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DABCO-Catalyzed Reaction of Allenic Esters and Ketones with Salicyl *N*-Tosylimines: Synthesis of Highly Functionalized Chromenes

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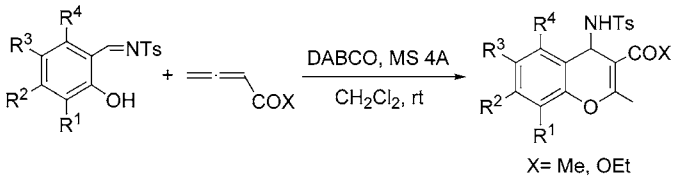
ABSTRACT



DABCO-catalyzed reactions of salicyl *N*-tosylimines with ethyl 2,3-butadienoate and penta-3,4-dien-2-one proceed smoothly at room temperature in dichloromethane to give the corresponding chromenes in good to excellent yields.

Heterocycles are of great value in the design and discovery of new biologically active compounds.[1] The development of efficient processes to construct heterocycles, using metal-free catalysts, has been drawing much attention over the past decades.[2] Recently, the reactions of allenic esters and ketones with *N*-tosylaldimines to give different kinds of heterocycles were reported.[3] To our surprise, using salicyl *N*-tosylimine as the electrophile was seldom mentioned, the only example was reported by Kwon, providing no product due to the presence of the acidic phenolic protons.[3c] We envisioned that the phenol group in salicyl *N*-tosylimine might participate in the reaction to produce new types of products using an appropriate catalyst. Herein, we report the discovery of the reactions of allenic esters and ketones with salicyl *N*-tosylimines to give highly functionalized chromene derivatives, which constitute one of the major classes of bioactive molecules.[4]

Different catalysts were first examined using the reaction of salicyl *N*-tosylimine **1a** with ethyl 2,3-butadienoate **2a** as a model. The results are presented in Table 1. Phosphorus-based catalysts, such as PPh_3 or PPh_2Me could induce the reaction to give the [3 + 2] cycloadduct **3a** (Table 1, entries 1 and 2).[3a,b] Stronger nucleophilic phosphine resulted in the decomposition of the imine (Table 1, entries 3−5), while nitrogen-based catalysts could induce the reaction to proceed through a different pathway and give a new cylcoadduct **4a** (Table 1, entries 6−8).

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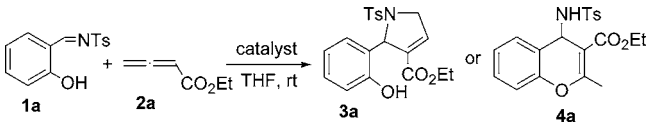
Table 1. Reaction of Ethyl 2,3-Butadienoate **2a** (1.2 equiv) with Salicyl *N*-Tosylimine **1a** (1.0 equiv) in the Presence of 25 mol % of Catalyst



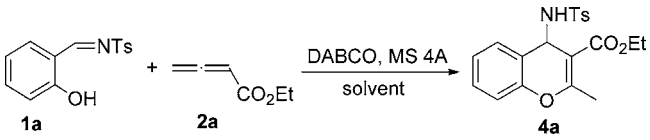
entry	catalyst	time (h)	yield[a] (%)
1	PPh_3	24	**3a**: 50
2	PPh_2Me	1	**3a**: 82
3	$PPhMe_2$	1	*b*
4	PMe_3	4	*b*
5	PBu_3	24	*b*
6	DABCO	1	**4a**: 60
7	DMAP	4	**4a**: 35
8	DBU	77	**4a**: 17

[a] Isolated yields. [b] Most of the imine was decomposed to the aldehyde and toluenesulfonamide, and only a trace amount of **3a** was formed.

The weak nucleophile diisopropylethylamine and inorganic catalysts, such as NaOH, Na_2CO_3, and $NaHCO_3$, showed no catalytic abilities for this reaction. Of the catalysts examined, DABCO was found to be the best (Table 1, entry 6). The structures of **3a** and **4a** were confirmed by X-ray diffraction (Supporting Information).

Using DABCO as the catalyst, the reaction conditions were further optimized. Adding molecular sieves 4A (100 mg for 0.5 mmol of **1a**) as a desiccant to prevent the decomposition of imines by ambient moisture could improve the yield of **4a** (Table 2, entry 1). Next, various solvents were examined.

Table 2. Reaction of Ethyl 2,3-Butadienoate **2a** (1.2 equiv) with Salicyl *N*-Tosylimine **1a** (1.0 equiv) in the Presence of 25 mol % of DABCO



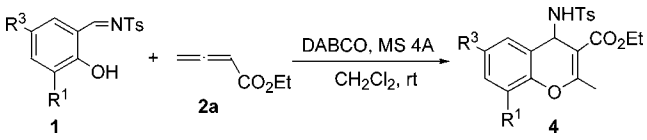
entry	solvent	*T* (°C)	time (h)	yield of **4a**[a] (%)
1	THF	rt	1	64
2	CH_2Cl_2	rt	1	78
3	CH_2ClCH_2Cl	rt	1	58
4	DMSO	rt	1	18
5	PhMe	rt	1	68
6	*tert*-armyl-OH	rt	1	44
7	Et_2O	rt	1	5
8	DMF	rt	1	46
9	CH_3CN	rt	1	65
10	CH_2Cl_2	40	1	77
11	CH_2Cl_2	0	1	76
12	CH_2Cl_2	−20	19	88
13[b]	CH_2Cl_2	rt	1	87
14[c]	CH_2Cl_2	rt	3	78

[a] Isolated yields. [b] 10 mol % of DABCO was used. [c] 5 mol % of DABCO was used.

Dichloromethane was found to be the best (Table 2, entries 1−9). At 40 or 0 °C, similar results were obtained (Table 2, entries 10 and 11). At −20 °C, **4a** was produced in higher yield, but a prolonged reaction time was required (Table 2, entry 12). Using 10 mol % of DABCO, **4a** was produced in higher yield under similar conditions (Table 2, entry 13), although using 5 mol % of DABCO, the yield of **4a** decreased (Table 2, entry 14). Thus, we established the optimal reaction conditions for this reaction: using 10 mol % of DABCO as a catalyst and dichloromethane as a solvent to perform the reaction at room temperature.

Under the optimized reaction conditions, several other salicyl *N*-tosylimines were examined in the reaction with **2a**. The corresponding chromenes **4** were obtained in good to excellent yields (Table 3, entries 1−6). For those imines with

Table 3. Reaction of Ethyl 2,3-Butadienoate **2a** (1.2 equiv) with Other Salicyl *N*-Tosylimine (1.0 equiv) in the Presence of 10 mol % of DABCO



entry	R^1	R^3	time (h)	yield of **4**[a] (%)
1	H	OMe	1	**4b**: 90
2	OMe	H	1	**4c**: 85
3	H	Me	1	**4d**: 78
4	Cl	Cl	24	**4e**: 81
5	H	Br	7	**4f**: 95
6[b]	H	NO_2	72	**4g**: 59

[a] Isolated yields. [b] 50 mol % of DABCO was used.

electron-withdrawing groups on the benzene ring, a prolonged reaction time was required (Table 3, entries 4−6). Similarly, penta-3,4-dien-2-one **2b** could also react with various salicyl *N*-tosylimines under identical conditions to give the corresponding chromenes **5** in good to excellent yields. The results are summarized in Table 4. Even for the sterically hindered substrate *N*-(2-hydroxynaphthalen-1-yl)-methylene-4-methylbenzenesulfonamide, this reaction proceeded smoothly to give the adduct **5i** in good yield after a prolonged reaction time (Table 4, entry 9). For those imines with electron-withdrawing groups on the benzene ring, a prolonged reaction time was required as well (Table 4, entries 7 and 8).

The mechanism for different activity shown by phosphine catalysts and nitrogen catalysts has not been unequivocally established. One reasonable explanation is shown in Scheme 1 on the basis of earlier reports[3a−c,5] and our investigations.

In the case of phosphine-catalyzed reaction, the catalyst reacts with the allene to generate a zwitterionic intermediate **6**, which serves as a dipole for the subsequent [3 + 2]

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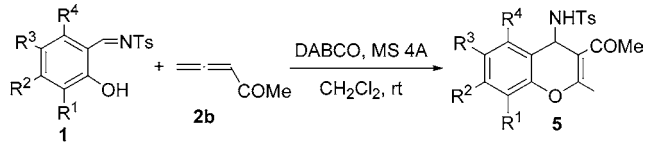
Table 4. Reaction of Penta-3,4-dien-2-one **2b** (1.2 equiv) with Salicyl *N*-Tosylimine (1.0 equiv) in the Presence of 10 mol % of DABCO

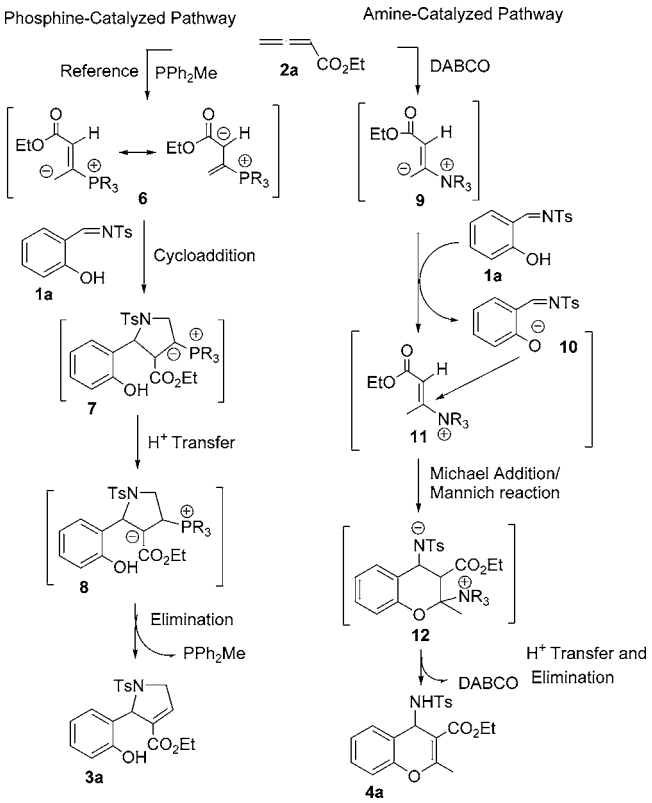


entry	R^1	R^2	R^3	R^4	time/(h)	yield of **5** (%)[a]
1	H	H	H	H	1	**5a**: 87
2	OMe	H	H	H	1	**5b**: 94
3	H	OMe	H	H	1	**5c**: 84
4	H	H	OMe	H	1	**5d**: 91
5	H	H	Me	H	1	**5e**: 99
6	H	H	Br	H	1	**5f**: 96
7	Cl	H	Cl	H	2	**5g**: 97
8	H	H	NO_2	H	24	**5h**: 94
9	H	H			45	**5i**: 54

[a] Isolated yields.

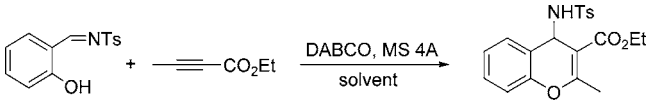
cycloaddition with **1a**.[3a] Then the facile 1,2-proton transfer and elimination take place to give the product **3a** and regenerate the catalyst. This mechanism, as proposed by others,[6] benefits from the ability of phosphorus to stabilize the ylide structure **7**. In contrast, the amine-catalyzed pathway does not benefit from the similar stabilization. The zwitterionic intermediate **9** deprotonates the phenol group in imine **1a** to give the intermediates **10** and **11**. Subsequent Michael addition/Mannich reaction, followed by proton transfer and elimination, produce chromene **4a** and regenerate the catalyst. The Michael addition step is assumed to be the rate-determining step, accounting for the longer reaction time required for those imines with electron-withdrawing groups on the benzene ring which decrease the nucleophilicity of the oxygen atom.

Scheme 1. Plausible Reaction Mechanism



According to the proposed reaction mechanism, ethyl 2-butynoate will also undergo the same reaction as ethyl 2,3-butadienoate. To examine this feasibility, ethyl 2-butynoate was employed as the substrate to the reaction under the same conditions. To our disappointment, the reaction proceeded very slowly (Scheme 2). Carrying out the reaction at 80 °C and using 30 mol % of DABCO, the reaction could complete within 6 h, while the yield was relatively low. This is presumably due to the fact that ethyl 2-butynoate is more sterically hindered than ethyl 2,3-butadienoate as undergoing nucleophilic attack by DABCO.

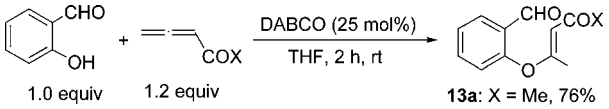
Scheme 2. Reaction of Salicyl *N*-Tosylimine with Ethyl 2-Butynoate



DABCO (10 mol%), CH_2Cl_2, rt, 156 h: 15%.
DABCO (30 mol%), CH_3CN, 80 °C, 6 h: 38%.

It should be noted that if using salicylaldehyde[7] instead of salicyl *N*-tosylimine, the corresponding phenolic Michael addition products **13a** and **13b** were formed rather than the corresponding chromenes presumably due to the fact that the alkoxide adduct formed by the aldol reaction undergoes proton transfer more slowly than the sulfonamide anion counterpart and retro-aldol reaction effectively competes to give the starting anion; subsequent elimination of DABCO provides the products **13** (Scheme 3).[8]

Scheme 3. Reaction of Salicylaldehyde with Ethyl 2,3-Butadienoate and Penta-3,4-dien-2-one



13a: X = Me, 76%
13b: X = OEt, 71%

In conclusion, we have presented an efficient, amine-catalyzed reaction of allenic esters and ketones with salicyl

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N-tosylimines, which provides an easy access to the synthesis of highly functionalized chromenes[9] under mild reaction conditions in good to excellent yields. Efforts are in progress to elucidate the mechanistic details of this reaction and to disclose its scope and limitations.

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Supporting Information Available: ^{13}C and ^{1}H NMR spectroscopic and analytic data for compounds **4**, **5** and **13**, X-ray crystal data of **3a** and **4a**. NOESY spectra of **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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