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Conjugate Addition of Lithiated Methyl Pyridines to Enones

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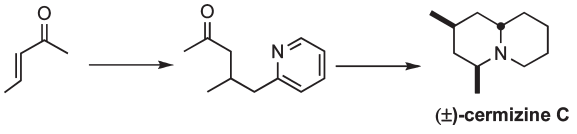
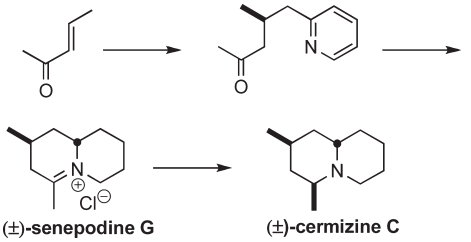


Preparatively useful conjugate addition of lithiated methyl pyridines to cyclic and acyclic enones is reported. Addition of 2-picoline to 3-penten-2-one led to a concise synthesis of the alkaloids (±)-senepodine G and (±)-cermizine C.

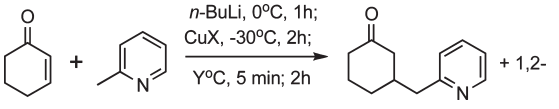
Pyridine and piperidine rings are not only ubiquitous structures in complex and physiologically active natural products but also versatile building blocks in synthetic organic chemistry.[1] In connection with an ongoing project on the synthesis of alkaloid (±)-cermizine C, we envisioned conjugate addition of metalated 2-picoline to an enone (Scheme 1). The existing alternative, as employed[2] in a recent asymmetric total synthesis of (+)-lycopladine A, has been the assembly of substituted pyridines from 1-azatrienes by a cascade sequence involving double-bond isomerization, 6π electrocyclization, and elimination of the amine.[3] Conjugate addition of the metalated 2-picoline would be much more direct. However, such a conjugate addition had been consistently reported not to be successful.[4a,b] Here, we report the successful conjugate addition of lithiated methyl pyridines to cyclic and acyclic enones and the use of this method in a simple preparation of the alkaloids (±)-senepodine G and (±)-cermizine C. We note that as this work was ready for publication, a parallel account of the successful conjugate addition of lithiated 2-picoline to cyclohexenone appeared[4c] that enabled a concise synthesis of (±)-lycopladine A.

SCHEME 1



Development of the Method. Recent efforts by others toward the 1,4-conjugate addition of metalated 2-picoline had shown that although the conjugate addition to α,β-unsaturated esters was successful, conjugate addition with enones was poor, leading mainly to the 1,2-addition product.[4a,b] We have examined in detail (Table 1) the conjugate addition of metalated 2-picoline to cyclohexenone. We reasoned that it might be a problem to make cuprate reagent from lithium reagent at 0 °C, as had been described,[4a,b] as it could decompose at that temperature.[5] Thus, we modified the procedure and prepared the cuprate at −30 °C. We were pleased to find that the conjugate addition worked for cyclohexenone, giving a 3:1 ratio of the separable 1,4- and 1,2-products in 79% combined yield (entry 1). More soluble copper salts improved the ratio (entries 2 and 4). Ratios were still better when the addition was carried out at lower temperature (entries 5 and 6).

TABLE 1. Optimization of the Conjugate Addition



entry	CuX	CuX (equiv)	temp (°C)	1,4:1,2	combined yield[a] (%)
1	CuCN	2	−20	3:1	79
2	CuCN2LiCI	2	−20	4.5:1	90
3	CuI	2	−20	2.8:1	88
4	$CuBrSMe_2$	2	−20	4.2:1	89
5	CuCN2LiCI	2	−78	6.3:1	87
6	CuBrSMe	2	−78	7:1	94

[a]Combined yields are for pure isolated products.

We briefly examined the scope of this optimized (Table 1, entry 6) conjugate addition (Table 2). The reaction with

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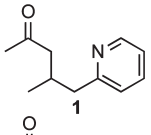
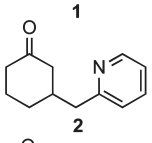
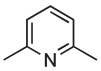
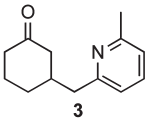
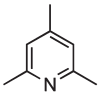
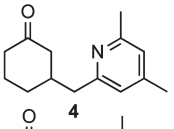
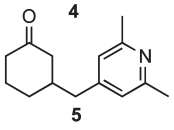
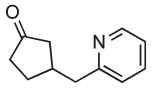
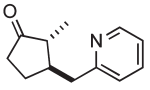
TABLE 2. Conjugate Addition of Lithiated Pyridines to Enones

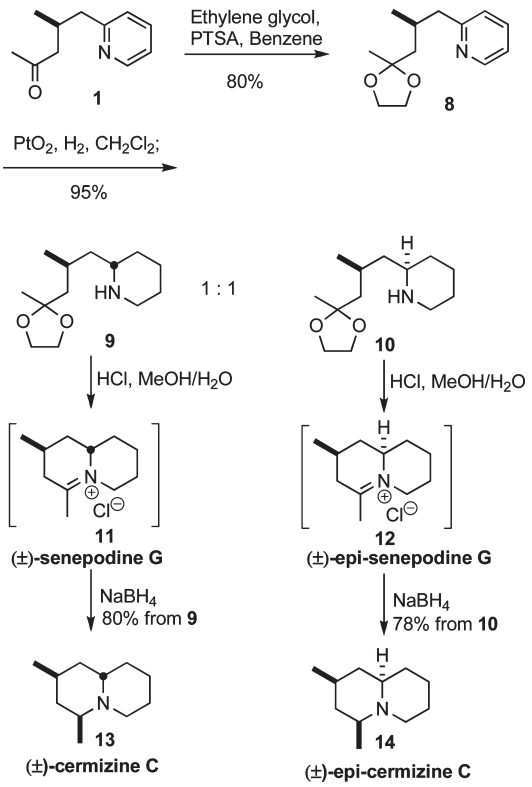
Entry	Enone	Pyridine	Product	Yield[a]
1			 **1**	45
2			 **2**	79[b]
3			 **3**	77
4			 **4**	46
			 **5**	21
5			 **6**	90
6			 **7**	61

[a]Yields are for pure isolated conjugate addition products. Additions were carried out by the method of Table 1, entry 6. The corresponding 1,2-adducts were observed but were not characterized. [b]Reference 4c.

different ring-sized cyclic enones proceeded efficiently. For the acyclic enone, conjugate addition delivered the 1,4-product in moderate yield. It is also noteworthy that 2,6-lutidine participated smoothly (entry 3). Conjugate addition with metalated 2,4,6-collidine led to the ortho-substituted derivative **4** and the para-substituted derivative **5** in a statistical 2:1 ratio (entry 4). With the results reported here, the conjugate addition of lithiated methyl pyridines to enones appears to be a generally applicable synthetic method.

Synthesis of (±)-Senepodine G and (±)-Cermizine C. The utility of this method for the formation of pyridine and piperidine derivatives was demonstrated by a simple preparation of (±)-senepodine G and (±)-cermizine C (Scheme 2). Isolated from the club moss of *Lycopodium chinese*, senepodine G shows cytotoxicity against murine lymphoma L1210 cells with an IC_{50} of 7.8 μg/mL.[6] To carry the synthesis forward, the 1,4-addition product **1** was protected (Scheme 2) as the ketal. Catalytic hydrogenation delivered a 1:1 ratio of the diastereomers **9** and **10** that it was possible to separate by chromatography. Separately, exposure of each diastereomer to acid gave the unstable alkaloids (±)-senepodine G and (±)-*epi*-senepodine G. Direct reduction of each with $NaBH_4$ delivered[7] the alkaloids (±)-cermizine C (**13**) and (±)-*epi*-cermizine C (**14**), each as a single diastereomer, allowing assignment of the structures of **9** and **10**.

SCHEME 2



Conclusion

We have established a procedure for the conjugate addition of lithiated methyl pyridines to enones that we think will be generally useful. This protocol allows an efficient assembly of synthetically valuable pyridines and piperidines. The utility of this reaction was demonstrated by the concise synthesis of (±)-senepodine G (four steps) and (±)-cermizine C (five steps). We expect that this conjugate addition protocol will have many applications both in natural product synthesis and in medicinal chemistry.

Experimental Section

3-(Pyridin-2-ylmethyl)cyclohexanone (2). To a stirred solution of 2-picoline (392 mg, 4.2 mmol) in THF (4 mL) was added *n*-BuLi (4.18 mmol, 2 mL, 2.09 M in hexane) at −78 °C. After being stirred at 0 °C for 1 h, the reaction mixture was cooled to −30 °C and added over 2 min to a stirred suspension of CuBr·SMe_2 (415 mg, 2.02 mmol) in THF (4 mL) at −30 °C. After being stirred for 2 h at −30 °C, the reaction mixture was cooled to −78 °C, and a solution of 2-cyclohexenone (91 mg, 0.95 mmol) in THF (3 mL) was added over 5 min. After being stirred at −78 °C for 2 h, the reaction mixture was quenched with water (5 mL) and partitioned between CH_2Cl_2 and, sequentially, water and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield ketone **2** (142 mg, 79% yield) as a pale yellow oil: TLC R_f(20% MTBE/CH_2Cl_2) = 0.29; IR (cm^{-1}) 2935, 1706, 1592, 1457; ^1H NMR δ 8.50 (app s, 1H),

(6) (a) Morita, H.; Hirasawa, Y.; Shinzato, T.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 7015–7023. (b) Nishikawa, Y.; Kitajima, M.; Kogure, N.; Takayama, H. *Tetrahedron* **2009**, *65*, 1608–1617. (c) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394–8395.

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7.55 (t, J = 7.9 Hz, 1H), 7.05 (m, 2H), 2.75 (m, 2H), 2.40−2.15 (m, 4H), 2.05 (m, 2H), 1.85 (m, 1H), 1.60 (m, 1H), 1.40 (m, 1H); ^{13}C NMR δ u[8] 211.4, 159.5, 47.6, 45.1, 41.4, 31.1, 25.0; d 149.4, 136.3, 123.6, 121.4, 39.6; HRMS calcd for $C_{12}H_{16}NO$ (MH^+) 190.1232, obsd 190.1237.

4-Methyl-5-(pyridin-2-yl)pentan-2-one (1). To a stirred solution of 2-picoline (399 mg, 4.29 mmol) in THF (4 mL) was added *n*-BuLi (4.19 mmol, 1.8 mL, 2.33 M in hexane) at −78 °C. After being stirred at 0 °C for 1 h, the reaction mixture was cooled to −30 °C and added over 2 min to a stirred suspension of CuBr·SMe_2 (425 mg, 2.06 mmol) in THF (4 mL) at −30 °C. After being stirred for 2 h at −30 °C, the reaction mixture was cooled to −78 °C, and a solution of 3-penten-2-one (90%, 102 mg, 1.09 mmol) in THF (3 mL) was added over 5 min. After being stirred at −78 °C for 2 h, the reaction mixture was quenched with water (5 mL) and partitioned between CH_2Cl_2 and, sequentially, water and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield ketone **1** (87 mg, 45% yield) as a pale yellow oil: TLC R_f (20% MTBE/CH_2Cl_2) = 0.33; IR (cm^{-1}) 1704, 1647, 1367; ^{1}H NMR δ 8.50 (app s, 1H), 7.55 (m, 1H), 7.10 (m, 2H), 2.65 (m, 2H), 2.50 (m, 2H), 2.25 (m, 1H), 2.05 (s, 3H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ u 208.7, 160.5, 50.3, 45.3; d 149.2, 136.3, 123.7, 121.2, 30.4, 30.2, 19.9; HRMS calcd for $C_{11}H_{16}NO$ (MH^+) 178.1232, obsd 178.1239.

2-(2-Methyl-3-(2-methyl-1,3-dioxolan-2- yl)propyl)pyridine (8). To a stirred solution of ketone **1** (910 mg, 5.14 mmol) in benzene (20 mL) were added *p*-toluenesulfonic acid monohydrate (120 mg, 0.60 mmol) and ethylene glycol (1.07 g, 17.3 mmol) at room temperature. The reaction mixture was stirred at reflux overnight with a Dean−Stark trap. After being cooled to room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL) and then partitioned between CH_2Cl_2 and, sequentially, water and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield ketal **8** (906 mg, 80% yield) as a pale yellow oil: TLC R_f (20% MTBE/CH_2Cl_2) = 0.29; IR (cm^{-1}) 2926, 1591, 1472, 1436; ^{1}H NMR δ 8.50 (d, J = 4.71 Hz, 1H), 7.55 (m, 1H), 7.05 (m, 2H), 3.90 (m, 4H), 2.85 (m, 1H), 2.55 (m, 1H), 2.20 (m, 1H), 1.70 (m, 1H), 1.55 (m, 1H), 1.30 (s, 3H), 0.95 (d, J = 6.65 Hz, 3H); ^{13}C NMR δ u 161.2, 110.3, 64.4, 64.2, 46.6, 44.9; d 149.2, 136.0, 123.6, 120.9, 30.2, 24.0, 20.7; HRMS calcd for $C_{13}H_{20}NO_2$ (MH^+) 222.1494, obsd 222.1494.

(2*S)-2-((2*S**)-Methyl-3-(2-methyl-1,3-dioxolan-2-yl)propyl)-piperidine (9) and (2*R**)-2-((2*S**)-Methyl-3-(2-methyl-1,3-dioxolan-2-yl)propyl)piperidine (10).** A suspension of ketal **8** (350 mg, 1.58 mmol) and PtO_2 (30 mg) in CH_2Cl_2 (3 mL) was stirred at room temperature under H_2 (1 atm) overnight. The reaction mixture was filtered and concentrated. The residue was chromatographed to yield amine **9** (172 mg, 48% yield) as a pale yellow oil and amine **10** (170 mg, 47% yield) as a pale yellow oil.

Piperidine 9: TLC R_f (10% Et_2NH/PE) = 0.43; IR (cm^{-1}) 2929, 1646, 1450; ^{1}H NMR (CD_3OD) δ 3.90 (m, 4H), 3.05 (m, 1H), 2.60 (m, 2H), 1.85−1.55 (m, 5H), 1.55−1.40 (m, 5H), 1.30 (s, 3H), 1.25−1.0 (m, 2H), 0.95 (d, J = 6.6 Hz,3H); ^{13}C NMR (CD_3OD) δ u 111.3, 65.4, 65.3, 47.4, 46.5, 45.8, 32.6, 26.4, 25.4; d 55.4, 26.1, 24.5, 22.2; HRMS calcd for $C_{13}H_{26}NO_2$ (MH^+) 228.1964, obsd 228.1961.

Piperidine 10: TLC R_f (10% Et_2NH/PE) = 0.49; IR (cm^{-1}) 2929, 1646, 1450; ^{1}H NMR (CD_3OD) δ 3.90 (m, 4H), 3.00 (m, 1H), 2.60 (m, 2H), 1.85−1.55 (m, 5H), 1.55−1.40 (m, 5H), 1.25 (s, 3H), 1.10 (m, 2H), 0.95 (d, J = 6.2 Hz, 3H); ^{13}C NMR (CD_3OD) δ u 111.4, 65.4, 65.3, 47.6, 47.0, 46.5, 33.7, 26.7, 25.7; d 55.4, 26.2, 24.5, 21.8; HRMS calcd for $C_{13}H_{26}NO_2$ (MH^+) 228.1964, obsd 228.1961.

(±)-Cermizine C TFA Salt (13). To a stirred solution of piperidine **9** (46 mg, 0.20 mmol) in MeOH (1 mL) was added HCl (3 M, 1 mL) at room temperature. After being stirred at room temperature overnight, the reaction mixture was concentrated, including high vacuum pumping, to give crude (±)-senepodine G (**11**).

To a stirred solution of the above crude (±)-senepodine G in MeOH (4 mL) was added $NaBH_4$ (20 mg, 0.52 mmol) at 0 °C. After being stirred at room temperature for 10 min, the reaction mixture was quenched with HCl (3 M, 2 mL) and then partitioned between CH_2Cl_2 and, sequentially, water and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield (±)-cermizine C (**13**) (27 mg, 80% yield) as a pale yellow oil: TLC R_f (Et_2O saturated with NH_4OH) = 0.60. To a solution of the (±)-cermizine C in MeOH (0.5 mL) was added TFA[5b,5c] (1 drop, 20 μL, excess). The mixture was concentrated to give (±)-cermizine C TFA salt as a yellow oil: IR (cm^{-1}) 2524, 1675, 1455, 1201; ^{1}H NMR (CD_3OD) δ 3.80 (m, 1H), 3.60 (m, 2H), 3.05 (m, 1H), 2.15 (m, 1H), 2.00−1.50 (m, 9H), 1.40−1.20 (m, 1H), 1.30 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H); ^{13}C NMR (CD_3OD) δ u 49.9, 41.8, 38.4, 24.6, 23.8, 18.4; d 61.4, 51.1, 25.5, 21.6, 17.6; HRMS calcd for $C_{11}H_{22}N$ (MH^+) 168.1752, obsd 168.1755.

(±)-*epi*-Cermizine C TFA Salt (14). To a stirred solution of piperidine **10** (40 mg, 0.18 mmol) in MeOH (1 mL) was added HCl (3 M, 1 mL) at room temperature. After being stirred at room temperature overnight, the reaction mixture was concentrated, including high vacuum pumping, to give crude (±)-*epi*-senepodine G (**12**).

To a stirred solution of the above crude (±)-*epi*-senepodine G in MeOH (4 mL) was added $NaBH_4$ (15 mg, 0.39 mmol) at 0 °C. After being stirred at room temperature for 10 min, the reaction mixture was quenched with HCl (3 M, 2 mL) and then partitioned between CH_2Cl_2 and, sequentially, water and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield (±)-*epi*-cermizine C (**14**) (23 mg, 78% yield) as a pale yellow oil: TLC R_f (Et_2O saturated with NH_4OH) = 0.78. To a solution of the (±)-*epi*-cermizine C in MeOH (0.5 mL) was added TFA[5b,5c] (1 drop, 20 μL, excess). The mixture was concentrated to give (±)-*epi*-cermizine C TFA salt as a yellow oil: IR (cm^{-1}) 2529, 1665, 1198; ^{1}H NMR (CD_3OD) δ 3.75 (m, 1H), 3.20−3.00 (m, 2H), 2.70 (m, 1H), 2.00−1.65 (m, 7H), 1.55 (m, 2H), 1.40−1.20 (m, 2H), 1.35 (d, J = 6.40 Hz, 3H), 0.95 (d, J = 6.40 Hz, 3H); ^{13}C NMR (CD_3OD) δ u 51.9, 41.8, 40.4, 32.2, 24.9, 23.2; d 65.4, 62.4, 30.0, 21.4, 17.9; HRMS calcd for $C_{11}H_{22}N$ (MH^+) 168.1752, obsd 168.1752.

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Supporting Information Available: General experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

(8) ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" and for methylene and quaternary carbons as "u".