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Palladium-catalysed [$_\pi$2a+$_\pi$2s] cycloadditions of α-bromoalkyl ketenes to cyclopentadiene

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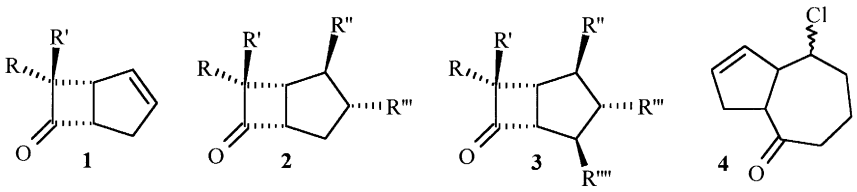
Abstract

7-Substituted bicyclo[3.2.0]hept-2-en-6-one derivatives were identified as intermediates towards biologically interesting compounds. An improved synthesis of 7-alkyl-7-bromobicyclo[3.2.0]hept-2-en-6-ones by palladium-catalysed [$_\pi$2a+$_\pi$2s] cycloaddition of α-bromoalkyl ketenes to cyclopentadiene is described. Increased yields and increasing *exo* alkyl cycloadducts were observed with various palladium catalysts under standard dehydrochlorination conditions.

Keywords: cycloadditions; palladium; ketenes; bicyclic aliphatic compounds.

Over the past 30 years the bicyclo[3.2.0]heptanone ring system has received vast amounts of attention.[1] Most notably it has been used extensively towards the synthesis of the potent, structurally diverse and biologically active prostaglandins.[2] 7,7-Disubstituted bicyclo[3.2.0]heptanone derivatives **1** have been particularly useful in organic synthesis:[3] the cyclobutanone ring can be cleaved, expanded or contracted in many ways;[2,3] functionalisation of derivatives such as **1** provides interesting steric characteristics which have been utilised in the synthesis of tetra[4] and penta-substituted[5] bicyclo[3.2.0]heptanone derivatives **2** and **3**, stereo- and regiospecifically (Scheme 1); and free-radical ring expansion of a derivative of **1** has enabled the construction of the 5,7-*cis*-fused bicyclic ring systems **4**.[3]



Scheme 1.

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† Taken from the PhD Thesis of I.J.S.F.

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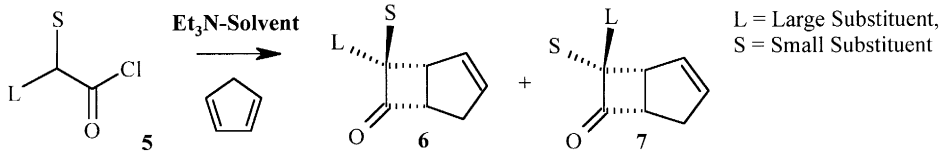
With the aim of synthesising biologically active compounds as a synthetic intermediate we required disubstituted bicyclo[3.2.0]heptane derivatives. An improved synthesis of the derivatives with the generic structure **1** is the subject of this report. Derivatives of **1** can be prepared by [$_{\pi}$2a+$_{\pi}$2s] intermolecular cycloaddition of stabilised ketenes, generated in situ from the corresponding acid chloride (such as **5**) by dehydrochlorination with triethylamine, to cyclopentadiene.[6] The [$_{\pi}$2a+$_{\pi}$2s] thermal cycloaddition proceeds in a concerted manner, yielding C7 alkyl *endo* **6** and *exo* **7** isomers (Scheme 2).[7]



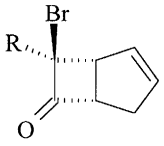
Scheme 2.

The major cycloadduct **6** is usually the one with the larger alkyl substituent in the *endo* position. The preferential formation of **6** can be explained by the fact that the ketene (with the larger group pointing away from the cyclopentadiene ring) must twist into position for cycloaddition to occur in a [$_{\pi}2_s$+$_{\pi}2_a$] manner.[7]

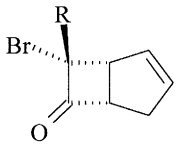
Derivatives of **1** were synthesised from several known α-bromo acid chlorides by a standard dehydrochlorination procedure.[8] It was found that on increasing the length of the alkyl chain a reduction in yield was observed (Table 1). Previous work, most notably that of Brady et al.,[6,9,10] revealed decreasing yields of cycloadducts as the C7 substituents were increased in size (from CH_3, *n*-C_3H_7, *i*-C_3H_7 to *t*-C_4H_9).

Table 1
Cycloadditions of α-bromoalkyl ketenes to cyclopentadiene

Endo	*Exo*
R = $Br(CH_2)_3$, **8**	R = $Br(CH_2)_3$, **9**
R = $CH_3(CH_2)_3$, **10**	R = $CH_3(CH_2)_3$,**11**
R = $CH_3(CH_2)_5$, **12**	R = $CH_3(CH_2)_5$,**13**
R = $CH_3(CH_2)_7$, **14**	
R = $CH_3(CH_2)_9$, **15**	
R = $CH_3(CH_2)_5$, **16**	



Endo



Exo

Entry	Alkyl Substituent	[$_{\pi}$2s + $_{\pi}$2a] Cycloaddition Without Catalyst*		[$_{\pi}$2s + $_{\pi}$2a] Cycloaddition with $PdCl_2$†	
		exo/ *endo*‡	Total Yield¶, ϕ (%)	*exo*/ *endo*‡	Total Yield¶, ϕ (%)
1	$Br(CH_2)_3$	1 : 1.7	46 (41)	1 : 1	91
2	$CH_3(CH_2)_3$	1 : 1.1	(58)	2 : 1	(60)
3	$CH_3(CH_2)_5$	1 : 2.8	50 (39)	1 : 2.4	65
4	$CH_3(CH_2)_7$	*endo* only	(38)	*endo* only	59
5	$CH_3(CH_2)_9$	*endo* only	(30)	*endo* only	(55)
6	$CH_3(CH_2)_{15}$	*endo* only	(23)	*endo* only	(42)

* 1.5 equiv. Et_3N, 2.2 equiv., cyclopentadiene. † as without catalyst with $PdCl_2$ (10mol%). ‡ Ratio of *exo* and *endo* isomers by GC. ¶ Yield by GC. ϕ Yields in parenthesis are isolated yields.

Mixtures of *endo* and *exo* products were observed for three of the α-bromoalkyl ketenes investigated (entries 1, 2 and 3). Increasing the alkyl chain to eight carbon atoms or more (entries 4, 5 and 6) led to the exclusive formation of the *endo*-isomer. The low yields of this reaction prompted us to investigate optimisation of the [$_{\pi}$2s+$_{\pi}$2a] cycloaddition of α-bromoalkyl ketenes to cyclopentadiene.

Current work in our laboratory has focused on the use of palladium complexes in organic synthesis. In the literature, to the best of our knowledge, palladium catalysis of the [$_{\pi}$2s+$_{\pi}$2a] cycloaddition reaction remains unreported.[1] It was rationalised that both cyclopentadiene and the α-bromoalkyl ketene

(generated in situ by dehydrochlorination with Et_3N in hexane) could co-ordinate to a palladium(II) transition metal complex. Preliminary studies were performed with palladium(II) chloride ($PdCl_2$) (10 mol%), 2,5-dibromopentanoyl chloride (1 equiv.), Et_3N (1.5 equiv.) and cyclopentadiene (2.2 equiv.) in hexane. This reaction afforded the corresponding cycloadducts **8** and **9** in 46 and 45% yield, respectively, as shown by GC. This promising result led to an investigation into $PdCl_2$ catalysis of various α-bromoalkyl ketenes under identical dehydrochlorination conditions (Table 1). Increased yields were observed for all the [$_\pi$2s+$_\pi$2a] cycloadditions studied, although it was again observed that yields decreased on increasing the length of the alkyl chain. The difference in the *exo*/*endo*-isomer distribution for entry **1** prompted further investigation of several palladium(II) complexes.

The palladium(II) complexes investigated produced more of the *exo*-isomer **9** when compared with the uncatalysed reaction (Table 2). [1,2-Bis(diphenylphosphine)ethane]dichloropalladium(II) ($Pd(dppe)Cl_2$) actually favours the formation of **8** (entry 5, Table 2). It is possible that the steric bulk of the dppe ligand influences the palladium(II)-mediated reaction, although there is no clear trend to suggest that the steric characteristics of the palladium ligand affects the *exo*/*endo* ratio. Bis(π-allyldiphenylphosphino)dichloropalladium(II) ($Pd(PPh_2allyl)_2$) complex, purely on steric grounds, would be expected to increase the formation of **8**, and this is clearly not the case when compared with $PdCl_2$. The electronic effects of the palladium ligands may be playing a more important role in this type of catalysis. It is interesting to note that of all the palladium catalysts investigated, the best yield was obtained with $PdCl_2$.

Table 2
Palladium catalysis of addition of 2,5-dibromopentyl ketene to cyclopentadiene*

Entry	Catalyst	Reaction Time/ Hours	% Yield[¶]		Ratio[†]
			exo **8**	*endo* **9**	
1	No Catalyst	3	8	13	1 : 1.6
		24	17 (14)	29 (21)	1 : 1.7
2	$PdCl_2$	3	30	30	1 : 1
		24	46	45	1 : 1
3	$Pd(PPh_3)_2BnCl$	3	18	17	1 : 1
		24	38 (36)	42 (38)	1 : 1.1
4	$Pd(acac)_2$	3	23	25	1 : 1.1
		24	40	47	1 : 1.2
5	$Pd(dppe)Cl_2$	3	11	8	1.3 : 1
		24	42 (36)	32 (26)	1.3 : 1
6	$Pd(PPh_2allyl)_2Cl_2$	3	19	19	1 : 1
		24	32	37	1 : 1.1

* 1mmol scale (10mls of hexane). [†] Ratio of *exo* and *endo* isomers by GC. GC-MS confirmed the molecular ion of each isomer. [¶] The numbers in parentheses are isolated yields.

In conclusion, an optimised procedure has been developed for the [$_\pi$2a+$_\pi$2s] cycloaddition of α-bromoalkyl ketenes to cyclopentadiene. The effect of palladium substituent, solvent polarity and temperature on the palladium(II)-mediated reaction will be reported in due course.

Typical procedure: To a magnetically stirred mixture of the α-bromoalkyl acid chloride (1 mmol), freshly distilled cyclopentadiene (2.2 mmol), palladium catalyst (10 mol%) in dry hexane (8 ml) at 0°C was added freshly distilled triethylamine (1.5 mmol) in dry hexane (2 ml) dropwise over 15 min. The mixture was stirred at 0°C for a further 15 min, then allowed to warm to 25°C over 1 h and stirred overnight. The reaction was monitored by GC after 3 and 24 h. The mixture was diluted with hexane (20 ml), filtered through Celite and concentrated in vacuo to give the crude cycloadducts. Separation of the cycloadducts was achieved by flash chromatography on silica gel (elution with 5% diethyl ether/hexane).

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