DBU-Catalyzed Addition Reactions of Sulfonylimidates

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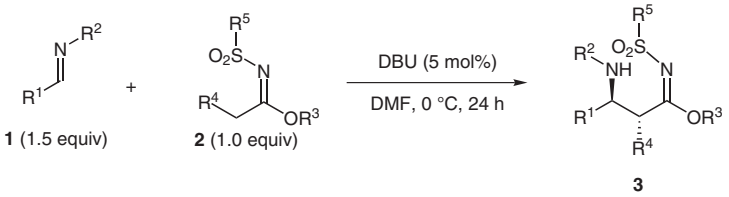
Received 14 July 2008

PSP No 131

Abstract: Sulfonylimidates react with various types of N-protected imines in the presence of a catalytic amount of DBU to afford β-aminosulfonylimidates in high yields and high *anti*-selectivities. The experimental procedure is described in detail.

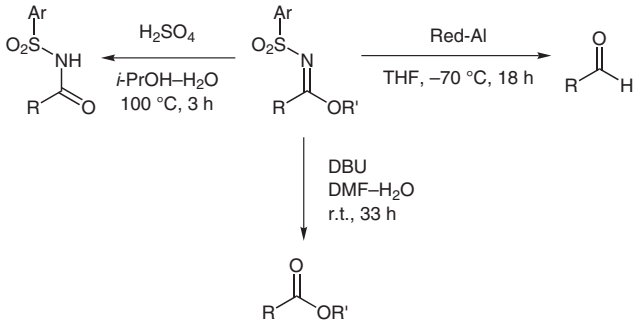
Key words: addition reaction, imine, catalysis, sulfonylimidate, direct reaction



Scheme 1 Direct Mannich-type reaction of sulfonylimidate

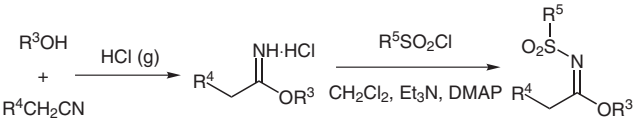
The abstraction of an α-proton from a carbonyl compound and the subsequent nucleophilic addition reaction of the formed enolate is a fundamental sequence of transformation in synthetic organic chemistry. Among the carbonyl compounds, the use of esters or substrates at the oxidation level of an ester (e.g., thioester or amide) as nucleophiles is particularly important as the products can be readily transformed to other functionalities after the addition reactions. In general, a stoichiometric amount of base is necessary in the deprotonation step; however, for the purpose of practical synthesis, an ideal scenario would be to use only a catalytic amount of base for enolate formation. Several groups have reported successful catalytic systems for the α-functionalization of ester oxidation level carbonyl compounds.[1]

Recently sulfonylimidates have been reported to function as an ester oxidation level nucleophile.[2] For example, in the presence of a catalytic amount of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), N-protected imines react with sulfonylimidates to afford β-aminosulfonylimidates, which could be further transformed to the corresponding *N*-sulfonylamides, aldehydes, and esters in one step (Scheme 2). In contrast to preactivated carbonyl nucleophiles such as metalated enolates, sulfonylimidates are stable in air and easy to handle. In view of its practical usefulness and novelty as a nucleophile, we report herein the detailed reaction protocol of sulfonylimidate synthesis as well as the subsequent nucleophilic addition reactions.



Scheme 2 Transformation of sulfonylimidate to other functional groups

Sulfonylimidates could be synthesized in two steps from the corresponding alcohol and nitrile (Scheme 3).[3] The first step was bubbling of HCl gas into a mixture of alcohol and nitrile for 10–20 minutes. Although the reaction was exothermic, it was not explosive even on a one mole scale. Cooling to 0 °C should be safer, but retarded the reaction significantly. Evaporation of the solvents,[4] followed by recrystallization provided a white, hygroscopic imidate HCl salt in moderate yield. The relatively low yield could be ascribed to the loss of volatile starting materials during the exothermic reaction. Sulfonylation was carried out according to the standard procedure. To a sus-



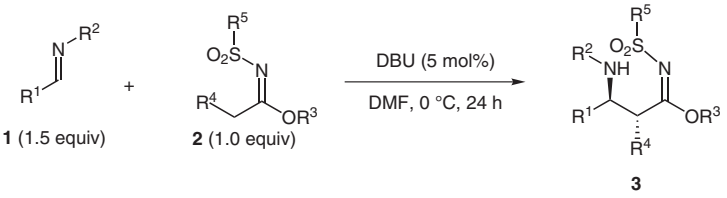
Scheme 3 Preparation of sulfonylimidates

SYNTHESIS 2008, No. 18, pp 3009–3011
Advanced online publication: 04.09.2008
DOI: 10.1055/s-2008-1067251; Art ID: Z16308SS

pension of the imidate HCl salt in CH_2Cl_2 were added Et_3N, a sulfonyl chloride, and a catalytic amount of DMAP, successively. The reactions were generally complete within 24 hours. Purification by chromatography on silica gel provided the desired sulfonylimidate in high yield. Most of the sulfonylimidates used in this report were solid at room temperature, further purification was possible by recrystallization. Direct recrystallization of the crude sulfonylimidate without column chromatography is also possible.

The scope of the direct-type Mannich reactions of sulfonylimidates was proved to be broad (Scheme 1, Table 1). Aromatic imines as well as aliphatic imines[5] gave the products in high yields, and the selectivities were generally high. The addition of molecular sieves suppressed the

Table 1 DBU-Catalyzed Mannich-Type Reaction of Various Imines and Sulfonylimidates



1 (1.5 equiv) **2** (1.0 equiv) **3**

Entry	R^1	R^2	R^3	R^4	R^5	Yield (%)	*anti*/*syn*[a]	**3**
1	Ph	Boc	*i*-Pr	Me	2,5-xylyl	95	96:4	**3a**
2	Ph	Boc	*i*-Pr	Et	2,5-xylyl	94	97:3	**3b**
3[b,c,d]	Ph	EtO_2C	Et	H	Ph	79	–	**3c**
4[c]	Ph	Ts	*i*-Pr	Me	2,5-xylyl	91	96:4	**3d**
5[e]	4-$MeOC_6H_4$	Boc	*i*-Pr	Me	2,5-xylyl	91	95:5	**3e**
6	4-FC_6H_4	Boc	*i*-Pr	Me	2,5-xylyl	87	97:3	**3f**
7	3-MeC_6H_4	Boc	*i*-Pr	Me	2,5-xylyl	quant	97:3	**3g**
8[e]	2-MeC_6H_4	Boc	*i*-Pr	Me	2,5-xylyl	64	93:7	**3h**
9	3-vinylC_6H_4	Boc	*i*-Pr	Me	2,5-xylyl	97	97:3	**3i**
10	2-furyl	Boc	*i*-Pr	Me	2,5-xylyl	92	95:5	**3j**
11	2-thienyl	Boc	*i*-Pr	Me	2,5-xylyl	90	98:2	**3k**
12	2-pyridyl	Boc	*i*-Pr	Me	2,5-xylyl	91	98:2	**3l**
13[c]	PhCH=CH	Ts	*i*-Pr	Me	2,5-xylyl	80	98:2	**3m**
14[c]	cyclopropyl	Ts	*i*-Pr	Me	2,5-xylyl	84	87:13	**3n**
15[c,d]	cyclopropyl	Boc[f]	*i*-Pr	Me	2,5-xylyl	quant	88:12	**3o**
16[c,d,g]	*c*-C_6H_{11}	Ts[f]	Me	Me	4-MeC_6H_4	51	83:17	**3p**
17[c,d,g]	*c*-C_6H_{11}	Ts[f]	*i*-Pr	Me	4-MeC_6H_4	59	84:16	**3q**
18[c,d,g]	*i*-Pr	Ts[f]	Me	Me	4-MeC_6H_4	56	69:31	**3r**
19[c,d,g]	*i*-Pr	Ts[f]	*i*-Pr	Me	4-MeC_6H_4	54	87:13	**3s**
20[c,h]	*t*-Bu	Ts	Me	Me	4-MeC_6H_4	51	14:86	**3t**
21[c,d]	EtO_2C	4-$MeOC_6H_4$	*i*-Pr	Me	2,5-xylyl	80	55:45[i]	**3u**

[a] Determined by ^1H NMR spectroscopy of the crude product or isolated product.
[b] Compound **2** (5 equiv) and **1** (1 equiv) were used.
[c] MS 4A (167 g/mol) were added.
[d] Amount of DBU used: 10 mol%.
[e] Time: 38 h.
[f] Amount of **1** used: 3 equiv.
[g] Room temperature.
[h] Conditions: 40 °C, 36 h.
[i] Major/minor.

hydrolysis of sulfonylimidates (sulfonylimidates are relatively labile under basic conditions) and effectively improved the yield.

In conclusion, we have developed a catalytic direct-type, Mannich-type reactions of sulfonylimidates, which allows straightforward access to β-aminosulfonylimidates in high yields.

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECX-400, JNM-ECX-500 and JNM-ECX-600 spectrometers in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as internal standard (δ = 0) for ^{1}H NMR, and $CDCl_3$ (δ = 77.0) was used as internal standard for ^{13}C NMR. IR spectra were measured on a JASCO FT/IR-610 spectrometer. Column chromatography was conducted on Silica gel 60 (Merck) and preparative thin-layer chromatography was carried out using Wakogel B-5F. All reactions were carried out under an argon atmosphere in dried glassware. All solvents were dried and distilled by standard procedures.

Isopropyl Propionimidate HCl Salt; Typical Procedure

HCl gas was bubbled to a mixture of propionitrile (75.65 g, 1.373 mol) and *i*-PrOH (77.11 g, 1.28 mol) for 10 min (exothermic), after which the mixture was kept for 2 h under argon. Removal of all the volatiles by evaporation gave the almost pure imidate HCl salt. Further purification was possible by washing the solid with anhyd Et_2O (200 mL); yield: 78.2 g (41%). Imidate HCl salts are hygroscopic, but can be kept under inert gas atmosphere in the refrigerator (–20 °C) for at least one year.

Isopropyl *N*-(2,5-Xylylsulfonyl)propionimidate (2a); Typical Procedure

Et_3N (13.8 mL, 98.22 mmol) was added dropwise to a solution of isopropyl propionimidate HCl salt (5 g, 32.74 mmol) in CH_2Cl_2 (78 mL) at r.t. DMAP (402.9 mg, 3.27 mmol) and 2,5-xylylsufonyl chloride (6.7 g, 32.74 mmol) were added to the resultant suspension. The mixture was stirred until complete consumption of 2,5-xylylsulfonyl chloride (24 h). The mixture was poured into aq $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organics were dried (Na_2SO_4). Filtration and evaporation of the solvent afforded the crude product, which was purified by column chromatography on silica gel to give the title compound; yield: 8.41 g (91%); mp 32–33 °C.

IR (neat): 3055, 2988, 1590, 1458, 1308, 1265, 1154, 1092, 1066, 896, 740, 705, 642, 459, 413 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.20 (s, 1 H), 6.90 (d, *J* = 7.4 Hz, 1 H), 6.84 (dd, *J* = 7.4, 1.4 Hz, 1 H), 4.74 (sept, *J* = 6.3 Hz, 1 H), 2.91 (q, *J* = 7.4 Hz, 2 H), 2.77 (s, 3 H), 1.94 (s, 3 H), 1.07 (t, *J* = 7.4 Hz, 3 H), 0.83 (d, *J* = 6.3 Hz, 6 H).

^{13}C NMR ($CDCl_3$): δ =176.2, 141.2, 135.9, 134.4, 133.0, 132.2, 128.9, 71.2, 28.4, 21.1, 20.6, 20.2, 10.4.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{22}NO_3S$ [M + H]$^+$: 284.1320; found: 284.1323.

Isopropyl *anti*-3-(*tert*-Butoxycarbonylamino)-2-methyl-3-phenyl-*N*-(2,5- xylylsulfonyl)propionimidate (*anti*-3a); Typical Procedure (Table 1, Entry 1)

DMF (18.5 mL), MS 4A (1.67 g), and isopropyl *N*-(2,5-xylylsulfonyl)propionimidate (**2a**; 2.844 g, 10.0 mmol) were added successively in this order to a solution of *tert*-butyl benzylidenecarbamate (benzaldehyde-derived *N*-Boc-imine, 3.09 g, 15.1 mmol). The mixture was cooled to 0 °C and a solution of DBU (76.4 mg, 0.50 mmol) in DMF (1.5 mL) was added. The mixture was stirred for 24 h and then diluted with Et_2O (100 mL). The mixture was filtered over Celite; the filtrate was washed with H_2O (3 × 40 mL) and dried (Na_2SO_4). Filtration and removal of solvents afforded the crude product. The diastereomer ratio was determined to be *anti*/*syn* = 96:4 by ^{1}H NMR analysis of the crude product. Purification of the crude product was conducted by chromatography on silica gel (hexane–acetone, 10:1) to afford the desired product **3a**; yield: 4.86 g (99%); mp 122–123 °C.

IR (neat): 3060, 3032, 2841, 2936, 2881, 1715, 1588, 1513, 1495, 1456, 1389, 1365, 1299, 1267, 1248, 1225, 1155, 1102, 1066, 1053, 1004, 973, 930, 910, 884, 851, 824, 738, 707, 644, 599, 553, 499, 465 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.19 (s, 1 H), 7.36 (d, *J* = 6.8 Hz, 2 H), 6.93–7.05 (m, 4 H), 6.89 (d, *J* = 7.3 Hz, 1 H), 6.62 (d, *J* = 9.6 Hz, 1 H), 5.03 (t, *J* = 10.5 Hz, 1 H), 4.87 (quint, *J* = 6.2 Hz, 1 H), 4.48 (sext, *J* = 5.9 Hz, 1 H), 2.86 (s, 3 H), 1.96 (s, 3 H), 1.34 (s, 9 H), 1.15 (d, *J* = 5.7 Hz, 3 H), 0.98 (d, *J* = 6.2 Hz, 3 H), 0.91 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 177.5, 154.7, 141.4, 140.5, 136.1, 134.5, 133.4, 132.4, 128.9, 128.3, 127.9, 127.7, 78.6, 72.1, 58.9, 46.0, 28.4, 21.0, 21.0, 20.6, 20.6, 14.9.

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{37}N_2O_5S$ [M + H]$^+$: 489.2423; found: 489.2417.

Acknowledgment

This work was partially supported by a Grant-in-Aid for Scientific Research from Japan Society of the Promotion of Sciences (JSPS).

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(4) Thorough evaporation of the solvents provided the imidate HCl salt (a solid). The solidification of imidate salt could be encouraged by keeping it under argon at –20 °C. The exposure to air should be avoided as this salt readily absorbs moisture to form a gum-like solid, from which it was found to be difficult to remove the starting materials.

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