Note

Yttrium triflate-catalyzed reactions of indoles with electron-deficient olefins

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The reaction condition for Michael addition of indoles to a series of electron-deficient olefins catalyzed by Y(OTf)$_3$ has been carefully optimized at ambient temperature and the reaction affords the corresponding Michael adducts in good to excellent yields with high selectivity. Y(OTf)$_3$ is also found to be able to catalyze the Michael addition of furan.

**Keywords**: Yttrium triflate, Michael addition, indoles, furan

Many indole derivatives such as Hapalosiphon, Uleine, Fischer indole alkaloids[1], are associated with important pharmacological and biological activity. Based on high reactivity in the 3-position of indole towards electrophilic substitution reactions, the Michael addition of indole to electron-deficient olefins have been widely investigated because this reaction could be employed to synthesize these indole alkaloids. Either protic[2] or Lewis acids[3] have proved to be able to promote the Michael reaction, but the dimerization or polymerization of starting materials could not be prevented under acidic condition.

Unlike conventional Lewis acids such as AlCl$_3$, TiCl$_4$, SnCl$_4$, *etc*., Ln(OTf)$_3$ (Ln = La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu) and Yttrium (Y) triflate were shown to be moisture tolerant and recovered even after aqueous work-up. In organic reactions promoted by conventional Lewis acids, large amounts of Lewis acids are always used and treatment of the residues of Lewis acids may cause serious environmental problems, whereas rare-earth metal triflate-catalyzed reactions are always very clean and triflates are known as environmentally friendly catalysts. These rare-earth metal triflates are now playing important roles in a series of organic transformations[4]. Generally, Ln(OTf)$_3$ and Y(OTf)$_3$ show lower catalytic activity than Sc(OTf)$_3$ (ref. 4); however, Y(OTf)$_3$ has been employed as a powerful Lewis acid catalyst for the Mannich reaction[5] and the aldol reaction[6] in recent literature. In this report, Y(OTf)$_3$ has proved to be a highly efficient catalyst for the Michael addition of indoles to electron-deficient olefins. Further research indicated that Y(OTf)$_3$ is also an efficient catalyst for the Michael addition of furan to MVK.

Results and Discussion

First of all, a number of traditional metal chlorides and triflates were systematically examined as the catalyst for the reaction of indole **1a** (1.0 equiv.) with MVK **2a** (1.0 equiv.) in CH$_2$Cl$_2$ (**Scheme I**). The results are presented in **Table I**. Both LaCl$_3$ and La(OTf)$_3$ were ineffective for this reaction. Traditional Lewis acids such as SbCl$_3$, ZnCl$_2$ and AlCl$_3$, showed low catalytic activity towards this reaction (11-25% yield, entry 2, 3, 5, **Table I**). The catalytic activity of BiCl$_3$ is higher than the above three metal chlorides (40% yield, entry 1, **Table I**). Y(OTf)$_3$ was found to be superior to all other catalysts and the product could be separated in 90% yield after 2 hr at RT with 5 or 10 mol% Y(OTf)$_3$ (entry 9, 10, **Table I**). Encouraged by this result, the reaction was carried out using different solvents. In terms of yields, dichloromethane was best among all examined
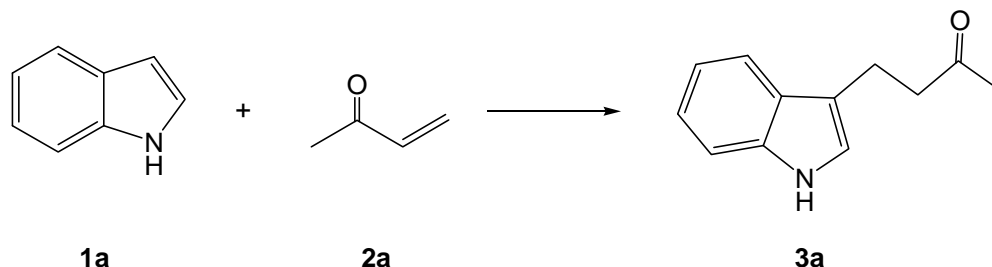
Scheme I

Entry	Catalyst	Amount/mol %	Yield (%)[a,b]
1	$BiCl_3$	20	40
2	$SbCl_3$	20	25
3	$ZnCl_2$	20	15
4	$LaCl_3$	20	0
5	$AlCl_3$	20	11
6	$La(OTf)_3$	20	0
7	$Y(OTf)_3$	0.5	72
8	$Y(OTf)_3$	1	83
9	$Y(OTf)_3$	5	90
10	$Y(OTf)_3$	10	90
11	$Y(OTf)_3$	20	87

[a] The reaction was carried out in CH_2Cl_2; [b] Isolated yields.

solvents such as THF, toluene, Et_2O, MeOH and $CHCl_3$. It was also found that the yield of Michael adduct **3a** could be improved to 95% when the ratio of indole to MVK was 1:2 under catalysis with 5 mol% $Y(OTf)_3$.

To extend the scope of the reaction, the reaction was carried out with different electron-deficient olefins such as methyl vinyl ketone **2a**, 2-cyclohexen-1-one **2b**, β-nitrostyrene **2c** and dibenzylidene acetone **2d**. In the case of dibenzylidene acetone **2d**, no bis-alkylated product was observed and the mono-alkylated product **3d** could be isolated in 70% yield (entry 4, **Table II**). This suggests that dibenzylidene acetone **2d** is more electron-deficient than its mono-alkylated product **3d**. The reaction of indole **1a** with 2-cyclohexen-1-one **2b** or β-nitrostyrene **2c** produced the corresponding 3-alkylated indole (entry 2, 3, **Table II**) in excellent yield (90% yield). Similar results could be found in **Table II** with 2-methyl-indole **1b** as Michael donor (entry 5, 6, 7). It is interesting to find that $Y(OTf)_3$ could catalyze the Michael addition of furan **1c** to MVK **2a** (entry 8, **Table II**). Although furan **1c** is very sensitive to acidic conditions[7], the bis-alkylated product **3h** could be separated in 70% yield without the isolation of monoalkylated product. This suggests that $Y(OTf)_3$ could be successfully employed as a catalyst for the Michael addition of furan derivatives to electron-deficient olefins and further research on this topic is in progress.

The reactions were clean and the products were all separated in high yields without the simultaneous formation of triindolylalkane[8]. The procedure does not require anhydrous conditions and the use of inert atmosphere.

Experimental Section

^{1}H NMR was recorded at 500 MHz. Commercially available reagents were used as received without further purification. All reactions were monitored by TLC with Huanghai GF254 silica gel coated plates. Flash column chromatography was carried out using 200-300 mesh silica gel. Melting points are uncorrected. For infrared spectra, samples were prepared in KBr pellets. Products **3a** (Ref. 3c), **3b** (Ref. 3e), **3c** (Ref. 3c), **3d** (Ref. 3c), **3e** (Ref. 3c), **3f** (Ref. 3d,3e), **3g** (Ref. 3f) and **3h** (Ref. 9) are all known compounds.

General procedure for Michael addition: A mixture of indole or furan (0.3 mmol), electron-deficient olefin (0.6 mmol), and $Y(OTf)_3$ (5 mol%) in CH_2Cl_2 (5 mL) was stirred at ambient temperature (25ºC) for 2 hr. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phases were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by column chromatography to obtain the pure product.

3a: ^{1}H NMR (CDCl₃): δ 2.10 (s, 3H), 2.73 (t, J = 8.0Hz, 2H), 2.87 (t, J = 8.0Hz, 2H), 7.00 (s, 1H), 7.12-7.24 (m, 2H), 7.27 (d, J = 8.0Hz, 1H), 7.39 (d, J =8.0Hz, 1H), 7.98 (br s, 1H); IR(KBr): 3407, 2923, 1707, 1355, 1162, 745 cm⁻¹; m.p. 70-71ºC.
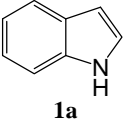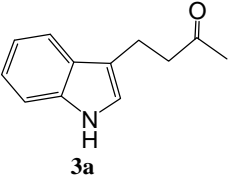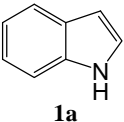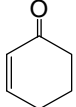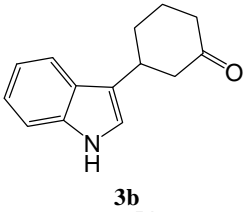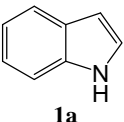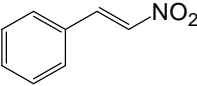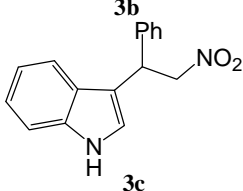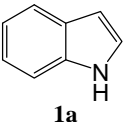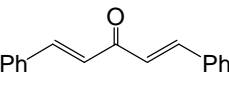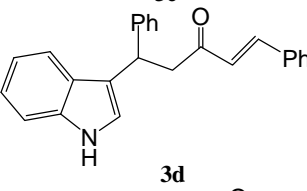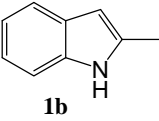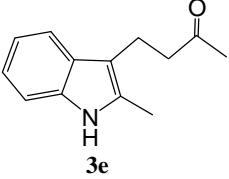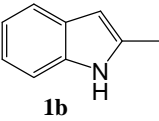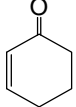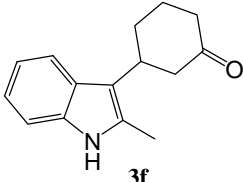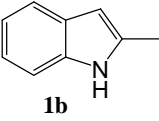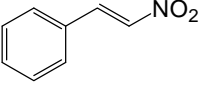
3b: ^{1}H NMR (CDCl₃): δ 1.56-2.09 (m, 3H), 2.24-2.49 (m, 3H), 2.64 (t, J = 14.0Hz, 1H), 2.80 (dd, J = 14.0, 4.5Hz, 1H), 3.43-3.48 (m, 1H), 7.00 (s, 1H), 7.13 (dd, J = 7.0, 8.0 Hz, 1H), 7.21 (dd, J = 7.0, 8.0Hz, 1H), 7.38 (d, J = 8.0Hz, 1H), 7.63 (d, J = 8.0Hz, 1H), 8.01 (br s, 1H, NH).

3c: ^{1}H NMR(CDCl₃): δ 4.83 (dd, J = 8.5, 12.5Hz, 1H), 5.00 (dd, J = 7.5, 12.5Hz, 1H), 5.11 (dd, J = 7.5, 8.5Hz, 1H), 6.83 (s, 1H), 7.02 (ddd, J = 1.0, 7.0, 8.0Hz, 1H), 7.13 (ddd, J = 1.0, 7.0, 8.0Hz, 1H), 7.21-7.35 (m, 6 H), 7.40 (d, J = 8.0Hz, 1H), 7.98 (br s, 1H, NH).
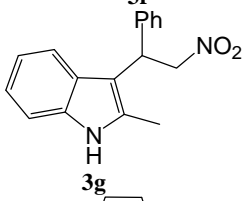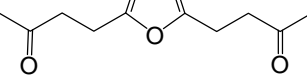
3d: ^{1}H NMR (CDCl₃): δ 3.25-3.50 (m, 2H), 4.80 (dd, J =8.0, 15.0 Hz, 1H), 6.60 (d, J =16.5Hz, 1H), 6.85 (t, J =7.0Hz, 1H), 6.90 (t, J = 7.0Hz, 1H), 7.02 (d, J = 2.4Hz, 1H), 7.15-7.45 (m, 12H), 10.20 (br s, 1H, NH); m.p. 64-65ºC.

3e: ^{1}H NMR(CDCl₃): δ 2.10 (s, 3H), 2.47 (s, 3H), 2.7 (t, J = 7.5Hz, 2H), 2.87 (t, J = 7.5Hz, 2H), 6.98 (s, 1H), 7.12 (dd, J = 7.0, 8.0Hz, 1H), 7.21 (dd, J = 7.0, 8.0Hz, 1H), 7.38 (d, J = 8.0Hz, 1H), 7.63 (d, J =

Table II — Michael addition of indoles and furan with electron-deficient olefins

Entry	Substrate	Substrate	Products	Yields (%)
1	1a	2a	3a	95
2	1a	2b	3b	90
3	1a	2c	3c	90
4	1a	2d	3d	70
5	1b	2a	3e	95
6	1b	2b	3f	90
7	1b	2c	3g	90
8	1c	2a	3h	70

8.0Hz, 1H), 8.01 (br s, 1H, NH); IR(KBr): 3410, 3030, 2925, 1715, 1460, 1370, 1220, 750 cm^{-1}.

3f: ^{1}H NMR (CDCl$_3$): δ 1.89-1.96 (m, 2H), 2.13-2.18 (m, 2H), 2.25 (s, 3H), 2.50-2.66 (m, 4H), 3.38-3.37 (m, 1H), 7.00 (s, 1H), 7.12 (dd, J = 7.0, 8.0Hz, 1H), 7.21 (dd, J = 7.0, 8.0Hz, 1H), 7.38 (d, J = 8.0Hz,

1H), 7.63 (d, J = 8.0Hz, 1H), 8.01 (br s, 1H, NH); IR(KBr): 3407, 2400, 1714, 1605, 1455, 1360, 1166 cm^{-1}.

3g: 1H NMR(CDCl$_3$): δ 2.01 (s, 3H), 4.84 (dd, J = 8.5, 12.5 Hz, 1H), 4.95 (dd, J = 7.5, 12.5Hz, 1H), 5.12 (dd, J = 7.5, 8.5Hz, 1H), 6.83 (d, J = 2.5Hz, 1H), 7.02 (ddd, J = 1.0, 7.0, 8.0Hz, 1H), 7.13 (ddd, J = 1.0, 7.0, 8.0Hz, 1H), 7.21-7.35 (m, 5 H), 7.39 (d, J = 8.0Hz, 1H), 7.98 (br s, 1 H).

3h: ^{1}H NMR (CDCl$_3$): δ 2.08 (s, 6H), 2.67 (t, J = 7.2Hz, 4H), 2.78 (t, J = 7.2Hz, 4H), 5.78 (s, 2H); IR(KBr): 1695, 1575, 1427, 1304, 1263, 750, 719 cm^{-1}.

Conclusion

In summary, Y(OTf)$_3$ has been demonstrated as an efficient Lewis acid for the alkylation of indoles or furan with electron-deficient olefins. The advantages of the use of Y(OTf)$_3$ as catalyst for the reactions are efficiency, mild reaction conditions and compatibility with acid-sensitive substrates.

Acknowledgement

References

1 (a) Moore R E, Cheuk C, Yang X Q, Patterson G M L, Bonjouklian R, Smitka T A, Mynderse J, Foster R S, Jones N D, Swartzendruber J K & Deeter J B, *J Org Chem,* 52, **1987**, 1036; (b) Borris R P, Lankin D C & Cordell G A, *J Nat Prod,* 46*,* **1983**, 200; (c) Stratmann K, Moore R E, Bonjouklian R, Deeter J B, Patterson G M L, Shaffer S, Smith C D & Smitka T A, *J Am Chem Soc,* 116*,* **1994**, 9935.

2 (a) Szmuszkovicz J, *J Am Chem Soc,* 79, **1975**, 2819; (b) Iqbal Z, Jackson A H & Rao K R N, *Tetrahedron Lett,* 29, **1988**, 2577; (c) Bandini M, Fagioli M & Uma-Ronchi A, *Adv Synth Catal,* 345, **2004**, 545; (d) Noland W E, Christensen G M, Sauer G L & Dutton G G S, *J Am Chem Soc,* 77, **1955**, 456.

3 (a) Bartoli G, Bartolacci M, Bosco M, Foglia G, Giuliani A, Marcantoni E, Sambri L & Torregiani E, *J Org Chem,* 68, **2003**, 4594; (b) Loh T P & Wei L L, *Synlett,* **1998**, 975; (c) Yadav J S, Abraham S, Reddy B V S & Sabitha G, *Synthesis,* **2001**, 2165; (d) Giacomini M, Melchiorre P, Selva S & Umani-Ronchi A, *J Org Chem,* 67, **2002**, 3700; (e) Alam M M, Varala R & Adapa S R, *Tetrahedron Lett,* 44, **2005**, 5115; (f) Marco B, Paolo M, Alfonso M & Achille U-R, *Synthesis,* **2002**, 1110.

4 Kobayashi S, Sugiura M, Kitagawa H & Lam W W L, *Chem Rev,* 102, **2002,** 2227.

5 Zhang C X, Dong J C, Cheng T M & Li R T, *Tetrahedron Lett,* 42, **2001**, 401.

6 Kobayashi S, *Lanthanides: Chemistry and Use in Organic Synthesis*, edited by Kobayashi S (Springer, Berlin), **1999**, p 63.

7 Webb I D & Borcherdt G T, *J Am Chem Soc,* 73, **1951**, 752.

8 Shi M, Cui S C & Li Q J, *Tetrahedron,* 60, **2004**, 6679.

9 Li Z G, Shi Z J & He C, *J Organomet Chem,* 690, **2005**, 5049.