Convenient Access to Cycloalk-2-enone-Derived *N*-Sulfonyl Imines

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Abstract: The first synthesis of *N*-tosyl imines from various cyclopent-2-enones and cyclohex-2-enones was achieved by direct condensation with tosyl amide in the presence of $TiCl(OEt)_3$ and Et_3N. In addition, *N*-*tert*-butylsulfonyl imines from five- to seven-membered cycloalk-2-enones were obtained through formation of the respective oximes and subsequent Hudson reaction. These compounds are easy to handle solids and they are interesting starting materials for a variety of transformations.

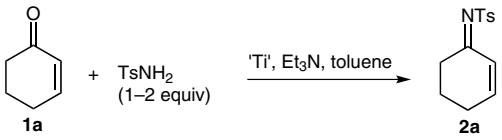
Key words: condensation, enones, imines, titanium, sulfonamides

N-Sulfonyl imines form a synthetically very useful class of compounds that are commonly employed in a range of transformations including addition of nucleophiles and pericyclic reactions as well as in the preparation of oxaziridines and aziridines.[1] On the one hand, this is a consequence of the central role played by nitrogen in the bioactivity of organic compounds, making imines valuable starting materials. On the other hand, the electron-withdrawing effect of the sulfonyl moiety strongly activates the C=N double bond so that its reactivity becomes comparable to that of a C=O double bond.[2] Therefore, *N*-sulfonyl imines are typically the first choice when intending to transfer a reaction that is known for carbonyls to the respective aza analogues.

In the case of aldehydes or ketones with stabilizing aryl or 2-arylethenyl groups, *N*-sulfonyl imines are readily prepared by condensation with primary sulfonamides in the presence of strong Brønsted or Lewis acids such as $TiCl_4$ or $AlCl_3$.[3,4] *N*-Sulfonyl imines of aliphatic ketones, however, are rather labile, making them much more difficult to synthesize. They have been formed from the respective oximes through reaction with sulfinyl chlorides[5] or sulfonyl cyanides[6] with subsequent radical rearrangement (Hudson reaction), by palladium-catalyzed isomerization of terminal alkene-derived *N*-tosyl aziridines,[7] by reaction of arenesulfonyl azides with alkenes,[8] or by oxidation of secondary alcohols with chloramine-T in the presence of saccharin-lithium bromide.[9] Another approach is to proceed through oxidation of the respective *N*-sulfinyl imines, which are more readily prepared from carbonyls due to the higher nucleophilicity of sulfinamides compared with sulfonamides.[10] *N*-Sulfonyl imines derived from plain cycloalk-2-enones have not been described in the literature, even though the corresponding ketones belong to the most prominent building blocks in organic synthesis. In connection with our research on asymmetric 1,2- and 1,4-additions of organometallic reagents to cycloalk-2-enones,[11] we became interested in the analogous *N*-tosyl imines and now report the first successful preparation of such compounds.

In contrast to *N*-sulfonyl imines, *N*-sulfinyl imines have already been prepared by condensing cycloalk-2-enones with *tert*-butanesulfinamide in the presence of $Ti(OEt)_4$ as a mild Lewis acid.[12] When adopting this method for the condensation of cyclohex-2-enone (**1a**) with the less reactive tosyl amide, the desired imine **2a** was obtained in poor yield due to incomplete conversion (Table 1, entry 1). The strong Lewis acid $TiCl_4$ was also not suitable, leading mainly to decomposition of the starting material (entry 2). By employing a 5:1 mixture of $Ti(O\textit{i}Pr)_4$ and $TiCl_4$, decomposition was less pronounced, and a moderate yield was achieved (entry 3). Better results were obtained with a 3:1 mixture of $Ti(OEt)_4$ and $TiCl_4$ when Et_3N was present in a 1:1 ratio calculated based on the amount of chloride (entries 4 and 5).

Table 1 Optimization of the Formation of *N*-Tosyl Imine **2a**



Entry	Titanium reagent (equiv)	Et_3N (equiv)	*T* (°C)	*t* (h)	Yield (%)[a]
1	$Ti(OEt)_4$ (4.0)	–	80	2	15
2[b]	$TiCl_4$ (1.0)	2.0	r.t.	3	26
3	$Ti(O\textit{i}Pr)_4$ (1.7) + $TiCl_4$ (0.3)	–	Δ	24	40
4	$Ti(OEt)_4$ (3.0) + $TiCl_4$ (1.0)	–	Δ	4	0
5	$Ti(OEt)_4$ (3.0) + $TiCl_4$ (1.0)	4.0	Δ	4	68
6	$TiCl(OEt)_3$ (2.0)	2.0	Δ	1	78
7[c]	$TiCl(OEt)_3$ (1.2)	1.5	Δ	1	24[d]

[a] Determined by ^1H NMR analysis of the crude product.
[b] Performed in CH_2Cl_2.
[c] Performed in benzene.
[d] Conversion of starting material **1a**.

Finally, use of the preformed mixed reagent $TiCl(OEt)_3$ turned out to be advantageous, and the conversion was complete after 1 h heating to reflux in toluene, whereas

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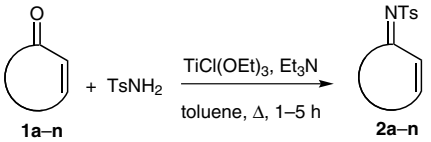
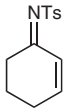
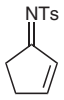
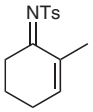
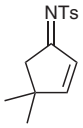
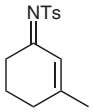
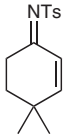
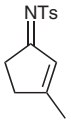
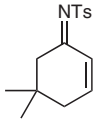
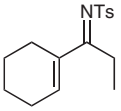
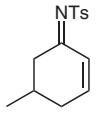
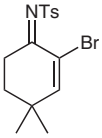
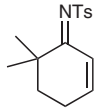
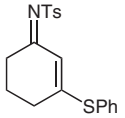
only 24% conversion was observed after the same time in benzene heated to reflux (entries 6 and 7).

Under the optimized conditions, ketimine **2a** was isolated in a 66% yield as a 62:38 mixture of *E*- and *Z*-isomers (Table 2, entry 1).[13] No evidence for competing 1,4-addition of tosyl amide to the enone moiety was detected,[14] and inferior yields were observed when trying to prepare imine **2a** by Hudson reaction[6] or by oxidation of the respective *p*-toluenesulfinyl imine.[10] To evaluate substituent effects, this protocol was then applied to a set of methyl-substituted cyclohex-2-enones **1b**–**g**, and the imines were obtained in yields ranging from 61 to 74% (entries 2–7). In the case of five-membered rings, cyclopent-2-enone **1h** furnished a negligible yield of imine **2h** due to rapid decomposition (entry 8), whereas the substituted derivatives **1i**–**k** were more stable and furnished the imines in yields ranging from 49 to 77% (entries 9–11). With cyclohept-2-enone as starting material, complete conversion occurred but the crude product consisted of an inseparable 2:1 mixture of the desired imine and the tautomeric cyclohept-1,3-dienyl tosyl amide. Moreover, enone **1l**, with an exocyclic carbonyl moiety, also underwent imine formation to deliver **2l** in a 63% yield (entry 12).[15] As examples of functionalized cycloalkenones, 2-chloro-, 2-bromo-, and 3-(phenylsulfonyl)cyclohex-2-enone were subjected to this reaction; however, imine formation was accompanied by elimination to yield *N*-phenyltosyl amide in high purity. This smooth aromatization was suppressed in the case of enone **1m** with two geminal methyl groups, and imine **2m** was obtained in good yield (entry 13). In addition, this method tolerates electron-donating groups: an excellent yield was achieved in the case of substrate **1n**, with a phenylthio group at C-3 (entry 14). All imines **2** are colorless to off-white solids, stable against chromatography on silica gel and handling under air, can be stored at –28 °C, and only slowly hydrolyze in the presence of water.

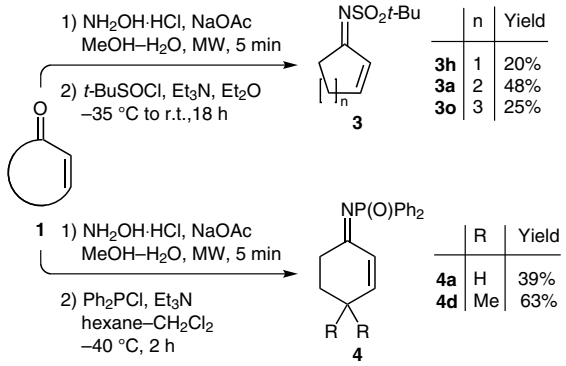
Tosyl amides are readily deprotected under reductive conditions.[16] In contrast, *tert*-butylsulfonyl (busyl) groups can be cleaved under acidic conditions and thus represent an orthogonal protecting group.[17] For this reason, and due to problems with the preparation of *N*-tosyl imines from cyclopent-2-enone and cyclohept-2-enone, synthesis of the corresponding *N*-busyl imines was pursued by adopting a two-step sequence that was developed by Weinreb et al. for the transformation of several aromatic and saturated aliphatic aldehydes and ketones.[5c] First, the cycloalkenones were converted into the corresponding oximes, in a reaction that proceeded rather slowly with conventional heating but could be accelerated tremendously with microwave irradiation (Scheme 1).[18] The crude products thus obtained were immediately converted by using a Hudson reaction to deliver the *N*-busyl imines **3**. Again, the six-membered ring furnished a better yield than the five- or seven-membered rings, which were clearly less stable under these conditions.

Table 2 Synthesis of α,β-Unsaturated *N*-Tosyl Ketimines



Entry	Imine **2**	Yield (%)[a]	Entry	Imine **2**	Yield (%)[a]
1	 **a**	66 (62:38)	8	 **h**	9 (69:31)
2	 **b**	61 (100:0)	9	 **i**	75 (74:26)
3	 **c**	64 (55:45)	10	 **j**	49 (100:0)
4	 **d**	74 (65:35)	11	 **k**	77 (60:40)
5	 **e**	62 (57:43)	12	 **l**	63 (0:100)
6	 **f**	68 (61:39)	13	 **m**	72 (100:0)
7	 **g**	70 (100:0)	14	 **n**	91 (62:38)

[a] Isolated yield; values in parentheses indicate the *E*/*Z* ratio as determined by NOESY analysis after purification.



Scheme 1 Synthesis of *N*-busyl and *N*-phosphinoyl imines

Besides sulfonyl groups, the diphenylphosphinoyl (dpp) group also effectively activates C=N double bonds towards nucleophilic attack.[2] Moreover, this group can be cleaved under rather mild acidic conditions.[16] The preparation of such imines from various substituted cyclohex-2-enones has already been reported by Hutchins et al.[19] However, the products were immediately subjected to subsequent reductions and, thus, neither purified nor analytically characterized because rapid hydrolysis was anticipated. We have prepared the cyclohex-2-enone-derived dpp-imine for the first time as well as the 4,4-dimethyl-substituted homologue already prepared by Hutchins et al. (Scheme 1).[19b] Both compounds are stable against chromatography on silica gel, can be handled under air, and can be stored for extended time at –28 °C.

In conclusion, we have achieved the first preparation of cycloalk-2-enone-derived *N*-tosyl imines.[20] The choice of an appropriate titanium reagent turned out to be critical for this success, and several five- and six-membered compounds were obtained in good yields. In addition, the first preparation of five- to seven-membered cycloalkenone-derived *N*-busyl imines is reported. All these compounds are promising building blocks for subsequent reactions with nucleophiles, and we are working on employing them in asymmetric 1,2- and 1,4-additions.

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(20) ***N*-(Cyclohex-2-en-1-ylidene)-4-methylbenzenesulfonamide (2a); Typical Procedure:** To a solution of $TiCl(OEt)_3$ (4.37 g, 20.0 mmol) in toluene (10 mL) was added Et_3N (2.79 mL, 20.0 mmol). The resulting mixture was stirred for 5 min at r.t. before $TsNH_2$ (3.42 g, 20.0 mmol) was added, and the reaction mixture was heated to reflux for 15 min. A solution of **1a** (961 mg, 10.0 mmol) in toluene (20 mL) was added dropwise over 15 min to the refluxing solution, and stirring was continued for 1 h. The reaction mixture was poured into a stirred and precooled (0 °C) suspension of $NaHCO_3$ (5.0 g) in acetone–H_2O (200 mL, 100:1), diluted with pentane (100 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the crude product was purified by flash chromatography (CH_2Cl_2; R_f = 0.26) on silica gel to furnish ketimine **2a** (1.65 g, 66%) as a pale-yellow oil that crystallized in the freezer.
^{1}H NMR (300 MHz, $CDCl_3$): δ (62:38 *E*/*Z*-ratio, asterisk denotes minor isomer peaks) = 7.86 (m_c, 2 H), 7.32 (m_c, 2 H), 7.32* (m_c, 1 H), 6.94 (m_c, 1 H), 6.14 (dt, *J* = 10.0, 1.9 Hz, 1 H), 3.18 (m_c, 2 H), 2.54* (m_c, 2 H), 2.43 (s, 3 H), 2.40–2.30 (m, 2 H), 2.01–1.90 (m, 2 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 180.1, 178.0*, 151.6*, 150.6, 143.4, 138.6, 130.1, 129.4, 127.1*, 127.0, 124.1*, 35.5*, 31.4, 26.0*, 25.2, 22.1*, 21.53, 21.49. HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd. for $C_{13}H_{15}NO_2SNa$: 272.0716; found: 272.0711.
***N*-(Cyclohex-2-en-1-ylidene)-*tert*-butanesulfonamide (3a); Typical Procedure:** To a solution of **1a** (500 mg, 5.20 mmol) in MeOH–H_2O (9:1, 5.0 mL) in a 10 mL microwave reaction vessel were added hydroxylamine hydrochloride (398 mg, 5.72 mmol) and sodium acetate (512 mg, 6.24 mmol). The vessel was sealed, and the mixture was heated in a microwave reactor at 135 °C for 5 min and then cooled to r.t. The reaction mixtures of three such batches were combined, poured into H_2O (30 mL) and extracted with $CHCl_3$ (3 × 30 mL). The combined organic phases were washed with sat. $NaHCO_3$ (3 × 30 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give the crude oxime (1.70 g).
The crude oxime was dissolved in Et_2O (30 mL), Et_3N (3.18 mL, 23.0 mmol) was added, and the solution was cooled to –35 °C. Then, *tert*-butylsulfinyl chloride (4.28 g, 30.6 mmol) was added dropwise, and the resulting suspension was stirred at –35 °C for 1.5 h before the cooling bath was removed. Stirring was continued for 16 h, and the reaction mixture was then filtered over Celite and concentrated under vacuum. Purification by flash chromatography (pentane–EtOAc, 5:1; R_f = 0.38) on silica gel furnished ketimine **3a** (1.62 g, 48%) as a pale-yellow oil that crystallized in the freezer.
^{1}H NMR (300 MHz, $CDCl_3$): δ (62:38 *E*/*Z*-ratio, asterisk denotes minor isomer peaks) = 7.12* (dt, *J* = 10.2, 2.0 Hz, 1 H), 6.90–6.80 (m, 1 H), 6.12 (dt, *J* = 10.0, 2.0 Hz, 1 H), 3.04 (t, *J* = 6.7 Hz, 2 H), 2.51* (t, *J* = 6.7 Hz, 2 H), 2.35–2.25 (m, 2 H), 1.97–1.83 (m, 2 H), 1.42 (s, 9 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 180.7, 178.7*, 150.4*, 149.8, 130.2, 124.5*, 58.7, 35.5*, 31.5, 26.0*, 25.2, 23.9, 22.2*, 21.5. HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd. for $C_{10}H_{18}NO_2S$: 216.1053; found: 216.1054.

