCl_3$ or CD_3SOCD_3 with tetramethylsilane as the internal standard. Mass spectra were recorded with an HP-5989 instrument and HRMS was measured by an Ion Spec 4.7 Tesla FTMS mass spectrometer. Satisfactory CHN microanalyses were obtained with a Carlo–Erba 1106 analyzer. Melting points were obtained by means of a micro melting point apparatus and are uncorrected.

Typical reaction procedure for DABCO-catalyzed reaction of but-3-yn-2-one with salicyl *N*-tosylimine (1a): Molecular sieves 4 Å (100 mg), DABCO (5.6 mg, 0.05 mmol), salicyl *N*-tosylimine **1a** (138 mg, 0.50 mmol), CH_2Cl_2 (2.0 mL), and but-3-yn-2-one **2a** (47 μL, 0.60 mmol) were added in turn to a flame-dried Schlenk tube at room temperature. The reaction mixture was stirred at room temperature for 24 h. Then the solvent was removed under reduced pressure and the residue was purified by flash chromatography (eluent: EtOAc/Petroleum ether 1:4–2:1) to yield **3a** (122 mg, 71 %) as a colorless solid. M.p. 184–186 °C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): $\delta = 2.12$ (s, 3H; Me), 2.39 (s, 3H; Me), 5.38 (d, $^3J(H,H) = 5.4$ Hz, 1H; NH), 5.51 (d, $^3J(H,H) = 5.4$ Hz, 1H; CH), 6.98–7.03 (m, 1H; Ar), 7.08–7.11 (m, 1H; Ar), 7.16 (d, $^3J(H,H) = 8.4$ Hz, 2H; Ar), 7.24–7.34 (m, 2H; Ar), 7.45 (d, $^3J(H,H) = 8.4$ Hz, 2H; Ar), 7.68 ppm (s, 1H; CH); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) $\delta = 21.5$, 24.8, 45.1, 116.1, 116.5, 119.3, 125.1, 127.0, 129.0, 129.2, 130.6, 138.9, 142.7, 150.4, 153.8, 195.5 ppm; IR (KBr): $\nu = 3339$, 1659, 1641, 1331, 1233, 1149 cm^{-1}; MS (70 eV): *m*/*z* (%): 188 (62.7) [$M^+ - 155$], 173 (100) [$M^+ - 170$]; elemental analysis calcd (%) for $C_{18}H_{17}NO_4S$: C 62.96, H 4.99, N 4.08; found: C 62.94, H 4.86, N 3.98.

Acknowledgements

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