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Activation and stabilization of aldimines by an *ortho*-trifluoromethyl substituent in direct vinylogous Mannich-type reactions

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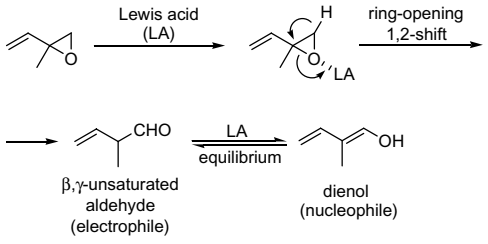
Abstract—Lewis acid catalyzed direct vinylogous Mannich-type reaction with a weak nucleophile dienol, generated in situ by ring-opening and rearrangement of vinyloxiranes, could be demonstrated in excellent yields under mild conditions using benzylidene(4-methoxy-2-trifluoromethyl)aniline (MTMA) as an electrophile. The *o*-trifluoromethyl substituent can stabilize imines by a steric effect and activate by an electron-withdrawing effect. It proved to be an easily deprotectable protecting group for direct Mannich-type reactions.

The Mannich reaction is an important synthetic procedure to prepare nitrogen-containing compounds, which has been applied to the synthesis of heterocyclic building blocks, biologically active compounds, and natural products. Several kinds of nucleophiles have been used for nucleophilic addition at the imino carbon, for example, enolates, malonates, and silyl or tin enol-ethers.[1] In every cases, the imine was less reactive as an electrophile than the corresponding aldehyde and many imines are unstable under typical reaction conditions. In the Lewis acid catalyzed Mannich-type reaction, lower temperature and/or active nucleophiles were required to prevent acid catalyzed decomposition of imines.[2] Recently Lewis acid catalyzed Mannich-type reactions could be performed under mild conditions but the reaction with a weak nucleophile, such as an enol, led to formation of side products.[3] We report, activated and stabilized aldimines[4] derived from 4-methoxy-2-trifluoromethylaniline (MTMA)[5] and aromatic aldehydes react with a weak nucleophilic dienol, generated from a vinyloxirane. This is a new application of direct vinylogous Mannich-type reactions produced via Lewis acid catalyzed ring opening and rearrangement of vinyloxiranes.[6]

In the direct vinylogous Mannich-type reaction, 2-methyl-2-vinyloxirane was converted to the corresponding β,γ-unsaturated aldehyde by Lewis acid catalyzed ring opening and rearrangement (Scheme 1).[7] This aldehyde is easily isomerized to the dienol under the reaction conditions where it behaves as a nucleophile in a direct vinylogous Mannich-type reaction. Representative results are listed in Table 1. Phenyl and tolyl aldimine **1a**, **1b** gave the corresponding δ-amino-α,β-unsaturated aldehydes **2a**, **2b** as Mannich adducts in quantative yields (entry 1 and 2) under mild conditions (THF, 0 °C) in the presence of a catalytic amount $BF_3{\cdot}OEt_2$ (20 mol %). An *o*-trifluoromethyl group on an aniline ring enhanced the stability of the imines toward hydrolysis and also activated the imino carbon to nucleophilic addition. Thus, reactions occurred without



Scheme 1. Lewis acid catalyzed rearrangement of vinyloxirane to the corresponding β,γ-unsaturated aldehyde.

Keywords: Mannich-type; Vinylogous; Vinyloxirane; Rearrangement.
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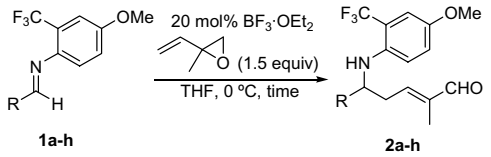
Table 1. $BF_3{\cdot}OEt_2$ catalyzed rearrangement of vinyloxirane and direct vinylogous Mannich-type reactions



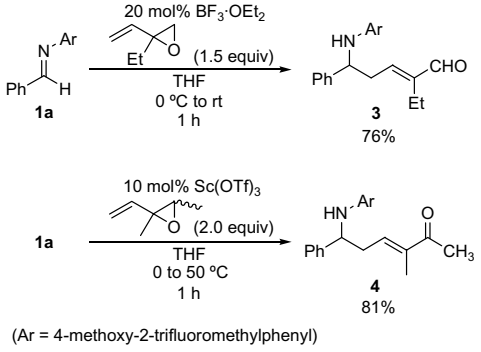
Entry	R		Time (h)	Yield[a] (%)
1	Ph	**a**	3	99
2	4-Me–Ph	**b**	3	99
3	4-Cl–Ph	**c**	3	90
4	2-Cl–Ph	**d**	3	90
5	2-Br–Ph	**e**	3	96
6	2-I-Ph	**f**	3	93
7	4-MeO–Ph	**g**	5	73
8	*t*-Bu	**h**	2	30

[a] Isolated yield.

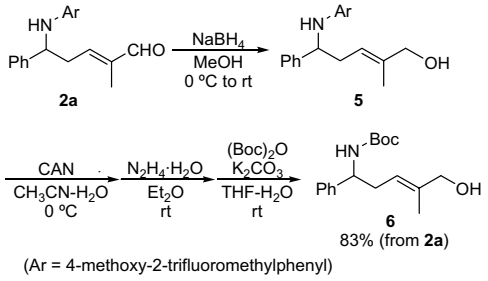
side reactions and *o*-chloro, *p*-chloro, *o*-bromo, and *o*-iodophenyl aldimine **1c–f** also gave the Mannich adduct in over 90% yields under the same conditions (entry 3–6). *p*-Methoxyphenyl aldimine **1g** gave the adduct in moderate yield (entry 7, **2g**, 73%) however *tert*-butyl aldimine **1h** gave low yield due to steric effects (entry 8, **2h**, 30% yield).

We investigated the reactivity of other vinyloxiranes to determine the scope of the reaction (Scheme 2). 2-Ethyl-2-vinyloxirane also generated the corresponding dienal by $BF_3{\cdot}OEt_2$ catalyzed rearrangement. This dienal seemed to be less reactive and the Mannich addition to **1a** only proceeded at room temperature to give a δ-amino-α,β-conjugated aldehyde **3** in 76% yield. By the same approach, α,β-conjugated ketone **4** also could be obtained. 2,3-Dimethyl-2-vinyloxirane rearranged to the diketal and reacted with aldimine **1a** in 80% yield. Higher temperature (50 °C) was required due to less nucleophilicity of the diketal than the dienal. In this case, $Sc(OTf)_3$ gave good result as a Lewis acid catalyst.

An added advantage of the MTMA group is its ease of deprotection under oxidative conditions after reduction of the amino aldehyde **2a** to an amino alcohols **5** with $NaBH_4$. Oxidization of **5** with CAN (ceric ammonium nitrate) in CH_3CN–H_2O and treatment with $N_2H_4{\cdot}H_2O$[8]



Scheme 2. Reactivity of other types of vinyloxiranes.



Scheme 3. Deprotection by oxidative conditions.

and re-protection with $(Boc)_2O$ without purification gave the corresponding Boc-protected amino allyl alcohol **6** in 83% yield (Scheme 3).

A typical experimental procedure for the direct vinylogous Mannich-type reactions is as follows: To a solution of aldimine **1a** (249 mg, 0.892 mmol) and 2-methyl-2-vinyloxirane (132 μL, 1.34 mmol) in THF (1.8 mL) was added a 1.0 M solution of $BF_3{\cdot}OEt_2$ in toluene (0.18 mL, 0.18 mmol) at 0 °C. After stirring for 3 h at the same temperature, the resulting mixture was quenched with saturated $NaHCO_3$. Extractive workup and purification by column chromatography on silica gel (hexane/EtOAc = 7:1 to 4:1 as eluent) gave the corresponding δ-amino-α,β-unsaturated aldehyde **2a** as a colorless viscous oil (319 mg, 0.879 mmol, 99% yield).[9]

Acknowledgements

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4. Prepared by condensation of the corresponding aldehyde and 4-methoxy-3-trifluoromethylaniline (toluene, reflux, Dean-Stark trap).
5. Prepared from 3-trifluoromethylphenol in ca. 30–40% yield (three steps): (i) Nitration (conc HNO_3, CH_2Cl_2, 0 °C); (ii) Methylation (MeI, K_2CO_3, acetone, reflux); (iii) Reduction (C, $FeCl_3$, $N_2H_4{\cdot}H_2O$, MeOH, reflux).

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9. Selected spectroscopic data are as follows: 2-Trifluoromethyl-4-methoxyaniline: yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (1H, d, $J = 2.7$ Hz, 3-H), 6.91 (1H, dd, $J = 8.7$, 2.7 Hz, 5-H), 6.70 (1H, d, $J = 8.7$ Hz, 6-H), 3.88 (2H, br, NH_2), 3.76 (3H, s, OMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 138.2 (d, $J = 2$ Hz), 126.5, 122.8, 119.7, 118.9, 111.1 (q, $J = 5$ Hz), 55.8; IR (film) 3481, 3386, 3235, 3003, 2942, 2833, 1636, 1623, 1511, 1429, 1290, 1229, 1106, 1038, 892, 821, 733 cm^{-1}; HRMS (ESI) calcd for $C_8H_9F_3NO$ [(M+H)$^+$]: 192.0630. Found: 192.0630.
Benzylidene(4-methoxy-2-trifluoromethyl)aniline (**1a**): yellow crystal, mp = 53–54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (1H, s, CH=N), 7.93–7.90 (2H, m, Ar–H), 7.50–7.46 (3H, m, Ar–H), 7.22 (1H, s, Ar–H), 7.07 (2H, d, $J = 1.2$ Hz, Ar–H), 3.86 (3H, s, OMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 157.3, 143.4, 136.1, 131.5, 129.0, 128.7, 125.5, 124.9, 124.5, 121.9, 120.1, 117.9, 112.0 (q, $J = 5$ Hz), 55.7; IR (film) 3058, 3003, 2942, 2833, 1630, 1494, 1429, 1314, 1229, 1127, 1042, 872, 817, 773 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{12}F_3NO$ (M^+): 279.0871. Found: 279.0876.
N-(4-Methoxy-2-trifluoromethylphenyl)-5-amino-2-methyl-5-phenylpent-2-en-1-nal (**2a**): yellow viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39 (1H, s, CHO), 7.38–7.24 (5H, m, Ar–H), 7.01 (1H, d, $J = 2.7$ Hz, Ar–H), 6.79 (1H, dd, $J = 8.7$, 2.7 Hz, Ar–H), 6.49 (1H, d, $J = 7.2$ Hz, 3-CH), 6.44 (1H, d, $J = 8.7$ Hz, Ar–H), 4.58 (1H, td, $J = 6.3$, 6.3 Hz, 5-CH), 4.45 (1H, br, NH), 3.70 (3H, s, OMe), 2.95–2.79 (2H, m, 4-CH_2), 1.74 (3H, s, 2-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 151.0, 148.3, 142.0, 141.8, 138.4, 129.0, 127.7, 126.6, 126.1, 123.0, 119.0, 115.0, 114.9, 114.5, 112.1 (q, $J = 6$ Hz), 57.3, 55.8, 38.1, 9.3; IR (film) 3447, 3058, 2935, 2833, 2710, 1684, 1514, 1426, 1324, 1218, 1100, 1042, 885, 811 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{21}F_3NO_2$ [(M+H)$^+$]: 364.1518. Found: 364.1526.