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5-Substituted Bicyclo[3.2.0]hept-2-en-6-ones: Synthesis and Ring-opening Reactions

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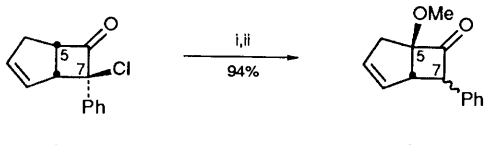
5-Methoxy- and 5-dialkylamino-bicyclo[3.2.0]hept-2-en-6-one derivatives **2** and **3** are formed in high yield by *cine* substitution at the fused *exo*-chlorocyclobutanone **1**, subsequent reactions yielding 2-phenyltropone **6** and a cycloheptadienone enamine **8**.

Recently a η^5-(bicyclo[3.2.0]hepta-1,3-dienyl)cobalt(I) complex was observed to undergo a ring-opening reaction at 200 °C to yield an intermediate *ortho*-quinodimethane analogue which was trapped with dienophiles.[1] In order to perform this type of reaction at lower temperatures the synthesis of bicyclo[3.2.0]-hepta-1,3-dienyl complexes with suitable substituents (*e.g.* Ph, OH, OR) on the four-membered ring was desirable. Although easily accessible, 4-bromobicyclo[3.2.0]hept-2-ene derivatives are unsuitable starting compounds, because the dehydrobromination products rapidly rearrange to spiro[2.4]hepta-4,6-diene derivatives.[2] Systems bearing a substituent at C-5 are more promising since the bicyclo[3.2.0]hepta-1,3-dienyl anion had been prepared from 5-chlorobicyclo[3.2.0]hept-2-ene.[3] Here, *cine* substitution reactions[4] of **1** with O and N nucleophiles are presented which lead to the desired compounds in high yield.

Dreiding *et al.*[5] found, that the [2 + 2] cycloaddition of cyclopentadiene and chlorophenylketene gives the *exo*-7-chloro-*endo*-7-phenyl diastereoisomer **1** as the only observable product. According to Garin *et al.*[6] the *exo* leaving group is mandatory for *cine* substitution; the *endo*-7-chloro derivative would lead to Favorski ring contraction products. Garin *et al.* proposed a S_N2' reaction of the strained enolate to account for the *cine* substitution. We regard this as the cause of the *exo* stereospecifity of *cine* substitutions since S_N2' reactions are known to proceed *syn* stereospecifically.[7] The reaction of **1** was performed at room temperature with NaOMe (3 equiv.), followed by acidification, and yielded 94% of the *cine* substitution product **2** as a 88:12 mixture of the *endo*- and the *exo*-7-phenyl diastereoisomers (see Scheme 1).† This is interesting with regard to a recent communication by Hassner *et al.*,[8] who found the cycloadduct of chlorophenylketene and cyclopentadiene to be unreactive to MeO^-. With phenolate the reaction was less selective, the corresponding *cine* substitution product being observed by ^1H NMR spectroscopy along with numerous other products.

To obtain systems with substituents at C-5, which are more prone to elimination reactions, secondary amines were tested as nucleophiles. It was found that reactivity and chemo- as well as diastereo-selectivity are controlled by the steric bulk of the alkyl groups at nitrogen (see Scheme 2 and Table 1). With dimethylamine, in addition to 49% of **3a**, 22% of **4** was formed as a single diastereoisomer. Diethylamine gave the best yield (85%), and diisopropylamine requires long reaction times.

When a toluene solution of hydrochloride **5b** was refluxed in the presence of toluene-*p*-sulphonic acid, a ring-opening reaction to 2-phenyltropone **6** was observed (yield 72%). This suggests an amine elimination leading to a strained bicyclo-[3.2.0]hepta-1,3-dien-7-one followed by rupture of the C-1/C-5 bond and migration of a hydrogen atom from the α to the α′ position. Thus, *cine* substitution products appear to be possible intermediates in the known reactions of cycloadducts of cyclopentadiene and aryl- or alkyl-chloroketenes under solvolysis conditions, leading to 2-aryl- or 2-alkyl-tropones.



1 2

Scheme 1 *Reagents and conditions:* i, NaOMe (3 equiv.)/HOMe, 2 h, 25 °C; ii, H^+

Table 1 Reaction of **1** with secondary amines[a]

	R	*endo*:*exo*	Yield (%)	React. time
3a	Me	58:42	49 + 22 of **4**	14 h
3b	Et	61:39	85	17 h
3c	Pr^i	>90:10	83[b]	19 d

[a] Experimental details given in footnote †. [b] 75% conversion, starting material recovered.

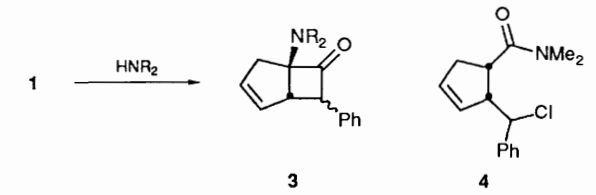
† Typical experimental procedures compound **2**: Sodium (15.75 g, 685 mmol) was dissolved in dry methanol (1300 ml). A solution of **1** (50.00 g, 229 mmol)[5] in methanol (80 ml) was added dropwise and the mixture stirred for 2 h at 25 °C. Water (3300 ml) was then added, and the mixture acidified with aqueous hydrochloric acid. It was then extracted with diethyl ether (3 × 2000 ml), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (500 ml) and water (500 ml), then dried ($MgSO_4$), and evaporated under reduced pressure. The remaining syrup was exposed to a vacuum (0.001 mbar) for 8 h to give compound **2** [46.23 g, 216 mmol, 94%, purity > 95% (NMR)]§ (*endo*:*exo* = 88:12). Further purification was possible by vacuum transfer at 80 °C/0.001 mbar with partial decomposition of the *endo* isomer.

Compound **3b**. A solution of **1** (20.00 g, 91.53 mmol)[5] in diethylamine (200 ml) was stirred for 17 h at 25 °C. The solvent was evaporated under reduced pressure and the residue was dissolved in diethyl ether. Precipitated ammonium salt was filtered off and the ethereal solution was extracted with 2M hydrochloric acid until the aqueous layer remained colourless. Aqueous NaOH was then added to the combined aqueous layers until they were basic. The mixture was extracted with diethyl ether (3 × 200 ml) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The material was purified by filtration through silica gel with pentane–diethyl ether (50:1). Removal of solvent under reduced pressure, and exposure of the resulting liquid to a vacuum (0.001 mbar) gave **3b** (19.83 g, 77.8 mmol, 85%)§ (*endo*:*exo* = 61:39).

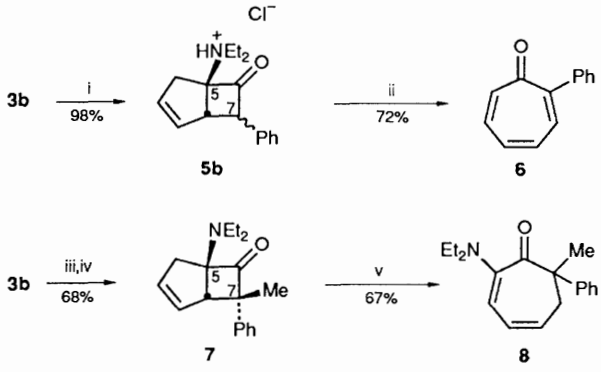
The *exo*-stereospecifity of the *cine* substitution, which is a result of the stereospecifity of the S_N2' reaction, provides an answer to the question why only *exo*-7-halogenobicyclo[3.2.0]hept-2-en-6-ones solvolyse with the formation of 2-substituted tropones.[9,*]

To prevent the migration of 7-H necessary for the formation of **6**, **3b** was diastereoselectively methylated at C-7; the aminoketone **7** at 170 °C ring opened with formation of the unsaturated enamine **8** (see Scheme 3).

All new compounds were fully characterised (IR, ^1H, ^{13}C NMR, MS, elemental analysis). A significant feature in the ^1H NMR spectra of *cine* substitution products **2** and **3** is the doublet assignable to 7-H.†



Scheme 2



Scheme 3 *Reagents and conditions:* i, HCl; ii, 110 °C, 24 h, H^+; iii, LDA, −78 → 0 °C; iv, MeI, −78 °C; v, 170 °C, 5 h

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* Bartlett *et al.* proposed a *cine* substitution intermediate in the course of the solvolytic transformation of 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one to 2-tropolone; however, for this reaction it is not necessary to break the bond between C-5 and its substituent. P. D. Bartlett and T. Ando, *J. Am. Chem. Soc.*, 1970, **92**, 7518.

† ^1H NMR data of selected new compounds (J values in Hz): *endo*-**2**: δ (400 MHz, $CDCl_3$) 2.53 [m, 1 H, *exo*-4-H, $^4J_{2,exo-4}$ *ca.* 2.2, $^3J_{3,exo-4}$ *ca.* 2.2, $^2J_{endo-4,exo-4}$ −17.6, $^5J_{exo-4,exo-7}$ *ca.* 0.7 $^4J_{1,exo-4}$ *ca.* 1.1], 2.83 (dt, 1 H, *endo*-4-H, $^4J_{2,endo-4}$ *ca.* 2.4, $^3J_{3,endo-4}$ *ca.* 2.4, $^4J_{1,endo-4}$ *ca.* 2.4), 3.47 (s, 3 H, OCH_3), 3.85 (m, 1 H, 1-H, $^3J_{1,2}$ *ca.* 2.4, $^4J_{1,3}$ *ca.* 1.3, $^3J_{1,exo-7}$ 10.4), 4.89 (d, 1 H, *exo*-7-H), 5.43 (m, 1 H, 2-H, $^3J_{2,3}$ 6.1), 5.78 (m, 1 H, 3-H), 7.13 (m, 2 H, *ortho*-H), 7.2–7.3 (m, 3 H, *meta*-, *para*-H); *exo*-**2**: δ 2.67 (m, 1 H, *exo*-4-H, $^4J_{2,exo-4}$ 1.6, $^3J_{3,exo-4}$ 2.4, $^2J_{endo-4,exo-4}$ −18.7, $^4J_{1,exo-4}$ > 0), 2.97 (m, 1 H, *endo*-4-H, $^4J_{2,endo-4}$ 2.8, $^3J_{3,endo-4}$ 2.2, $^4J_{1,endo-4}$ 1.8), 3.41 (s, 3 H, OCH_3), 3.59 (m, 1 H, 1-H, $^3J_{1,2}$ 2.8, $^4J_{1,3}$ > 0, $^3J_{1,endo-7}$ 6.1), 3.74 (m, 1 H, *endo*-7-H), 5.91 (m, 1 H, 3-H or 2-H, $^3J_{2,3}$ 5.7), 6.14 (m, 1 H, 2-H or 3-H); *endo*-**3b**: δ (200 MHz, $CDCl_3$) 1.10 [t, 6 H, $N(CH_2CH_3)_2$, ^3J 7.1), 2.5–3.0 [m, 5 H, $N(CH_2CH_3)_2$, *endo*-4-H, *exo*-4-H], 3.66 (m, 1 H, 1-H, $^3J_{1,exo-7}$ 10.1), 5.04 (d, 1 H, *exo*-7-H), 5.41 (m, 1 H, 2-H, $^3J_{2,3}$ 6.3, $^3J_{1,2}$ 4.6, $^4J_{2,endo-4}$ *ca.* $^4J_{2,exo-4}$ *ca.* 2.2), 5.80 (m, 1 H, 3-H), 7.1–7.4 (m, 5 H, phenyl-H); *exo*-**3b**: δ 1.05 [t, 6 H, $N(CH_2CH_3)_2$, ^3J 7.1], 2.5–3.0 [m, 6 H, $N(CH_2CH_3)_2$, *endo*-4-H, *exo*-4-H], 3.38 (m, 1 H, 1-H, $^3J_{1,endo-7}$ 4.9), 3.81 (d, 1 H, *endo*-7-H), 5.85 (m, 1 H, 3-H, $^3J_{2,3}$ 5.9), 6.02 (m, 1 H, 2-H, $^3J_{1,2}$ 4.7, $^4J_{2,endo-4}$ *ca.* $^4J_{2,exo-4}$ *ca.* 2.5), 7.1–7.4 (m, 5 H, phenyl-H); **4**: δ (400 MHz, $CDCl_3$) 2.76 (m, 1 H, α5-H, $^4J_{3,\alpha5}$ *ca.* 2.2, $^3J_{4,\alpha5}$ *ca.* 2.2 Hz, $^2J_{\alpha5,\beta5}$ −17.3 Hz, $^3J_{1,\alpha5}$ *ca.* 2.3, $^4J_{2,\alpha5}$ *ca.* 2.3), 3.17 (m, 1 H, β5-H, $^4J_{3,\beta5}$ *ca.* 2.2, $^3J_{4,\beta5}$ *ca.* 2.2, $^4J_{2,\beta5}$ *ca.* 2.3, $^3J_{1,\beta5}$ 10.1), 3.45 (s, 3 H, NCH_3), 3.64 (s, 3 H, NCH_3), 4.34 (m, 1 H, 2-H, $^3J_{2,3}$ *ca.* 2.2, $^4J_{2,4}$ *ca.* 2.2, $^3J_{1,2}$ 8.6, $^3J_{2,9}$ 7.5), 5.04 (m, 1 H, 3-H, $^3J_{3,4}$ 5.8), 5.09 (m, 1 H, 1-H, $^4J_{1,9}$ 0.9), 5.74 (m, 1 H, 4-H), 6.61 (dd, 1 H, 9-H), 7.21 (m, 2 H, *ortho*-H), 7.2–7.4 (m, 3 H, *meta*-, *para*-H); **7**: δ (200 MHz, $CDCl_3$) 1.09 (t, 6 H, 10-H, $^3J_{9',10}$ 7.1, $^3J_{9,10}$ 7.3), 1.85 (s, 3 H, 8-H), 2.43 (m, 2 H, *endo*-4-H, *exo*-4-H, $^4J_{2,endo-4}$ *ca.* 2.4, $^4J_{2,exo-4}$ *ca.* 2.4, $^3J_{3,endo-4}$ *ca.* 2.3, $^3J_{3,exo-4}$ *ca.* 2.3), 2.59 (m, 2 H, 9′-H, $^2J_{9,9'}$ −13.3), 2.76 (m, 2 H, 9-H), 3.08 (m, 1 H, 1-H, $^3J_{1,2}$ 2.4, $^4J_{1,3}$ 1.2), 5.44 (m, 1 H, 2-H, $^3J_{2,3}$ 6.1), 5.60 (m, 1 H, 3-H), 7.0–7.4 (m, 5 H, phenyl-H); **8**: δ (200 MHz, $CDCl_3$) 0.89 [t, 6 H, $N(CH_2CH_3)_2$, ^3J 7.1], 1.50 (s, 3 H, CH_3) 2.46 (dd, 1 H, 6b-H, $^2J_{6a,6b}$ −14.5, $^3J_{5,6b}$ 6.2), 2.80 [q, 4 H, $N(CH_2CH_3)_2$], 3.16 (dd, 1 H, 6a-H, $^3J_{5,6a}$ 6.2, $^4J_{4,6a}$ 1.2), 4.89 (d, 3-H, $^3J_{3,4}$ 6.4), 5.73 (dt, 1 H, 5-H, $^3J_{4,5}$ 10.6), 5.98 (ddd, 1 H, 4-H) and 7.1–7.4 (m, 5 H, phenyl-H). Complete analytical data will be published in a full paper.