HETEROCYCLES, Vol. 60, No. 8, 2003, pp. 1899 - 1905
Received, 6th May, 2003, Accepted, 20th June, 2003, Published online, 23rd June, 2003

YTTERBIUM TRIFLATE-CATALYSED SYNTHESIS OF ETHYL 1,2,3,4-TETRAHYDROISOQUINOLINE-1-CARBOXY-LATES USING ETHYL CHLORO(PHENYLSELANYL)-ACETATE

Huey-Min Wang,[a] Iou-Jiun Kang,[b] and Ling-Ching Chen*[b]

[a] Chung Hwa College of Medical Technology, Tainan, Taiwan 717, R.O.C.
[b] Graduate Institute of Pharmaceutical Sciences, Kaohsiung Medical University, Kaohsiung, Taiwan 807, R.O.C.

Abstract—The reaction of *N*-benzenesulfonyl-β-phenethylamines with ethyl chloro(phenylselanyl)acetate catalysed by ytterbium triflate provides a convenient methodology for the synthesis of ethyl 1,2,3,4-tetrahydroisoquinoline-1- carboxylates.

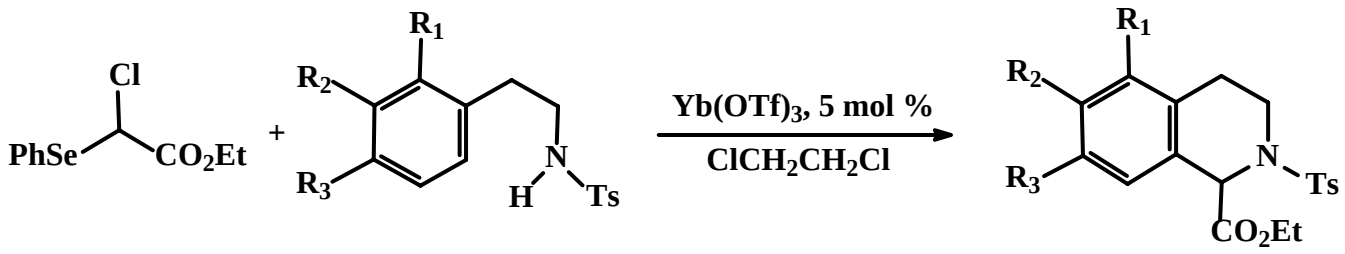
Pictet-Spengler condensation is one of the fundamental reaction for the preparation of 1,2,3,4-tetrahydroisoquinolines.[1] This cyclization occurs only when the ring-closure position is activated by electron donating substituents. However, β-phenethylamines bearing an electron withdrawing substituent on the benzene ring afford 1,2,3,4-tetrahydroisoquinoline derivatives in poor yields or do not give any cyclized product. Modifications of the original strategy to increase the electrophilicity of the iminium intermediate, which employ electron withdrawing groups on the nitrogen such as acyl [2] or sulfonyl [3] moieties are known.

Lanthanide trifluoromethanesulfonates[4] [lanthanide triflates; $Ln(OTf)_3$] work efficiently as versatile Lewis acids and have been employed in a number of reactions both in organic and aqueous media in catalytic quantities. Since the first utilization of $Yb(OTf)_3$ by Forsberg *et al.*,[5] it has found wide utility in organic synthesis. Recently, Kobayashi *et al.*[4] and Nakagawa *et al.*[6] have used $Yb(OTf)_3$ as the catalyst in Friedel–Crafts acylation reactions, imino ene reaction and Pictet-Spengler reaction, respectively. It was demonstrated in these reactions that the catalysts were easily recovered after the reactions were completed and could be reused.

As one of many synthetic applications of α-haloselenides, Silverira[7] has accomplished the preparation of 1,2,3,4-tetrahydroisoquinoline-1-carboxylates by the Pictet-Spengler condensation of *N*-sulfonyl-β-

phenethylamines with α-chloro-α-phenylselenoesters in the presence of stoichiometric quantities of a Lewis acid such as $SnCl_4$ or $ZnBr_2$. This methodology has been extended for a total synthesis of calycotomine.[8]

Herein, we describe an excellent method for the synthesis of ethyl 1,2,3,4-tetrahydroisoquinoline-1-carboxylates by means of Pictet-Spengler cyclization of *N*-benzenesulfonyl-β-phenethylamines with ethyl chloro(phenylselanyl)acetate catalysed by $Yb(OTf)_3$ (Scheme I).



1 **2** **3**

22-81 %

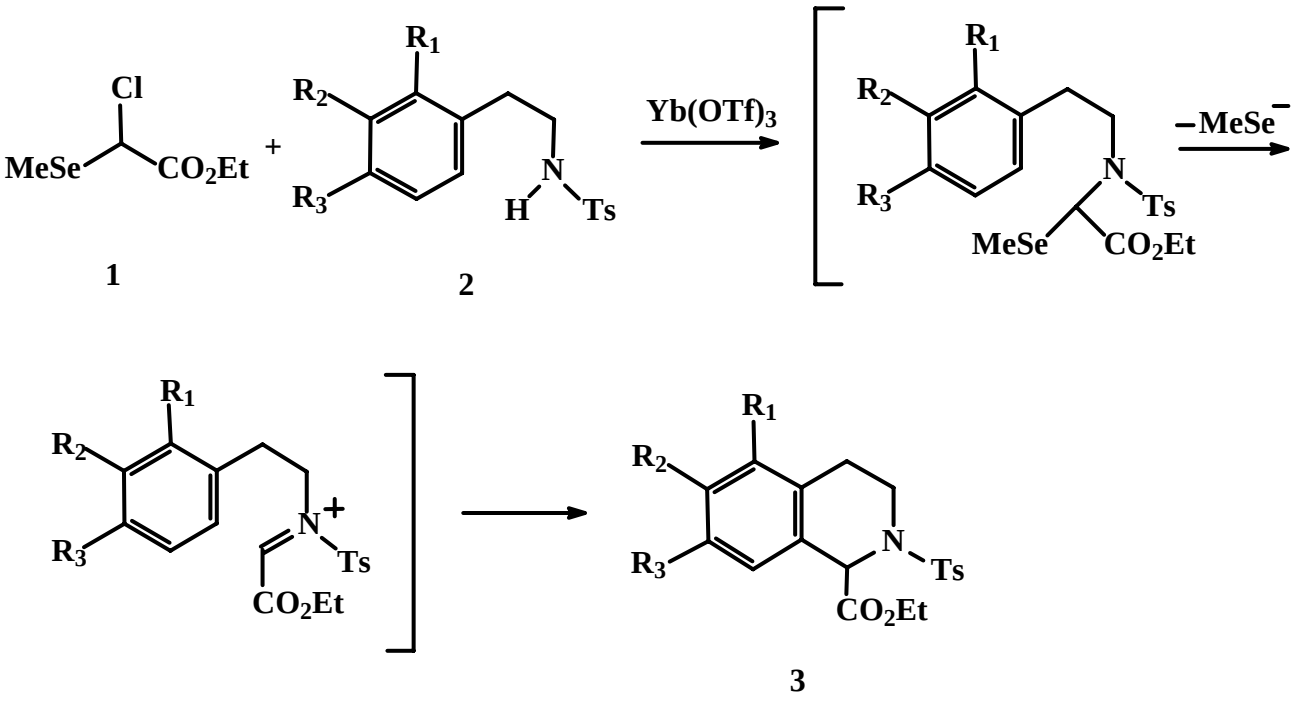
Scheme I

As shown in Table 1, the reaction of ethyl chloro(phenylselanyl)acetate (**1**) with *N*-benzenesulfonyl-β-phenethylamines (**2a, b**) in the presence of $Yb(OTf)_3$ (5 mol %) gave the cyclized products (**3a**, **b**) in 72 and 70% yields, respectively (Entries 1 and 2). On the other hand, the 3,4-dimethoxy derivative (**2c**), carrying activating substituent *para* to the ring closure position afforded the expected product **3c** in 81% yield (Entry 3). However, *N*-benzenesulfonyl derivatives such as **2d**, **2e**, **2f**, **2g** and **2h** containing deactivated aromatic rings also furnished the corresponding cyclized products in reasonable yields (Entries **4**, **5**, **6**, **7** and **8**). Interestingly, unlike the case of the sulfur-based reagent employed by Kohno,[9] no Friedel-Crafts reaction products were detected when activated phenethylamines were cyclized.[10]

A possible pathway of the cyclization is illustrated in Scheme II. The cyclization is assumed to proceed through iminium cation which would be formed by the alkylation of *N*-benzenesulfonyl-β-phenethylamines (**2**) with ethyl chloro(phenylselanyl)acetate (**1**) catalysed by $Yb(OTf)_3$ (Scheme II).

In conclusion, we have shown that the modified Pictet-Spengler cyclization of *N*-benzenesulfonyl-β-phenethylamines with ethyl chloro(phenylselanyl)acetate using $Yb(OTf)_3$ provides

moderate to good yields of ethyl 1,2,3,4-tetrahydroisoquinoline-1-carboxylates, even when deactivated starting sulfonamides are employed.



Scheme II

Table 1. The reaction of *N*-benzenesulfonyl-β-phenethylamines with ethyl chloro(phenylselanyl)acetate (**1**) using $Yb(OTf)_3$.

Entry	Compd	R_1	R_2	R_3	Product	Yield (%)
1	**2a**	H	H	H	**3a**	72
2	**2b**	H	H	OMe	**3b**	70
3	**2c**	H	OMe	OMe	**3c**	81
4	**2d**	Cl	H	H	**3d**	50
5	**2e**	H	Cl	H	**3e**	53
6	**2f**	H	H	Cl	**3f**	54
7	**2g**	H	H	Br	**3g**	48
8	**2h**	Cl	H	Cl	**3h**	22

ACKNOWLEDGEMENT

We gratefully acknowledge the National Science Council of the Republic of China for the financial support of this work (Grant No. 91-2113-M-037-008).

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27 G spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Unity Plus 400 MHz. Chemical shifts (δ) were measured in ppm with respect to TMS. MS were obtained on a JEOL JMS D-300 instrument.

1-Carbethoxy-2-*p*-tosyl-1,2,3,4-tetrahydroisoquinoline (3a); **Typical procedure**

A mixture of $Yb(OTf)_3$ (31 mg, 0.05 mmol), *N*-benzenesulfonyl-β-phenethylamine (**2a**) (275 mg, 1.0 mmol) and ethyl chloro(phenylselanyl)acetate (**1**) (415.5 mg, 1.5 mmol) in 1,2-dichloroethane (10 mL) was refluxed for 7 h. After cooling, the reaction mixture was quenched with water and extracted with dichloromethane. The extract was dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified by chromatography on a silica gel column with hexane-ethyl acetate (3:1) to give **3a**, mp 66-67 ℃ (AcOEt-*n*-hexane), yield 72 %. IR (KBr) ν : 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.16 (t, 3H, *J* = 7.2 Hz), 2.39 (s, 3H), 2.81-2.94 (m, 2H), 3.76-3.86 (m, 2H), 3.94-4.08 (m, 2H), 5.51 (s, 1H), 7.08-7.12 (m, 1H), 7.16-7.22 (m, 2H), 7.25-7.27 (m, 2H), 7.37-7.40 (m, 1H), 7.31-7.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 13.8, 21.4, 28.3, 40.7, 57.7, 61.5, 126.4, 127.1, 127.3, 127.8, 129.0, 129.5, 129.8, 134.0, 136.4, 143.4, 170.2; MS (EI) m/z : 359 (M^+), 286, 155, 131, 130, 103, 91, 89, 65; Anal. Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found; C, 63.27; H, 5.64; N, 4.12.

1-Carbethoxy-7-methoxy-2-*p*-tosyl-1,2,3,4-tetrahydroisoquinoline (3b)

Pale yellow oil, yield 70 %. IR (neat) ν : 1742 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ : 1.17 (t, 3H, *J* = 7.2 Hz), 2.39 (s, 3H), 2.77-2.82 (m, 2H), 3.77 (s, 3H), 3.78-3.81 (m, 2H), 3.98-4.13 (m, 2H), 5.47 (s, 1H), 6.77 (dd, 1H, *J* = 2.8, 8.4 Hz), 6.93 (d, 1H, *J* = 2.8 Hz), 7.00 (d, 1H, *J* = 8.4 Hz), 7.26 (d, 2H, *J* = 8.0 Hz), 7.70 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 14.1, 21.6, 27.7, 41.2, 55.5, 58.1, 61.7, 112.1, 114.6, 126.2, 127.3, 129.7, 130.2, 130.9, 136.8, 143.6, 158.2, 170.4; MS (FAB) m/z : 390 (M^++1), 316, 162, 160, 91, 89, 77; HRMS (FAB) m/z Calcd for $C_{20}H_{23}NO_5S$: 390.1296. Found: 390.1298.

1-Carbethoxy-5,6-dimethoxy-2-*p*-tosyl-1,2,3,4-tetrahydroisoquinoline (3c)

mp 103-104 ℃ (AcOEt-*n*-hexane), yield 81 %. IR (KBr) ν : 1721 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ : 1.16 (t, 3H, *J* = 7.2 Hz), 2.40 (s, 3H), 2.70-2.86 (m, 2H), 3.74-3.86 (m, 2H), 3.83 (s, 6H), 3.99-4.05 (m, 2H), 5.42 (s, 1H), 6.55 (s, 1H), 6.88 (s, 1H), 7.24-7.28 (m, 2H), 7.69-7.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 13.9, 21.4, 27.8, 40.7, 55.8, 55.9, 57.3, 61.4, 109.9, 111.3, 121.4, 126.2, 127.1, 129.5, 136.6, 143.3, 147.6, 148.6, 170.3; MS (EI) m/z : 419 (M^+), 346, 191, 104, 91, 89, 77, 65; Anal. Calcd for $C_{21}H_{25}NO_6S$: C, 60.13; H, 6.01; N, 3.34. Found: C, 60.25; H, 5.87; N, 3.42.

1-Carbethoxy-5-chloro-2-*p*-tosyl-1,2,3,4-tetrahydroisoquinoline (3d)

mp 86-87 ℃ (AcOEt-*n*-hexane), yield 50 %. IR (KBr) ν : 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ : 1.16 (t, 3H, *J* = 7.2 Hz), 2.40 (s, 3H), 2.77-2.98 (m, 2H), 3.74-3.81 (m, 2H), 3.92-4.14 (m, 2H), 5.54 (s, 1H), 7.13-7.34 (m, 5H), 7.52-7.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 13.8, 21.4, 26.0, 39.9, 57.3, 61.7, 126.0, 127.1, 128.6, 129.4, 129.5, 132.0, 132.1, 134.5, 136.4, 143.6, 169.7; MS (EI) m/z : 395 (M^++2), 393 (M^+), 320, 155, 103, 89, 77, 65; Anal. Calcd for $C_{19}H_{20}NO_4ClS$: C, 57.94; H, 5.12; N, 3.56. Found: C, 58.16; H, 5.28; N, 3.42.

1-Carbethoxy-6-chloro-2-*p*-tosyl-1,2,3,4-tetrahydroisoquinoline (3e)

Pale yellow oil, yield 53 %. IR (neat) ν : 1729 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ : 1.16 (t, 3H, *J* = 7.2 Hz), 2.40 (s, 3H), 2.77-2.91 (m, 2H), 3.73-3.85 (m, 2H), 3.94-4.13 (m, 2H), 5.50 (s, 1H), 7.10 (d, 1H, *J* = 2.0 Hz), 7.17 (dd, 1H, *J* = 2.0, 8.4 Hz), 7.27 (d, 2H, *J* = 8.0 Hz), 7.33 (d, 1H, *J* = 8.4 Hz), 7.68-7.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 13.8, 21.4, 28.0, 40.2, 57.2, 61.6, 126.7, 127.0, 128.4, 128.7, 128.8, 129.5, 135.5, 135.8, 136.4, 143.5, 169.8; MS (EI) m/z : 395 (M^++2), 393 (M^+), 165, 155, 130, 103, 91, 89, 77, 65; HRMS (EI) m/z Calcd for $C_{19}H_{20}NO_4ClS$: 393.0801. Found: 393.0804.

1-Carbethoxy-7-chloro-2-*p*-tosyl-1,2,3,4-tetrahydroisoquinoline (3f)

Pale yellow oil, yield 54 %. IR (neat) ν : 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ : 1.11 (t, 3H, *J* = 7.2 Hz), 2.42 (s, 3H), 2.98-3.12 (m, 2H), 3.47 (t, 2H, *J* = 8.4 Hz), 3.97 (q, 2H, *J* = 7.2 Hz), 5.68 (s, 1H), 7.14 (d, 1H, *J* = 2.0 Hz), 7.16-7.31 (m, 4H), 7.71-7.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 13.8, 21.5, 36.5, 47.3, 62.1, 65.7, 127.4, 128.6, 129.5, 130.3, 132.2, 136.4, 137.3, 143.8, 167.4; MS (EI) m/z : 395 (M^++2), 393 (M^+), 320, 139, 125, 103, 91, 86, 77, 65; HRMS (EI) m/z Calcd for $C_{19}H_{20}NO_4ClS$: 393.0801. Found: 393.0803.

1-Carbethoxy-7-bromo-2-*p*-tosyl-1,2,3,4-tetrahydroisoquinoline (3g)

Pale yellow oil, yield 48 %. IR (neat) ν : 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ : 1.17 (t, 3H, *J* = 7.2 Hz), 2.39

(s, 3H), 2.73-2.87 (m, 2H), 3.72-3.86 (m, 2H), 3.96-4.09 (m, 2H), 5.48 (s, 1H), 6.97 (d, 1H, *J* = 8.4 Hz), 7.27-7.28 (m, 2H), 7.31 (dd, 1H, *J* = 2.0, 8.4 Hz), 7.55 (d, 1H, *J* = 2.0 Hz), 7.68-7.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 13.7, 21.3, 27.7, 40.3, 57.1, 61.7, 119.8, 127.0, 129.5, 130.0, 130.6, 130.8, 131.7, 132.9, 136.2, 143.5, 169.5; MS (EI) m/z : 440 (M^++2), 438 (M^+), 366, 210, 155, 130, 102, 91, 77, 65; HRMS (EI) m/z Calcd for $C_{19}H_{20}NO_4{}^{79}BrS$: 437.0296. Found: 437.0295.

1-Carbethoxy-5,7-dichloro-2-*p*-tosyl-1,2,3,4-tetrahydroisoquinoline (3h)

Colorless oil, yield 22 %. IR (neat) ν : 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ : 1.12 (t, 3H, *J* = 7.2 Hz), 2.23 (s, 3H), 3.12-3.25 (m, 2H), 3.44-3.52 (m, 2H), 3.98 (q, 2H, *J* = 7.2 Hz), 5.70 (s, 1H), 7.16 (d, 1H, *J* = 2.4 Hz), 7.29 (d, 2H, *J* = 8.4 Hz), 7.34 (d, 1H, *J* = 2.4 Hz), 7.75 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 13.8, 21.5, 34.3, 45.2, 62.0, 65.8, 127.2, 127.5, 129.5, 132.0, 132.9, 134.8, 135.2, 136.2, 143.8, 167.3; MS (EI) m/z : 432 (M^++4), 430 (M^++2), 428 (M^+), 161, 159, 155, 91, 89, 65, 61; HRMS (EI) m/z Calcd for $C_{19}H_{19}NO_4Cl_2S$: 427.0411. Found: 427.0416.

REFERENCES

1. Reviews, see: W. M. Whaley and T. R. Govindachari, *Org. React*., 1951, **6**, 151; T. Kametani and K. Fukumoto, *in The Chemistry of Heterocyclic Compounds, Isoquinolines Part One,* ed. by G. Grethe and N. Y. Wiley, 1981, pp. 170-182; G. Jones, *in Comprehensive Heterocyclic Chemistry*, ed. by A. R. Katritzky and C. W. Rees, pergamon, Oxford, 1984, **2**, pp. 438-440.
2. S. Lazarus and R. R. Wittekind, *J. Heterocycl. Chem*., 1971, **8**, 495; N. M. Mollov and A. P. Venkov, *Synthesis*, 1978, 62; A. P. Venkov and L. K. Lukanov, *Synthesis*, 1989, 59; D. L. Comins and M. M. Badawi, *Tetrahedron Lett*., 1991, **32**, 2995.
3. O. O. Orazi, R. A. Corral, and J. Giaccio, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1977; J. Zinczuk, I. H. Sorokin, O. O. Orazi, and R. A. Corral, *J. Heterocycl. Chem.*, 1992, **29**, 859; K. Ito and H. Tanaka, *Chem. Pharm. Bull*., 1977, **25**, 1732; L. K. Lukanov, A. P. Venkov, and N. M. Mollov, *Synthesis*, 1987, 204.
4. A. Kawada, S. Mitamura, and S. Kobayashi, *J. Chem. Soc., Chem. Commun*., 1993, 1157; R. W. Marshman, *Aldrichim.Acta*, 1995, **28**, 77; S. Kobayashi, *Synlett*, 1994, 689; S. Kobayashi, M. Sugiura, H. Kitagawa, and W. W.-L. Lam, *Chem. Rev*., 2002, **102**, 2227.
5. J. H. Fosberg, V. T. Spaziano, T. M. Balasubramanian, G. K. Liu, S. K. Kinsley, S. A. Kinsley, J. J. Poteruca, P. S. Brown, and J. L. Miller, *J. Org. Chem*., 1987, **52**, 1017.
6. M. Yamanaka, A. Nishida, and M. Nakagawa, *Org. Lett*., 2000, **2**, 159; R. Tsuji, M. Yamanaka, A.

Nishida, and M. Nakagawa, *Chem. Lett*., 2002, 428.
7. C. C. Silveira, C. R. Bernardi, A. L. Braga, and T. S. Kaufman, *Tetrahedron Lett*., 1999, **40**, 4969.
8. T. S. Kaufman, *Synth. Commun.*, 1993, **23**, 473.
9. H. Kohno and K. Yamada, *Heterocycles*, 1999, **51**, 103.
10. C. C. Silveira, M. A. Araujo, E. J. Lenardão, A. L. Braga, and M. J. Dabdoub, *Synthesis*, 1995, 1305.