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Trimethylsilyl Triflate Promoted Addition of Allyltributylstannane to Aldonitrones; One-Pot Synthesis of 5-Iodomethylisoxazolidines

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Abstract: the trimethylsilyl triflate promoted allylation of nitrones with allyltributylstannane affords *O*-silylated hydroxylamines in high yield; when the crude reaction mixture is quenched with *N*-iodosuccinimide, 5-iodomethylisoxazolidines are formed in excellent yields. The overall one-pot two-step process represents a valuable improvement in terms of time, cost and overall yield with respect to the previously reported three stage procedure involving nitrone allylation, hydroxylamine *O*-silylation, and iodocyclisation.

Allylation of carbonyl compounds and imines by means of allylic organometallic compounds represents one of the most deeply explored methodologies for the regio and stereocontrolled construction of carbon-carbon bonds.[1] In the last few years our research group has been investigating the mechanistic aspects and the synthetic potential of the allylation of nitrones to give homoallylic hydroxylamines.[2-4] Depending on the nature of the metal involved and the presence/absence of an activator (Lewis acid), different products are obtained. When allylmagnesium or zinc complexes are used, a typical 1,3-addition leads to homoallylic hydroxylamines. In this case the presence of an activator increases reaction rates and affects the stereochemical outcome of the stereocentres that are formed.[4] On the other hand, the less polar allyltrimethylsilane **3a**, in the presence of trimethylsilyl triflate (TMSOTf), gives rise to either homoallylic hydroxylamines **5**[5] or isoxazolidines **6a**,[6] depending on the substrate. The corresponding mechanistic pathways are depicted in Scheme 1. The intermediate carbonium ion **4a**, generated from *N*-trimethylsilyloxyimonium ion **2** upon addition of **3a**, decomposes according to path **A**, affording a *O*-silylated hydroxylamine **5** when R = Ph or CO_2Et, or according to path **B** to give 5-trimethylsilylmethylisoxazolidines **6a** when R = alkyl.

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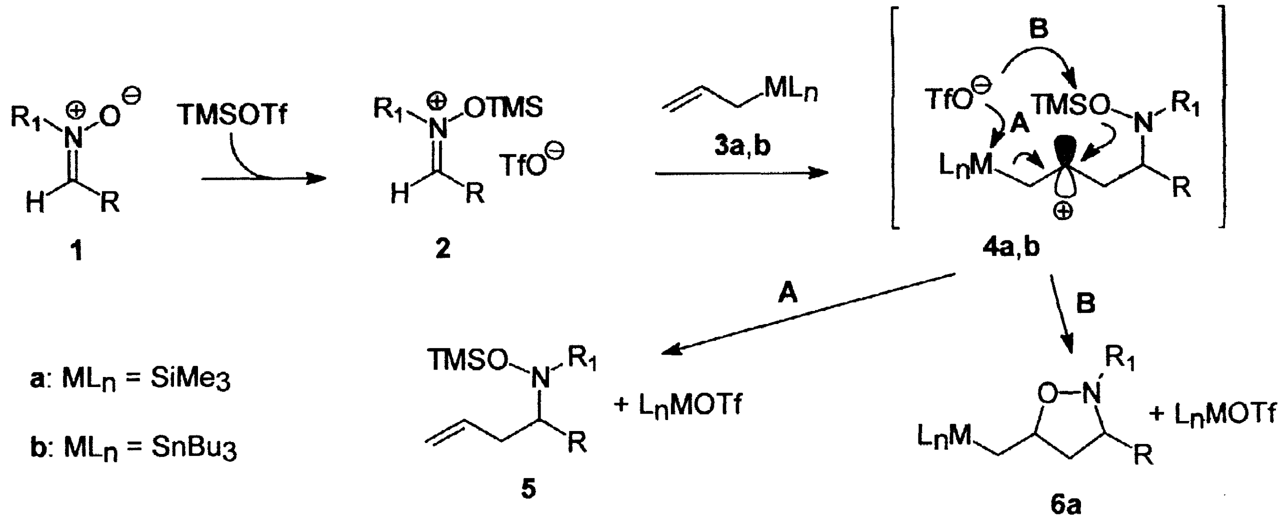
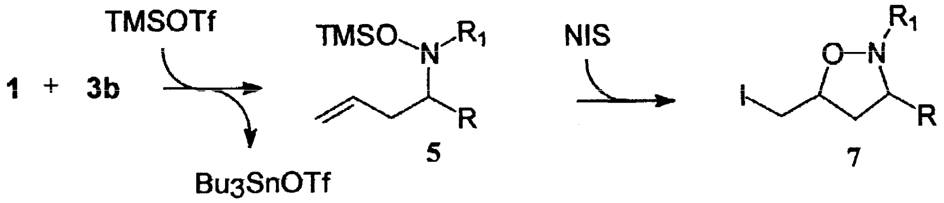


Scheme 1

Here we wish to report that: i) differently from **3a**, allyltributylstannane **3b** adds to aldonitrones in dichloromethane at room temperature in the presence of TMSOTf according to path **A** to give Bu_3SnOTf and **5** with a very high yield, independently of the nature of R; and, ii) treatment of the crude allylation mixture with *N*-iodosuccinimide (NIS) affords 5-iodomethylisoxazolidines **7** in a one pot process (Scheme 2) marked by high yields and fast reaction rates.



Scheme 2

In a typical experimental procedure (run 1, Table 1), TMSOTf (0.18 mL, 1 mmol) was added at 0°C to a solution of nitrone **1a** (163 mg, 1 mmol) in CH_2Cl_2 (6 mL); after 15 min the ice bath was removed, allyltributyltin (0.30 mL, 1 mmol) was added and the reaction mixture was stirred for 30 min at 20 °C. An aliquot was quenched with aq $NaHCO_3$ and analysed by GC-MS to verify reaction conversion and formation of **5**[7] (in a single experiment desilylated hydroxylamine[8] deriving from **5a** was isolated in 83% yield by flash chromatography). In the second step of our protocol NIS (270 mg, 1.2 mmol) was added to the crude allylation mixture and the reaction course was monitored by TLC. After stirring in the dark for 3 h at 0 °C, aq $Na_2S_2O_3$ was added, the aq phase was extracted with CH_2Cl_2 and isoxazolidines **7**[9] were purified by silica gel flash chromatography (cyclohexane/ethyl acetate mixtures as the eluent). It is worth mentioning that Bu_3SnOTf fails to promote allylation of nitrones by allyltributyltin under the experimental conditions reported above.

Table 1. One pot synthesis of 5-iodomethylsixazolidines 7.

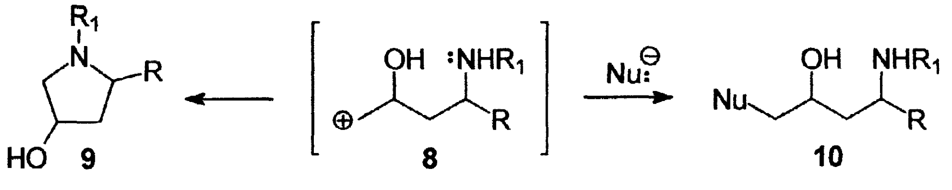
Run	Nitrone **1a-e**			t_1/t_2[a]	**5a-e**	**7a-e**	*cis*-**7**/*trans*-**7**	*cis*-**7**/*trans*-**7**
		R	R_1	(h)	Conv. (%)[b]	Yield (%)[c]		lit.values[2]
1	**a**	Et	Bn	0.5/3	>99	73	40/60	-
2	**b**	n-C_9H_{19}	Bn	1/2.5	98	72	55/45	-
3	**c**	*i*-Pr	Bn	0.5/0.75	>99	85	65/35	97/3
4	**d**	TBDMSOCH$_2$	Bn	0.5/0.75	>99	59	50/50	-
5	**e**	Ph	Me	1/2	>99	72	55/45	86/14
6	**f**	Ph	*t*-Bu	2/0.75	47	43	30/70	17/83

[a] t_1 and t_2 refer to allylation (carried out at 20°C) and iodocyclisation (carried out at 0°C) time, respectively. [b] Conversions evaluated by GC-MS. [c] Yields refer to pure isolated isoxazolidines **7**.

Shorter reaction time and better yield in the cyclisation steps are obtained with respect to previously reported iodocyclisation reactions carried out on pure **5** and promoted by NIS.[2-4] Moreover, the one-pot process displays lower *cis/trans* ratios than those observed using NIS (runs 3,5,6).[2] In our opinion NIS is not the actual iodinating agent in the present procedure; Bu_3SnOTf present in the reaction medium could activate NIS forming the highly reactive and not selective iodine(I) triflate, responsible for the lack of diastereocontrol of the ring closure reaction. *In situ* generated iodine(I) triflate, obtained from iodine and AgOTf[10] or from NIS and TfOH,[11] has been reported to act as a superelectrophile, capable to iodinate deactivated aromatics.

In conclusion, allylstannanes efficiently add to nitrones in the presence of TMSOTf to give *O*-silylated homoallylic hydroxylamines. We developed a one-pot two-step protocol for the synthesis of 5-iodomethylisoxazolidines **7** by simply trapping the crude allylation reaction mixture with NIS[12].

Iodomethylisoxazolidines **7**, synthetic equivalent of primary carbonium ions **8**, are being examined as precursors of useful target molecules such as pyrrolidines **9** and substituted β-aminoalcohols **10** (Scheme 3).



Scheme 3

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7. Unambiguously identified by GC-MS through characteristic M$^+$ - 15, and M$^+$ - 41 ions.
8. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.97 (3H, t, *J* = 7.4 Hz), 1.48-1.57 (1H, m, H2), 1.63-1.72 (1H, m, H2), 2.19-2.29 (1H, m, H4), 2.47-2.56 (1H, m, H4), 2.60-2.69 (1H, m, H3), 3.80 (1H, d, *J* = 13.4 Hz, CH$_2$Ph), 3.85 (1H, d, *J* = 13.4 Hz, CH$_2$Ph), 5.03-5.12 (3H, m, H6 + OH), 5.87 (1H, ddt, *J* = 17.1, 10.2, 7.2 Hz, H5), 7.22-7.38 (5H, m); ^{13}C NMR (75 MHz, CDCl$_3$) δ 11.1, 22.8, 33.8 (C4), 59.6 (CH$_2$Ph), 67.3 (C3), 115.9 (C6), 127.0, 128.2, 129.2, 136.9 (C5), 138.7.
9. NMR spectra of new isoxazolidines. *cis*-**7a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.92 (3H, t, *J* = 7.4 Hz), 1.33-1.47 (2H, m), 1.79 (1H, dt, *J* = 12.5, 6.9 Hz, H4), 2.70 (1H, dt, *J* = 12.5, 7.5 Hz, H4), 2.83-2.92 (1H, m, H3), 3.17 (1H, t, *J* = 9.4 Hz, CH$_2$I), 3.34 (1H, dd, *J* = 9.4, 5.1 Hz, CH$_2$I), 3.90 (1H, d, *J* = 13.7 Hz, CH$_2$Ph), 3.98 (1H, d, *J* = 13.7 Hz, CH$_2$Ph), 4.33-4.42 (1H, m, H5), 7.20-7.41 (5H, m); ^{13}C NMR (75 MHz, CDCl$_3$) δ 8.9 (CH$_2$I), 10.9, 26.6, 41.0 (C4), 60.7 (CH$_2$Ph), 67.7 (C3), 76.4 (C5), 127.1, 128.2, 128.7, 137.4. *trans*-**7a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.95 (3H, t, *J* = 7.4 Hz), 1.31-1.49 (2H, m), 2.21 (2H, t, *J* = 7.4 Hz, H4), 2.81-2.93 (1H, br m, H3), 3.14 (1H, dd, *J* = 9.8, 8.0 Hz, CH$_2$I), 3.31 (1H, dd, *J* = 9.8, 4.0 Hz, CH$_2$I), 3.96 (1H, d, *J* = 13.7 Hz, CH$_2$Ph), 4.02 (1H, d, *J* = 13.7 Hz, CH$_2$Ph), 4.11-4.19 (1H, m, H5), 7.21-7.40 (5H, m); ^{13}C NMR (75 MHz, CDCl$_3$) δ 9.0 (CH$_2$I), 10.8, 26.6, 40.4 (C4), 60.9 (CH$_2$Ph), 66.7 (C3), 76.4 (C5), 127.2, 128.2, 129.0, 137.3. *cis*-**7b**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.89 (3H, t, *J* = 6.5 Hz), 1.25 (16H, br s), 1.77 (1H, dt, *J* = 12.6, 6.9 Hz, H4), 2.70 (1H, dt, *J* = 12.6, 7.6 Hz, H4), 2.88-2.98 (1H, br m, H3), 3.17 (1H, t, *J* = 9.5 Hz, CH$_2$I), 3.33 (1H, dd, *J* = 9.5, 5.1 Hz, CH$_2$I), 3.88 (1H, d, *J* = 13.7 Hz, CH$_2$Ph), 3.96 (1H, d, *J* = 13.7 Hz, CH$_2$Ph), 4.32-4.41 (1H, m, H5), 7.22-7.40 (5H, m); ^{13}C NMR (75 MHz, CDCl$_3$) δ 8.9 (CH$_2$I), 14.1, 22.6, 26.7, 29.3, 29.49, 29.54, 31.8, 33.8, 41.5 (C4), 60.7 (CH$_2$Ph), 66.3 (C3), 76.5 (C5), 127.1, 128.2, 128.8, 137.5. *trans*-**7b**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.89 (3H, t, *J* = 7.1 Hz), 1.26 (16H, br s), 2.17-2.22 (2H, m, H4), 2.85-2.96 (1H, br m, H3), 3.13 (1H, dd, *J* = 9.8, 8.0 Hz, CH$_2$I), 3.30 (1H, dd, *J* = 9.8, 4.0 Hz, CH$_2$I), 3.89 (1H, d, *J* = 13.7 Hz, CH$_2$Ph), 4.04 (1H, d, *J* = 13.7 Hz, CH$_2$Ph), 4.10-4.20 (1H, m, H5), 7.23-7.40 (5H, m); ^{13}C NMR (75 MHz, CDCl$_3$) δ 9.0 (CH$_2$I), 14.1, 22.6, 26.6, 29.3, 29.5, 29.6, 31.9, 32.7, 40.9 (C4), 61.7 (CH$_2$Ph), 65.3 (C3), 76.5 (C5), 127.2, 128.2, 129.0, 137.5. *cis*-**7d**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.04 (3H, s), 0.05 (3H, s), 0.88 (9H, s), 1.91 (1H, dt, *J* = 12.9, 6.5 Hz, H4), 2.62 (1H, dt, *J* = 12.9, 7.8 Hz, H4), 3.14-3.21 (2H, m, H3 + CH$_2$I), 3.32 (1H, dd, *J* = 9.6, 5.0 Hz, CH$_2$I), 3.59 (1H, dd, *J* = 10.3, 6.0 Hz, CH$_2$OSi), 3.68 (1H, dd, *J* = 10.3, 6.6 Hz, CH$_2$OSi), 3.98 (1H, d, *J* = 13.7 Hz, CH$_2$Ph), 4.11 (1H, d, *J* = 13.7 Hz, CH$_2$Ph), 4.35-4.41 (1H, m, H5), 7.24-7.42 (5H, m); ^{13}C NMR (75 MHz, CDCl$_3$) δ -5.4, -5.36, 8.2 (CH$_2$I), 25.9, 29.7, 38.2 (C4), 61.7 (CH$_2$Ph), 65.0 (OCH$_2$Si), 67.2 (C3), 76.6 (C5), 127.1, 128.2, 128.8, 137.4. *trans*-**7d**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.05 (3H, s), 0.06 (3H, s), 0.89 (9H, s), 2.11-2.20 (1H, m, H4), 2.23-2.32 (1H, m, H4), 3.13-3.21 (2H, m, H3 + CH$_2$I), 3.31 (1H, dd, *J* = 9.9, 4.1 Hz, CH$_2$I), 3.64 (2H, d, *J* = 6.2 Hz, CH$_2$OSi), 4.00 (1H, d, *J* = 13.7 Hz, CH$_2$Ph), 4.09-4.13 (1H, m, H5), 4.22 (1H, d, *J* = 13.7 Hz, CH$_2$Ph), 7.24-7.40 (5H, m); ^{13}C NMR (75 MHz, CDCl$_3$) δ -5.46, -5.42, 8.3 (CH$_2$I), 25.9, 29.7, 38.2 (C4), 63.1 (CH$_2$Ph), 64.6 (OCH$_2$Si), 66.4 (C3), 76.6 (C5), 127.2, 128.2, 129.1, 137.5.
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