Pergamon

Tetrahedron Letters 40 (1999) 8133–8136

TETRAHEDRON
LETTERS

A Convenient Method for the Synthesis of $\Delta^{1,6}$-Bicyclo[4.n.0]alken-2-ones

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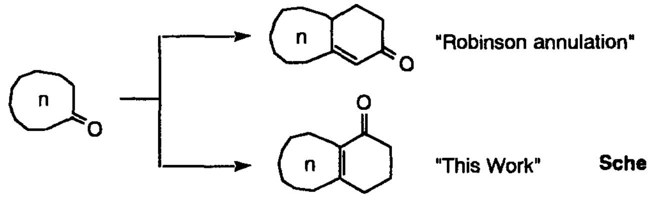
Received 19 August 1999; accepted 3 September 1999

Abstract

A convenient annulation method for the synthesis of bicyclic enones from cycloalkanones was developed. In the presence of a Pd(0) catalyst, enol triflates derived from ethyl 2-oxocycloalkanecarboxylates were treated with 3-(ethoxycarbonyl)propylzinc iodide to afford the corresponding diesters via a cross-coupling reaction. The diesters were easily transformed into $\Delta^{1,6}$-bicyclo[4.n.0]alken-2-ones through Dieckmann condensation followed by decarboxylation. The annulation method was also applicable for the synthesis of the corresponding cycloheptenone derivative. © 1999 Elsevier Science Ltd. All rights reserved.

Key words: annulation; bicyclic aliphatic compounds; enones; cyclohexenones

In relation to our study on a ring-expansion reaction directed by silicon,[1] preparation of a homologous series of $\Delta^{1,6}$-bicyclo[4.n.0]alken-2-ones was required. In general, an annulation strategy starting from cycloalkanones, such as the Robinson annulation reaction,[2] seems to be useful from a synthetic viewpoint.



Scheme 1

While the corresponding transformation for cyclopentenone synthesis, namely, the Nazarov reaction[3] is widely used in organic synthesis, only a scant number of papers concerning this type of cyclohexenone annulation were reported.[4] For example, Paquette has reported that a cyclic enol triflate can be converted to the corresponding cyclohexenone derivative through a five-step sequence involving a palladium-catalyzed cross-coupling reaction and a Diels-Alder reaction (Scheme 2).[4a]

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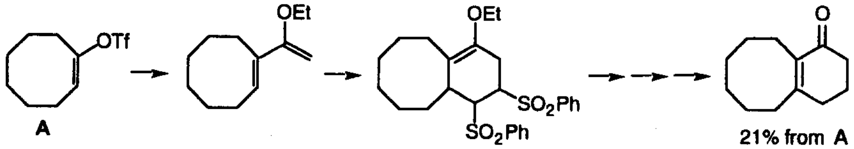
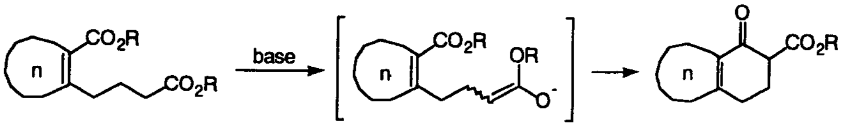
PII: S0040-4039(99)01723-2



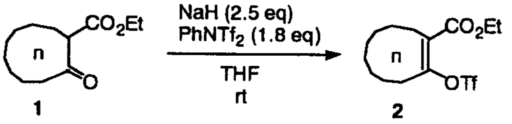
Scheme 2

In order to develop a more concise route for cyclohexenone annulation, we chose Dieckmann condensation[5] of a monocyclic diester as a key step (Scheme 3). It should be noted that the desired cyclization reaction requires selective enolate formation at the terminal ester moiety of the side chain. We envisioned that deprotonation at the α,β-unsaturated ester moiety would suffer from the poor co-planarity between the carbonyl group and the fully substituted carbon-carbon double bond.



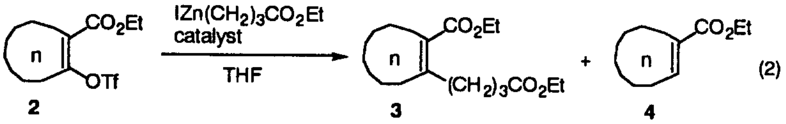
Scheme 3

Initially, enol triflates **2** were prepared in high yields by treating the corresponding ethyl 2-oxocycloalkanecarboxylates **1** with sodium hydride and *N*-phenyltrifluoromethanesulfonimide[6] (eq 1).



a: n = 6 (91%)
b: n = 7 (50%)
c: n = 8 (91%)
d: n =12 (91%)
(1)

Cross-coupling reactions[7] of enol triflate **2a** with 3-(ethoxycarbonyl)propylzinc iodide[8] were examined in the presence of several catalysts. While $NiCl_2(dppp)$ (10 mol %) merely mediated a sluggish transformation (entry 1), use of $Pd(PPh_3)_4$ (10 mol %) or $PdCl_2(dppf)$ (3 mol %) afforded diester **3a** in good yields (entries 2 and 3). In the presence of $Pd(PPh_3)_4$, however, eight- and twelve-membered enol triflate **2c** and **2d** mainly underwent reduction to give **4c** and **4d**, respectively (entries 6 and 8). On the other hand, use of $PdCl_2(dppf)$, which effectively suppressed the reduction pathway (entries 7 and 9), gave satisfactory results in all cases.

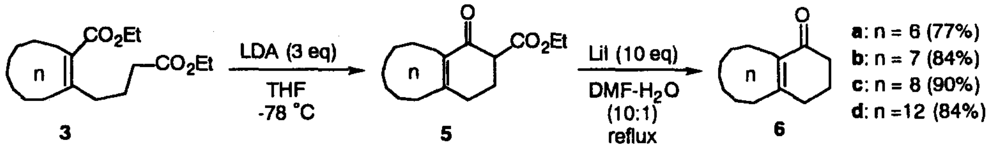


(2)

Entry	n	Catalyst	Conditions	3	4
1	6	$NiCl_2(dppp)^a$	50 °C, 10 h	42%^{c}	-
2		$Pd(PPh_3)_4{}^a$	50 °C, 2 h	75%	-
3		$PdCl_2(dppf)^b$	50 °C, 1.5 h	88%	-
4	7	$Pd(PPh_3)_4$	rt, 2.5 h	84%	-
5		$PdCl_2(dppf)$	50 °C, 1 h	93%	-
6	8	$Pd(PPh_3)_4$	rt, 2.5 h	10%	61%
7		$PdCl_2(dppf)$	50 °C, 1.5 h	86%	-
8	12	$Pd(PPh_3)_4$	50 °C, 1 h	27%	48%
9		$PdCl_2(dppf)$	50 °C, 2 h	93%	-

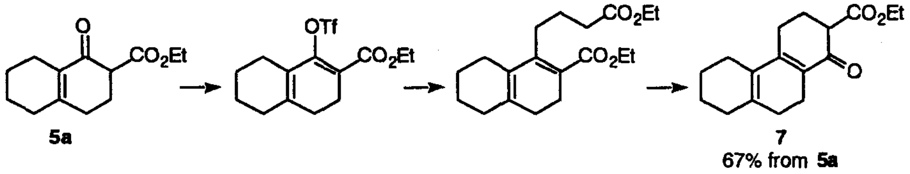
[a] 10 mol %. [b] 3 mol %. [c] 43% of **2** was recovered.

Treatment of diester **3** with lithium diisopropylamide (LDA) at -78 °C induced Dieckmann condensation to give ketoester **5**. The crude product was transformed into the desired bicyclic enone **6** through decarboxylation by heating with an excess amount of lithium iodide in *N,N*-dimethylformamide-water.[9]



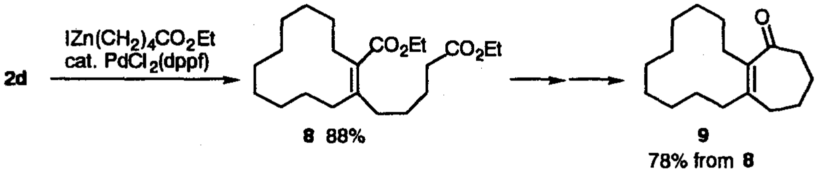
(3)

Since annulation product **5** has a β-ketoester moiety, the annulation procedure can be applied repeatedly to give policyclic enones as shown in eq 4.



(4)

The present annulation method is also applicable to preparation of the corresponding cycloheptenone derivatives. For example, a cross-coupling reaction of **2d** with 3-(ethoxycarbonyl)butylzinc iodide afforded diester **8** which was subjected to Dieckmann condensation followed by decarboxylation to give enone **9** in good overall yield.



(5)

Typical procedure for preparation of enol triflate 2: To a suspension of NaH (1.1 g, 46 mmol) in THF (40 mL) was added ketoester **1a** (4.6 g, 29 mmol) at 0 °C. After being stirred for 1 h, *N*-phenyltrifluoromethanesulfonimide (1.1 g, 46 mmol) was added. After being stirred overnight at room temperature, water was added. The mixture was separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with brine, and dried over $MgSO_4$. Concentration under reduced pressure followed by silica gel column chromatography afforded enol triflate **2a** (6.9 g, 28 mmol, 95 %) as a colorless oil: ^1H NMR (270MHz, $CDCl_3$) δ 1.32 (t, 3 H, *J* = 7.0 Hz), 1.60-1.83 (m, 4 H), 2.37-2.51 (m, 4 H), 4.27 (q, 2 H, *J* = 7.0 Hz); ^{13}C NMR (67.5MHz, $CDCl_3$) δ 13.83, 20.94, 22.18, 26.07, 28.41, 61.45, 123.21, 151.21, 164.68; IR (neat) 2980, 2940, 2870, 1720, 1660, 1420, 1210, 1140 cm^{-1}.

Typical procedure for preparation of diester 3: To a solution of enol triflate **2d** (790 mg, 2.0 mmol) and $PdCl_2$(dppf) (45 mg, 0.06 mmol) in THF (6 mL) was added a 1 M THF solution of 3-(ethoxycarbonyl)-propylzinc iodide[8b] (4.1 mL, 4.1 mmol). After being stirred for 2 h at 50 °C, a saturated aqueous $NaHCO_3$ solution was carefully added. Usual work-up (see above) followed by silica gel column chromatography afforded diester **3d** (670 mg, 1.9 mmol, 93 %) as a colorless oil: ^1H NMR (270MHz, $CDCl_3$) δ 1.24 (t, 3 H, *J* = 7.0 Hz), 1.28 (t, 3 H, *J* = 7.2 Hz), 1.20-1.60 (m, 16 H), 1.62-1.78 (m, 2 H), 2.10-2.37 (m, 8 H), 4.10 (q, 2 H, *J* = 7.0 Hz), 4.18 (q, 2 H, *J* = 7.2 Hz); ^{13}C NMR (67.5MHz, $CDCl_3$) δ 14.23, 14.31, 22.56, 22.60, 23.92, 24.80, 24.96, 25.11, 25.55, 25.72, 26.24, 27.02, 28.32, 32.31, 34.19, 60.06, 60.19, 130.66, 144.40, 170.60, 173.49; IR (neat) 2980, 2930, 2860, 1740, 1720 cm^{-1}.

Typical procedure for preparation of enone 6: A solution of LDA was prepared from diisopropylamine (0.82 mL, 6.3 mmol) in THF (4 mL) and a 1.48 M hexane solution of BuLi (3.9 mL, 5.7 mmol). To this was added a THF (2 mL) solution of diester **3d** (670 mg, 1.9 mmol) at -78 °C. After being stirred for 1 h, 3 N HCl was added. Usual work-up gave ketoester **5d** which was used for the next step without purification. The crude product was dissolved in a 2 M solution of LiI (9.5 mL) in a 10:1 mixture of DMF and water. After heating at 150° C for 7 h, the reaction mixture was diluted with brine. Usual work-up followed by silica gel column chromatography afforded enone **6d** (375 mg, 1.6 mmol, 84 % from **3d**) as a colorless oil: ^{1}H NMR (270MHz, $CDCl_3$) δ 1.14-1.64 (m, 16 H), 1.81-1.92 (m, 2 H), 2.20-2.36 (m, 8 H); ^{13}C NMR (67.5MHz, $CDCl_3$) δ 21.96, 22.50, 22.80, 22.89, 24.22, 25.08, 25.48, 25.60, 26.21, 26.94, 30.32, 31.83, 38.31, 135.46, 159.25, 199.41; IR ($CDCl_3$) 2940, 2860, 1650, 1610 cm^{-1}.

In conclusion, a convenient method for cyclohexenone- and cycloheptenone annulation was developed on the basis of the Dieckmann condensation reaction. The present method shows promise for construction of the polycyclic carbon framework of terpenoids, and synthetic studies on the natural products are under way.

Acknowledgments

This work was partially supported by Grants from the Ministry of Education, Science, Sports, and Culture of the Japanese Government.

References

1. Sugai, M.; Tanino, K.; Kuwajima, I. *Synlett* **1997**, 461-462.
2. Reviews of the Robinson annulation reaction: (a) Jung, M. E. *Tetrahedron* **1976**, *32*, 3-31. (b) Gawley, R. E. *Synthesis* **1976**, 777-794. (c) Piers, E.; Boulet, S. L. *Synlett* **1998**, 516-518.
3. Habermas, K. L.; Denmark, S. E. *Org. React.* **1994**, *45*, 1-158.
4. (a) Paquette, L. A.; Ra, C. S.; Edmonson, S. D. *J. Org. Chem.* **1990**, *55*, 2443-2445. (b) Ballester, P.; García-Raso, A.; Mestres, R. *Synthesis* **1985**, 802-806.
5. (a) Schaefer, J. P.; Bloomfield, J. J. *Org. React.* **1967**, *15*, 1-203. (b) Davis, B. R.; Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, Chapter 3.6, pp 799-829.
6. Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, 4607-4610.
7. (a) A review of cross-coupling reactions of enol triflates: Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47-54. (b) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955-958. (c) Lipshutz, B. H.; Vivian, R. W. *Tetrahedron Lett.* **1999**, *40*, 2871-2874.
8. (a) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 5559-5562. (b) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390-2392.
9. Paquette, L. A.; Roberts, R. A.; Drtina, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6690-6693.