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Pyridine-Derived Triflating Reagents: An Improved Preparation of Vinyl Triflates from Metallo Enolates.

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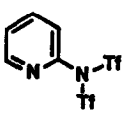
Abstract: *Metallo enolates of ketones are trapped with an N-(2-pyridyl)triflimide at low temperatures to give vinyl triflates.*

Since vinyl trifluoromethanesulfonates (triflates) were first reported in 1969[1], they have been widely used as synthetic precursors for vinyl cations and alkylidene carbenes, and as substrates for regiospecific coupling reactions.[2,3] Vinyl triflates are also valuable as intermediates in a mild, two-step procedure for the deoxygenation of ketones. First the ketone is converted to a vinyl triflate, then hydrogenolysis gives a high yield of the saturated hydrocarbon.[4,5]

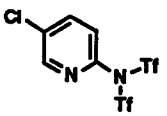
A ketone can be converted to a vinyl triflate on treatment with triflic anhydride and the sterically hindered base, 2,6-di-*t*-butyl-4-methylpyridine.[6] This procedure is governed by Markovnikov's rule and results in the formation of the more substituted vinyl triflate as the major product. For formation of a vinyl triflate from a regiospecifically generated metallo enolate, McMurry's method using *N*-phenyltriflimide as the trapping agent has been very popular.[7] A disadvantage of using *N*-phenyltriflimide as the triflating agent is that it is not very reactive and requires several hours at 0°C to efficiently trap a ketone metallo enolate. At this temperature some enolates are unstable or may equilibrate. Also, *N*-phenyltriflimide byproducts are sometimes difficult to remove from the desired vinyl triflate by chromatography.

To circumvent these occasional problems, we investigated the synthesis and reactivity of two pyridine-derived triflating reagents, *N*-(2-pyridyl)triflimide (**1**) and *N*-(5-chloro-2-pyridyl)triflimide (**2**). These reagents are conveniently prepared from commercially available (Aldrich Chemical Co.) aminopyridines, triflic anhydride and pyridine in methylene chloride (RT, 12 h). Both reagents are stable, white crystalline solids (**1**, mp 41-42°C; **2**, mp 47-48°C) easily purified by Kugelrohr distillation. These pyridine-derived reagents were chosen for study on the premise that the electron deficient aromatic ring would withdraw electron density from the triflimide group causing it to be more susceptible to nucleophilic attack. There is also the possibility of activation through chelation by the pyridyl nitrogen to the metal of the metallo enolate as shown below (**3**). Presumably for similar reasons, the amides of 2-(methylamino)pyridine are exceptionally reactive toward organometallics.[8,9]

Several reactions of **1** and **2** with various ketone metallo enolates were performed and the results are given in the Table.



1



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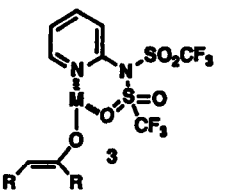

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Table. Preparation of Vinyl Triflates from Ketone Enolates.

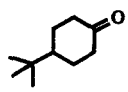
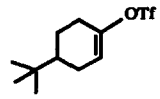
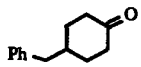
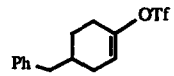
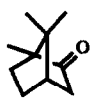
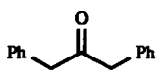
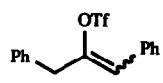
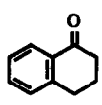
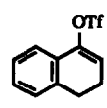
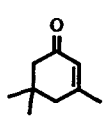
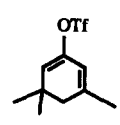
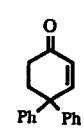
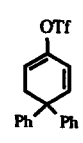
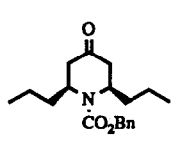
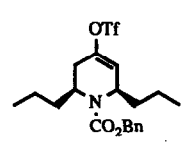
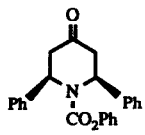
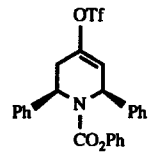
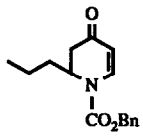
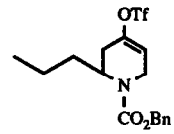
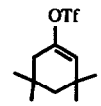
entry[a]	ketone	base; reagent	conditions[b]	product	yield[c],%
a		LDA; 2	-78°C, 2 h		87
b	"	NaHMDS; 2	-78°C, 2 h	"	92
c		LDA; 2	-78°C, 2 h		73
d	"	NaHMDS; 2	-78°C, 3 h	"	80
e	"	LDA; 1	-78°C, 3 h	"	76
f		LDA; 2	-78°C, 2 h		77
g		LDA; 2	-78°C, 3 h		79
h	"	LDA; $PhN(Tf)_2$	-78°C, 3 h	"	<1
i		LDA; 2	-78°C, 2 h; -23°C, 4 h; -16°C, 12 h		80
j	"	LDA; 1	-78°C, 2 h; -23°C, 4 h; -16°C, 12 h	"	76
k	"	NaHMDS; 2	-78°C, 2 h; -23°C, 4 h;	"	75
l		LDA; 2	-78°C, 2 h		86
m		LDA; 2	-78°C, 2 h		88
n		LDA; 2	-78°C, 4 h		78

Table. Preparation of Vinyl Triflates from Ketone Enolates. (continued)

entry[a]	ketone	base; reagent	conditions[b]	product	yield[c], %
o		LDA; 2	-78°C, 2 h		88
p		L-Selectride®; 2	-23°C, 2 h		80
q		$LiMe_2Cu$; 2	O°C, 4 h		80

[a]The reactions were generally performed on a 1-2 mmol scale in THF. [b]The workup consisted of addition of water, extraction with ether, washing with 10% NaOH, and drying over K_2CO_3. [c]Yield of products obtained from radial preparative-layer chromatography (silica gel, EtOAc/hexanes). Satisfactory IR, ^1H and ^{13}C NMR, and microanalysis data were obtained for all new compounds.

Reagents **1** and **2** proved to be substantially more reactive than *N*-phenyltriflimide allowing most vinyl triflates to be prepared at -78°C in only 2 to 4 hours (See entries g-h). Ketone enolates generated by LDA/THF, by organocuprate 1,4-addition to an enone, and by L-Selectride® 1,4-reduction of an enone all reacted with **2** to give good to excellent yields of vinyl triflates. Although most of the reactions examined used triflimide **2**, reagent **1** exhibits similar reactivity (entries e and j). In all cases, the product was easily separated from byproducts on chromatography over silica gel (EtOAc/hexanes). Further applications of triflating reagents **1** and **2** are being investigated in our laboratories.

Preparation of *N*-(5-Chloro-2-pyridyl)triflimide (2).

To a stirred solution of 5-chloro-2-aminopyridine (1.8 g, 14.0 mmol) in dry CH_2Cl_2 (55 mL) was added dry pyridine (2.4 mL, 29.4 mmol). The solution was cooled to -78°C and triflic anhydride (4.71 mL, 29.4 mmol) in 5.0 mL of CH_2Cl_2 was added dropwise. The mixture was stirred at -78°C for 1 h and at room temperature for 12 h. Water (10 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with 10-mL portions of cold 10% NaOH, water, and brine. The organic phase was dried ($MgSO_4$), filtered through Celite, and concentrated to give 4.95 g of crude product. Purification by Kugelrohr distillation (bp 80-95°C, 0.25 mmHg) afforded 4.42 g (80%) of **2** as a white solid, mp 47-48°C. [10]

[Reagent **1** was prepared (83%) in an analogous fashion from 2-aminopyridine (Kugelrohr bp 80-90°C, 0.25 mmHg; mp 41-42°C).][11]

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10. NMR data for **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, 1 H, J = 8.8 Hz), 7.88-7.92 (dd, 1 H, J = 8.8, 2.93 Hz), 8.58 (d, 1 H, J = 2.93 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.8, 117.1, 121.4, 125.7, 126.2, 135.8, 139.3, 143.8, 149.3.
11. NMR data for **1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.55 (m, 2H), 7.91-7.97 (dt, J = 8.1, 2.2 Hz), 8.62-8.64 (dd, 1 H, J = 4.4 , 1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 112. 8, 117.1, 121.4, 125.5, 125.7, 126.8, 139.7, 146.0, 150.3.

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