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Synthesis of novel β-functionalized α-oximinoketones via hetero-Michael addition of alcohols and mercaptans to enones

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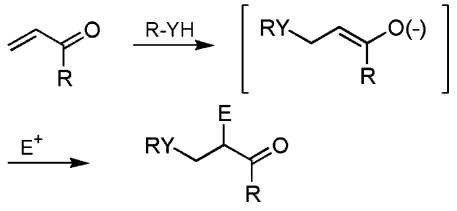
Abstract—A new methodology has been developed for the preparation of β-alkoxy and β-sulfenyl ketones by hetero-Michael addition of the corresponding alcohols and thiols to enones under acidic and basic conditions. The direct conversion of enones into β-alkoxy and β-sulfenyl α-oximinoketones was also described.

Michael addition to conjugate acceptors by a nucleophile constitutes a milestone reaction in organic synthesis for the β-functionalization of carbonyl compounds.[1] Stabilized carbanions have been the most significant nucleophiles among the numerous classes of homonucleophiles. A large number of representative examples have also been reported for the conjugate addition of heteronucleophiles.[1a,2] Unlike alcohols and mercaptans, amines are found among the most reactive and attractive heteronucleophiles,[3] providing highly valuable products such as β-amino acids, β-lactams, and pyrrolidine ring systems.[4] Thiols are also effective nucleophiles in 1,4-additions to conjugate acceptors, preferring bases, Lewis acids, or even iodine as catalysts.[5] Owing to their hardness, alcohols react less efficiently, and their addition needs to be promoted by strong bases, Brönsted acids, phosphines, or transition metals.[6]

The versatility of Michael addition reactions has been greatly improved by coupling the conjugate addition with the trapping of the resulting enolate by an appropriate electrophile.[7] This tandem reaction has been extensively and successfully applied in organic synthesis when a homo-Michael donor initiates the process, but the reactions initiated by a 1,4-addition of a hetero-Michael donor have been scarcely used (Scheme 1).[1a,7a,8]



Scheme 1.

As a part of our interest in the reactivity and preparation of β-functionalized captodative olefins,[9] we have reported the conjugate addition of amines and thiols,[10] as well as the diastereoselective 1,4-addition of amines and lithium amides to captodative olefins.[11] Now, we wish to report a study of the Lewis acid- and base-promoted hetero-Michael addition of alcohols and thiols to enones, and the tandem Michael reaction/electrophilation as an efficient process in the synthesis of functionalized α-oximinoketones.

Although a large variety of Lewis acid catalysts has been used to carry out oxa-Michael addition reactions of alcohols to α,β-unsaturated ketones,[12] it seems that $BF_3{\cdot}Et_2O$ has not been studied yet. We found that $BF_3{\cdot}Et_2O$ catalyzes the addition of alcohols to conjugate ketones satisfactorily at low temperatures (0 °C) (Scheme 2). Table 1 summarizes the results of addition with a range of alkyl, allyl, and chiral alcohols **2** to methyl vinyl ketone (**1a**) (entries 1–7) and to ethyl vinyl ketone (**1b**) (entries 8–10) promoted by $BF_3{\cdot}OEt_2$ catalysis, to give Michael adducts **3** and **4**, respectively, in

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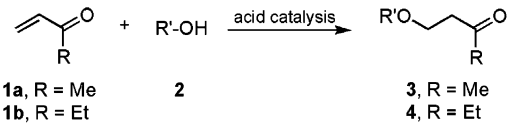


Scheme 2.

Table 1. Acid-catalyzed hetero-Michael additions of alcohols to enones **1a** and **1b**[a]

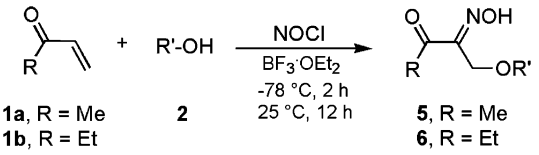
Entry	Enone	2 [R′]	*t* (days)[b]	3/4 (%)[c]	3/4 (%)[d]
1	**1a**	**2a** [Me]	2	**3a** (70)	**3a** (79)
2	**1a**	**2b** [Et]	2	**3b** (85)	**3b** (86)
3	**1a**	**2c** [*i*-Pr]	2	**3c** (80)	**3c** (83)
4	**1a**	**2d** [$CH_2CH{=}CH_2$]	2	**3d** (72)	**3d** (65)
5	**1a**	**2e** [Bn]	5	**3e** (80)	[e]
6	**1a**	**2f** [(−)-Myrtenol]	4	**3f** (52)	**3f** (40)
7	**1a**	**2g** [(−)-Menthol]	7	**3g** (20)	**3g** (35)
8	**1b**	**2a** [Me]	5	**4a** (90)	**4a** (92)
9	**1b**	**2b** [Et]	5	**4b** (85)	**4b** (80)
10	**1b**	**2c** [*i*-Pr]	5	**4c** (87)	**4c** (84)

[a] With 10 mL of alcohols **2a**–**c**, and 2.5 mol equiv for alcohols **2d**–**g**. For $BF_3{\cdot}OEt_2$ (0.2 mol equiv) trials, at 0 °C for 2 h, then at 25 °C for the reaction times shown in the table. For H_2SO_4 (1.5 mol equiv)/$NaNO_2$ (3.0 mol equiv) trials, at 0 °C for 12 h.
[b] Reaction times of the $BF_3{\cdot}OEt_2$ trials.
[c] Yields of the $BF_3{\cdot}OEt_2$ trials, after purification.
[d] Yields of the $H_2SO_4/NaNO_2$ trials, after purification.
[e] Benzaldehyde as the main product.

high yields. The reactivity was significantly modified by changing the enone, since the reaction with cyclohexenone (**1c**) in the presence of alcohols **2a**–**c** furnished the 1,4-addition products in low yields (20–30%).

Recently, Spencer et al. described an analogous reaction by using sulfuric acid as the protic catalyst, where the starting material was consumed after 72 h.[2c] We found, however, that the reaction time could be significantly reduced (12 h) by adding sodium nitrite, maintaining comparable yields to those furnished by the $BF_3{\cdot}OEt_2$-catalyzed process (Table 1). It is likely that a species other than the proton, such as the nitrosonium ion, can also catalyze the process.[13] When the reaction is allowed to continue for 24 h at 0 °C, a second product appears in the reaction mixture in low yield (22%). The NMR and MS spectra revealed that it was the corresponding α-oximinoketone **5**. Therefore, we investigated the potential of using the nitrosonium ion or one of its carriers as the electrophile in the tandem hetero-Michael-electrophilation reaction to give compounds **5** or **6** (Scheme 3).

Table 2 summarizes the reaction conditions and the yields of products **5** or **6**. Compounds **5** were obtained



Scheme 3.

Table 2. Tandem acid-catalyzed hetero-Michael addition/nitrosation reaction of alcohols to enones **1a** and **1b**[a]

Entry	Enone	2 [R′]	5/6 (%)[b]
1	**1a**	**2a** [Me]	**5a** (65)
2	**1a**	**2b** [Et]	**5b** (50)
3	**1a**	**2c** [*i*-Pr]	**5c** (45)
4	**1a**	**2d** [$CH_2CH{=}CH_2$]	**5d** (30)
5	**1a**	**2e** [Bn]	**5e** (20)
6	**1a**	**2f** [(−)-Myrtenol]	**5f** (50)
7	**1a**	**2g** [(−)-Menthol]	**5g** (45)
8	**1a**	**2h** [CH_2CCH]	**5h** (40)
9	**1a**	**2i** [*n*-Pr]	**5i** (55)
10	**1a**	**2j** [CH_2CH_2OMe]	**5j** (60)
11	**1b**	**2a** [Me]	**6a** (63)
12	**1b**	**2b** [Et]	**6b** (58)
13	**1b**	**2c** [*i*-Pr]	**6c** (70)

[a] With 10 mL of alcohols **2a**–**c** and **2i**,**j**, and 5.0 mol equiv for alcohols **2d**–**h** in 10 mL of CH_2Cl_2. With $BF_3{\cdot}OEt_2$ (0.16 mol equiv), at −78 °C for 2 h, then at −10 °C for 12 h.
[b] Yields of the pure α-oximinoketones **5** or **6**.

in moderate yields as stable oily products.[14] The yield of **5e** was particularly low due to the difficulties found in its separation from benzyl alcohol (**2e**) by column chromatography, and by the oxidation of the latter to benzaldehyde produced by the presence of the in situ formed nitrous acid.[15] In the case of alcohols **2d**, **2f**, and **2g**, mixtures of the α-oximinoketone and the 1,4-addition product, **5d**/**3d** (1:1), **5f**/**3f** (3:1), and **5g**/**3g** (3:1), respectively, were obtained, which were readily separated by column chromatography.

It is interesting to note that, for all compounds **5**, a single isomer was obtained, as shown by the ^1H NMR spectra of the crude mixtures. NOE experiments showed that the structure corresponded to the (*E*) isomer, with the preference of the conformation of the α-oximinocarbonyl moiety as *s-trans* (Fig. 1). This preference may be due to the formation of an intramolecular hydrogen bond between the proton of the oximino OH group and the ether oxygen atom. This was supported by HF/6-31G** calculations of the α-oximinoketones **5a** and **5b**, which show that the most stable configuration-conformation of these compounds corresponds to the (*E*)-*s-trans* geometry (Fig. 1).

It is noteworthy that β-chloro α-oximinoketone **7a** was also observed as a minor product of the addition of NOCl to **1a** (Scheme 4), which suggests that compounds **5** could arise from the substitution reaction of the chlorine atom by the alkoxy group. This hypothesis could be

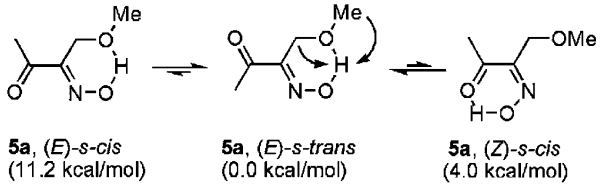
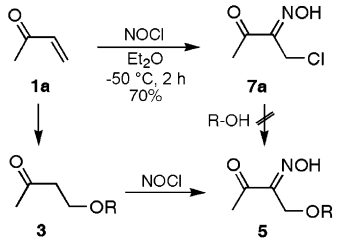


Figure 1. NOE observed upon irradiation of protons of **5a**, and HF/6-31G** optimized structures and relative energies (kcal/mol) of *Z* and *E* isomers of α-oximinoketone **5a**.



Scheme 4.

ruled out by the fact that there was no reaction between **7a** and alcohols **2a** or **2b**, under the same or even more drastic reaction conditions (Et_3N or DABCO or DBU or NaH or RONa, THF, reflux) than those used for the preparation of compounds **5**. Actually, compound **7a** was prepared in good yield (70%),[16] when an ether solution of **1a** was treated with NOCl at −50 °C for 2 h. It is then likely that the mechanism of formation of compounds **5**, and probably **6** as well, goes through the 1,4-addition products **3**, which undergo in situ α-nitrosation (Scheme 4).

We also investigated the reaction with thiols. Thus, when the reaction was carried out with enone **1a** in the presence of thiophenol (**9a**), under analogous conditions as those used for the preparation of compounds **5** and **6**, it gave rise to the quantitative formation of phenyl disulfide.[17]

The hetero-Michael addition of thiols to enones catalyzed by bases has been widely illustrated in the literature.[5,18] In particular, the use of tertiary amines has been a very efficient method.[5a,19] However, to the best of our knowledge, the 1,4-addition reactions of thiols promoted by amines such as DMAP or DABCO are hitherto unknown.[20] For that reason, we carried out the reaction between methyl vinyl ketone (**1a**) and thiophenols **9a–c** in the presence of catalytic amounts of these amines (Table 3). With DMAP, the reaction proceeded at room temperature for 24 h (Scheme 5, procedure a), while with DABCO, the reaction conditions were stronger (Scheme 5, procedure b). In both cases, the 1,4-addition products **10a–c** were prepared in excellent yields (Table 3, entries 1–6). Similar results were obtained by using cyclohexenone (**1c**) to give adducts **11a–c** (Table 3, entries 7–9).

Conversion of ketones **10a–c** into the β-sulfenyl α-oximinoketones **12** can be carried out by nitrosation of the substrates with the nitrosonium ion or alkyl nitrites.[21] Thus, the addition of concd HCl to a suspension of the respective ketones **10a–c** and sodium nitrite

Table 3. Preparation of the 1,4-addition products **10a–c** and **11a–c**, and the α-oximinoketones **12a–c**[a]

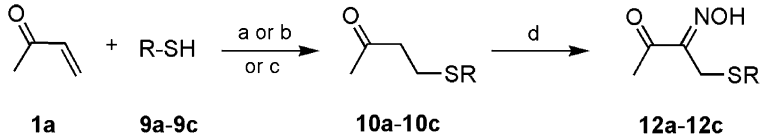
Entry	Ketone	Reagent (R)	Base	Product (%)[b]
1	**1a**	**9a** (Ph)	DMAP	**10a** (90)
2	**1a**	**9b** (C_6H_4–4-Cl)	DMAP	**10b** (85)
3	**1a**	**9c** (C_6H_4–4-Br)	DMAP	**10c** (90)
4	**1a**	**9a** (Ph)	DABCO	**10a** (95)
5	**1a**	**9b** (C_6H_4–4-Cl)	DABCO	**10b** (95)
6	**1a**	**9c** (C_6H_4–4-Br)	DABCO	**10c** (97)
7	**1c**	**9a** (Ph)	DABCO	**11a** (85)
8	**1c**	**9b** (C_6H_4–4-Cl)	DABCO	**11b** (90)
9	**1c**	**9c** (C_6H_4–4-Br)	DABCO	**11c** (92)
10	**10a**	NOCl	—	**12a** (95)[c]
11	**10b**	NOCl	—	**12b** (70)[c]
12	**10c**	NOCl	—	**12c** (56)[c]
13	**1a**	D	[d]	**12a** (87)[e]
14	**1a**	D	[d]	**12b** (62)[e]
15	**1a**	D	[d]	**12c** (50)[e]

[a] Under N_2 atmosphere, with 0.2 mol equiv of DMAP in CH_2Cl_2, at rt for 24 h; or with 0.2 mol equiv of DABCO in THF, at reflux for 4 h. For **12a–c**, treatment of ketones **10a–c** with NOCl at 0–5 °C for 12 h.
[b] After purification by column chromatography.
[c] As the overall yield of the two-step procedure.
[d] With 1.0 mol equiv of **9a–c**, 0.2 mol equiv of DABCO in THF, at reflux for 4 h, then addition of $NaNO_2$ and HCl at 0–5 °C for 2 h, then 20 °C for 12 h.
[e] As the overall yield of the one-pot two-step procedure.

(Scheme 5, procedure d), provided the desired products **12a–c** in moderate to good yields (Table 3, entries 10–12). Unfortunately, when enone **1c** was subjected to the same procedure, only the starting material was recovered.

Despite the good results in the preparation of α-oximinoketones **12a–c** via the isolation and nitrosation of thioketones **10a–c**, we decided to develop a one-pot two-step procedure for the preparation of **12** starting from enone **1a** (Scheme 5, procedure c). Thus, after reacting the corresponding thiols **9a–c** with **1a** in the presence of DABCO to reflux for 4 h, sodium nitrite and aqueous concd solution of HCl were successively added to give the α-oximinoketones **12a–c** in fairly good yields (Table 3, entries 13–15).[22]

In summary, this methodology allows access to the hetero-Michael addition products, **3**, **4**, **10**, and **11**, by adding alcohols or thiols to enones **1** under acid or base catalysis. We have developed a tandem 1,4-addition/electrophilation method for the conversion of enones **1**, with alcohols and nitrosyl chloride, into their corresponding β-alkoxy α-oximinoketones **5** and **6**. In addition, a straightforward sequential one-pot process has



Scheme 5. Reagents and conditions: (a) DMAP (0.2 mol equiv), CH_2Cl_2, rt, 24 h; (b) DABCO (0.2 mol equiv), THF, reflux, 4 h; (c) (i) DABCO (0.2 mol equiv), THF, reflux, 4 h; (ii) $NaNO_2$ (3.0 mol equiv), HCl (6.0 mol equiv), 0–5 °C, 2 h, 20 °C, 12 h; (d) $NaNO_2$ (3.0 mol equiv), HCl (6.0 mol equiv), 0–5 °C, 12 h.

been developed with thiols for the preparation of the corresponding β-sulfenyl α-oximinoketones **12**.

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14. Typical procedure for preparation of **5a**: 0.27 g (1.9 mmol) of $BF_3{\cdot}OEt_2$ was added dropwise to a solution of 0.84 g (0.012 mol) of **1a** in MeOH (20 mL) at −70 °C, and the mixture was stirred for 15 min. Then, at the same temperature, nitrosyl chloride (generated by adding 5.92 g (0.06 mol) of HCl (37%) to 2.07 g (0.03 mol) of $NaNO_2$) was bubbled into the solution through a glassware connector, which was packed with $NaNO_2$ and anhydrous Na_2SO_4. The mixture was stirred at −70 °C for 2 h, then at −10 °C for 12 h. The solvent was evaporated under vacuum by heating it to no more than 30 °C, and the residue was purified by column chromatography over silica gel (20 g, hexane/EtOAc, 95:5), to give 1.02 g (65%) of **5a** as a pale yellow oil: R_f 0.46 (hexane/EtOAc, 6:2); IR (film) 3700–2570, 1687, 1628, 1451, 1419, 1377, 1281, 1241, 1189, 1078, 1021, 942 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H, MeCO), 3.41 (s, 3H, MeO), 4.40 (s, 2H, H-4), 9.85 (br s, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 25.3, 59.4, 60.3, 155.0, 197.0; MS (70 eV) *m/z* 131 (M^+, 1), 113 (1), 87 (3), 71 (12), 61 (8), 55 (31), 43 (100). HRMS (FAB^+) [MH^+] (*m*NBA) calcd for $C_5H_{10}NO_3$: 132.0661; found: 132.0662.
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22. Typical procedure for preparation of **12a**: 0.77 g (0.011 mol) of **1a** was added to a mixture of 1.10 g (0.01 mol) of **9a** in THF (10 mL) and 0.224 g (0.002 mol) of DABCO® at room temperature, and the mixture was heated to reflux for 4 h. The mixture was cooled to 0 °C and a concd solution (37%) of HCl (5.92 g, 0.06 mol) was added. After stirring for 5 min, an aqueous saturated solution (5 mL) of $NaNO_2$ (2.07 g, 0.03 mol) was slowly added (30 min), maintaining the temperature at 0–5 °C. The mixture was stirred at the same temperature for 2 h, then at room temperature for 12 h. An aqueous saturated solution of $NaHCO_3$ was added until neutral, then the aqueous layer was saturated with NaCl and extracted with EtOAc (3 × 15 mL). The combined organic layers

were dried (Na_2SO_4) and the solvent was removed under vacuum. The oily residue crystallized and it was recrystallized (hexane) to give 1.82 g (87%) of **12a** as a white solid: R_f 0.50 (hexane/EtOAc, 8:2); mp 83–84 °C; IR (film) 3700–3500, 1655, 1578, 1433, 1374, 1330, 1163, 1089, 1000, 804, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H, MeCO), 3.96 (s, 2H, H-4), 7.20–7.32 (m, 3H, PhH), 7.40–7.48 (m, 2H, PhH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.5, 25.3, 127.3, 128.8, 131.5, 135.0, 156.5, 195.6; MS (70 eV) *m/z* 209 (M^+, 6), 165 (1), 150 (16), 149 (27), 123 (11), 109 (14), 65 (20), 45 (34), 43 (100). Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.39; H, 5.30; N, 6.69; S, 15.32. Found: C, 57.26; H, 5.21; N, 6.58; S, 15.49.