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Efficient Synthesis of 3-Methylene-2-Pyrrolidinone and Highly Exoselective Diels-Alder Addition to Cyclopentadiene

Frédéric Fotiadu, Olivier Pardigon, Gérard Buono*

Ecole Nationale Supérieure de Synthèse, de Procédés et d'Ingénicrie Chimiques d'Aix-Marseille,
UMR 6516 *"Synthèse, Catalyse et Chiralité"*, Av. Escadrille Normandie-Niemen, 13397 Marseille cedex 20. France.

Maurice Le Corre, Alain Hercouët*

Laboratoire de Synthèse Organique (UMR 6510), Université de Rennes I, Campus de Beaulieu,
Av. du Général Leclerc, 35042 Rennes cedex, France.

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Abstract: A new efficient synthesis of 3-methylene 2-pyrrolidinone **1** involving ylide-lactame **6** is reported. Diels-Alder cycloadditions of **1** to cyclopentadiene exhibited very high exoselectivities, regardless of the experimental conditions. These results confirm the generality of exoselectivity for conformationally restricted *s-cis* dienophiles and indicate that the dienophile functionality and dipole moment have little influence on its magnitude.

We reported in previous communications the remarkable exoselectivity observed in the Diels-Alder reactions of α-vinylidene and α-methylene γ-butyrolactones with cyclopentadiene, regardless of the experimental conditions.[1a,b] Since literature offers several other examples of similar behaviour from part of structurally related compounds, we suggested that an "exo rule" may apply to *all* exocyclic double bond dienophiles exhibiting rigid cisoïd conformation.[1] In order to confirm this assumption and evaluate the influence of the dienophile functionality on the cycloaddition stereochemistry, we focused our attention on α-methylene γ-butyrolactam, the lactamic counterpart of the former butyrolactone.

Structurally related 1-(*N*-carbamoyl)-3-benzylidenepyrrolidin-2-ones have been prepared by reaction of a 1-(*N*-carbamoyl)-3-phosphonium pyrrolidinone derivative with benzaldehyde in the presence of triethylamine.[2] The key 3-bromopyrrolidinone derivative was obtained in several steps from the acyclic isocyanate $Br(CH_2)_2CHBrCONCO$.

However, the parent 3-methylene-2-pyrrolidinone (α-methylene-γ-butyrolactam) **1** is not an easily accessible compound. It has been prepared for the first time in 1981 in moderate yield by dehydration of the corresponding 3-(hydroxymethyl) lactam.[3] We are now reporting a much more efficient and potentially versatile synthesis, as detailed in Scheme 1.[4] The first two steps were achieved by successive additions of phosphorus tribromide and triphenylphosphine to ethyl *N*-(3-hydroxypropyl) carbamate **2**, prepared according to a known procedure.[5] Ylide **5**, obtained through the reaction of potassium *tert*-butoxyde on a suspension of the phosphonium salt **4** in toluene, spontaneously cyclized into the secondary ylide **6** after one hour at 50 °C. Condensation of **6** with paraformaldehyde afforded compound **1** in 72% isolated yield (overall yield 51% from **2**).

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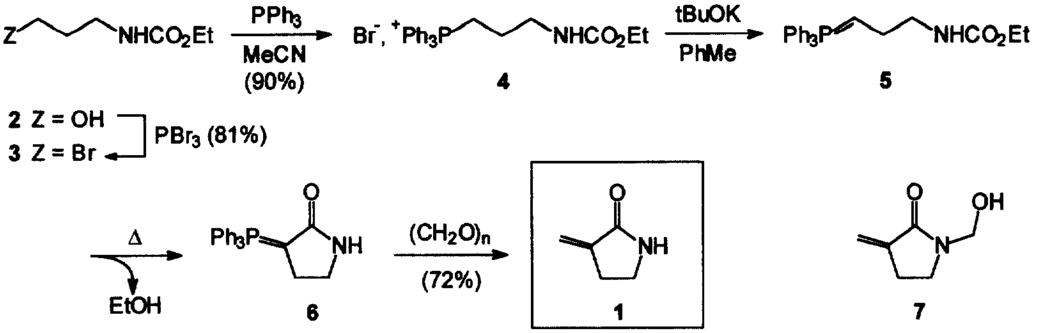
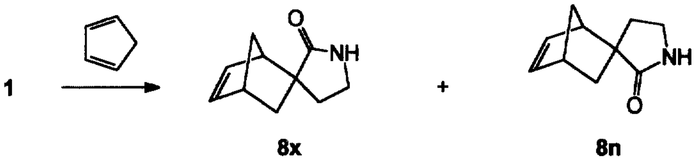


Scheme 1.

Cyclization of **5** might proceed through a nucleophilic attack of the ylide carbon on the carbamate group, which liberates an ethanolate anion. The nature of the base appeared to be of great importance. In fact, when sodium amide was used instead of tBuOK, no cyclization occurred and only primary ylide **5** was detected by ^{31}P NMR.[6]

When a large excess (3 equiv.) of paraformaldehyde was used, *N*-(hydroxymethyl) 3-methylene 2-pyrrolidinone **7**, resulting from *N*-addition of **1** to formaldehyde, was isolated as the sole product (71% yield). This revealed the unusual nucleophilic character exhibited by the amide nitrogen atom of **1**, since condensation of lactams with formaldehyde typically requires basic catalysis and ultrasound activation.[7] This feature might explain why 3-ethenylidene 2-pyrrolidinone, the allenic analogue of **1**, could not be obtained through condensing gaseous ketene on ylide **6** in a similar way that the one described to prepare α-ethenylidene lactones.[1a] Even at low temperature and high dilution, this procedure led only to unidentified polymeric material that might result from side reactions involving the amide nitrogen atom and the highly electrophilic allenic moiety.

We have then investigated the Diels-Alder reaction of **1** with cyclopentadiene (Scheme 2) under similar conditions to those previously used for lactonic dienophiles.[1b, 8] In all cases, we verified that the diastereomeric ratio remained constant throughout the course of the process, indicating that the reaction was under kinetic control. The results are summarised in Table1.



Scheme 2.

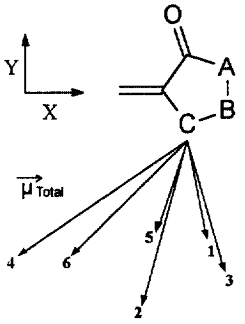
Table 1. Diels-Alder Reactions of 3-Methylene 2-Pyrrolidinone 1 with Cyclopentadiene.

entry	catalyst	solvent	temperature	*endo/exo* ratio[a]	yield %[a]
1	-	toluene	reflux	7:93	85
2	-	water[b]	r.t.	10:90	30
3	$ZnCl_2.xOEt_2$[c,d]	CH_2Cl_2	0 °C	5:95	88
4	$AlCl_3$[d]	CH_2Cl_2	-10 °C	8:92	70
5	$TiCl_2(OiPr)_2$[d]	CH_2Cl_2	0 °C	3:97	86

[a] Determined by GC of the reaction mixture on a capillary CARBOWAX column. *exo* adduct **8x** having the shorter retention time. [b] The reactants being hydrophobic, the reaction was performed under vigorous stirring in biphasic medium. The low yield was due to an extensive dimerization of cyclopentadiene. [c] Used as a 2.2 M solution in CH_2Cl_2 purchased from Fluka®. [d] Lewis acid catalyst (0.1 molar equiv. with respect to 1) was stirred 10 min with the solution of 1 before cyclopentadiene (2.5 equiv.) was added.

Very high exoselectivity was observed whatever the experimental conditions. The diastereomeric ratios were almost identical to those observed with α-methylene γ-lactone and α-methylene cyclopentanone,[1b] indicating that the dienophile functionality have negligible influence on the energy gap between *endo* and *exo* transition states. Roush and Brown suggested that the exo preference with conformationally restricted *s-cis* dienophiles may be due to the difference in dipole moment in the *exo* versus the *endo* transition states.[1c] We thus computed the dipole moments of a series of such dienophiles using the AM1 semi-empirical method (Table2).[9]

Table 2. Calculated Dipole Moments for Exocyclic Methylene Dienophiles and Vectors Plot.



entry	dienophile			dipole moment μ (D)			*endo/exo*
	A	B	C	μ_X[a]	μ_Y	μ_{Total}	ratio[b]
1	CH_2	CH_2	CH_2	0.58	-2.74	2.80	9:91[c]
2	O	CH_2	CH_2	-1.23	-4.54	4.70	8:92[c]
3	NH	CH_2	CH_2	1.03	-3.59	3.74	7:93
4	O	CO	CH_2	-4.63	-3.20	5.63	0:100[c]
5	O	CH_2	O	-0.83	-2.52	2.66	4:96[d]
6	O	CH_2	-	-3.17	-3.18	4.49	25:75[e]

[a] The X-axis was orientated along the dienophile CH_2=C bond (see scheme). [b] Experimental stereoselectivities for the reaction with cyclopentadiene in similar experimental conditions. [c] See ref. 1b. [d] Value for the 2-tert-butyl-5-methylene-1,3-dioxolan-4-one.[1b,c] [e] Value for the 4-methyl-3-methylene-1-oxetan-2-one.[10]

All dienophiles display a large dipole moment component along the Y-axis (that would be aligned with the dipole of cyclopentadiene in the transition states), supporting the dipole interaction hypothesis. Nevertheless, no obvious correlation appears between the calculated μ_{Total} and the extent of exoselectivity observed. In spite of large variations in relative magnitude and orientation of their dipole, five-member ring dienophiles (1-5) provide similar exoselectivities. On the opposite, α-methylene β-lactone (6), whose dipole moment spans in the same range, exhibits a much lower preference for exo addition. As this dienophile differs from the former ones by its ring size, and thus the relative position of its substituents, structural factors, and consequently steric effects, should influence the stereoselectivity more strongly than dipolar effects do.

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4. Typical procedure: to a solution of ethyl *N*-(3-hydroxypropyl) carbamate **2** [5] (13.00 g, 88 mmol) in dry toluene (110 ml) at room temperature, PBr_3 (27.0 g, 100 mmol) in toluene (25 ml) was added over 1.5 h. After being refluxed for 40 min, the reaction mixture was washed with 2 × 100 ml of water. The aqueous phase was saturated with NaCl and extracted three times with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give bromide **3** (15.03 g, 81%) that was used without further purification. Bromide **3** (13.00 g, 62 mmol) was then added to a solution of PPh_3 (17.00 g, 65 mmol) in acetonitrile (80 ml). After 24 h at reflux, the solution was concentrated and 200 ml of AcOEt were added affording 26.33 g (90%) of the phosphonium salt **4** as a white precipitate: mp 178-180 °C; 40.5 MHz ^{31}P NMR ($CDCl_3$) δ 23.5. A suspension of **4** (6.48 g, 13.7 mmol) in toluene (60 ml) was dried by azeotropic distillation (10 ml collected), then tBuOK (1.60 g, 14.3 mmol) was added at rt. After the yellow-orange solution being stirred for 1 h at 50 °C, dry paraformaldehyde (0.45 g, 14.4 mmol) was added at this temperature. After 10 min, ^{31}P NMR revealed the reaction was completed. The reaction mixture was filtered and concentrated. Ph_3PO was removed by flash chromatography on silica gel (Et_2O, then AcOEt). Kugelrohr distillation (130 °C, 0.6 mmHg) followed by recrystallization from AcOEt afforded pure **1** (0,93 g, 70%) as colourless crystals: mp 106 °C [lit.[3] 106-108 °C].
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6. Highly air sensitive ylide **5** was isolated as an orange solid: 100 MHz ^{1}H NMR ($CDCl_3$) δ 7.45 (15 H, m), 5.75 (1 H, t), 4.10 (2 H, m), 3.30 (3 H, m), 2.30 (2 H, q), 1.25 (3 H, t); 25 MHz ^{13}C NMR ($CDCl_3$) δ 156.88, 132.66 (d, $J_{P\text{-}C}$ = 129.9 Hz), 131.64, 130.90, 128.44, 60.59, 41.43, 27.09 (d, $J_{P\text{-}C}$ = 72.0 Hz), 23.36, 14.65.
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8. Cycloadducts **8x**, **8n** were separated by chromatography on silicagel (1:1 cyclohexane-Et_2O) and major *endo* adduct **8n** was purified by recrystallization from a 1:1 mixture of hexanes-AcOEt: 100 MHz ^{1}H NMR ($CDCl_3$) δ 7.11 (1 H, s), 6.30 (1 H, m), 6.17 (1 H, m), 3.38-3.16 (2 H, m), 2.91 (1 H, s), 2.81 (1 H, s), 2.26-1.63 (4 H, m), 1.05 (1 H, d, ^2J = 2.84 Hz), 0.94 (1 H, d, ^2J = 2.84 Hz); 25 MHz ^{13}C NMR ($CDCl_3$) δ 183.77, 139.51, 134.96, 65.43, 49.36, 47.07, 42.79, 39.16, 38.78, 34.91. The respective stereochemistries of the aducts were unambiguously elucidated from 100 MHz 2D-^{1}H NOESY NMR experiments. The *endo* epimer **8n** exhibited a nuclear Overhauser effect between the methylene group of the pyrrolidone ring in *exo* position and the proton of the methylene bridge facing it, whereas the *exo* adduct **8x** lacked this effect.
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