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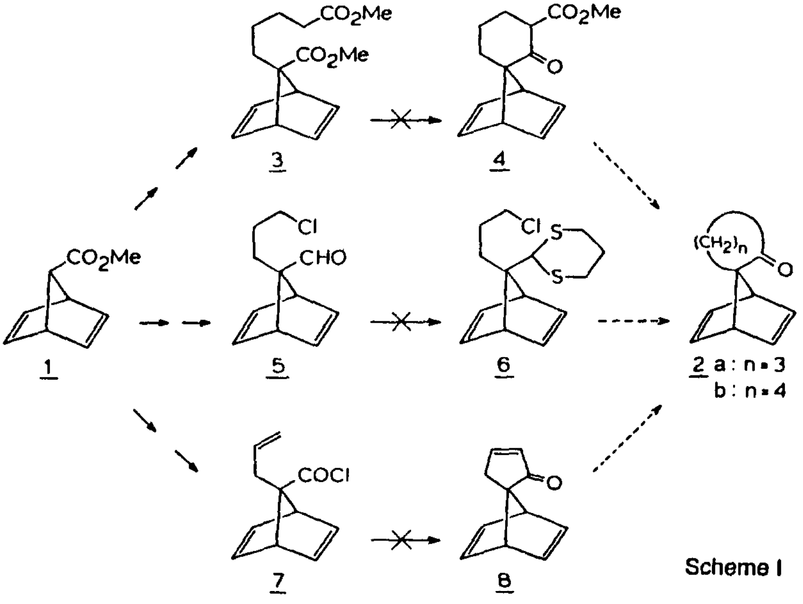
SPIRO KETONE SYNTHESIS VIA LITHIUM-IODINE EXCHANGE OF α-(ω-IODOALKYL) ESTERS

T. van der Does, G.W. Klumpp, M. Schakel *
Scheikundig Laboratorium, Vrije Universiteit
De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands

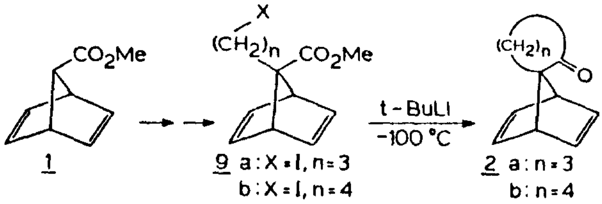
Abstract: The title reaction (2 eq. of *t*-BuLi, -100°C) provides a new route to five- and six-membered ring ketones and has permitted the synthesis of two spiro ketones that were inaccessible by conventional methods.

A recent report on the lithium-halogen exchange initiated cyclization of iodo carbonyl compounds[1] prompts us to disclose related findings concerning the synthesis of spiro ketones, some of which were inaccessible by other methods. Known methods for the synthesis of cyclic ketones that proved unsuccessfull for the preparation of spiro ketones 2a,b from 1 are shown in Scheme I.



Scheme I

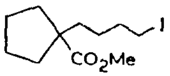
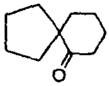
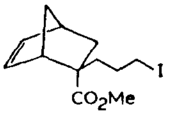
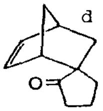
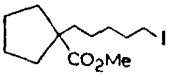
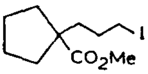
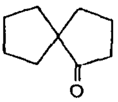
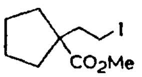
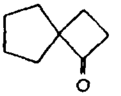
Attempts at Dieckmann condensation[2] of 3 did not yield 4 under a variety of reaction conditions (LDA, THF, -70° to 0°C; KH, THF, r.t.[3]; KH, benzene, 5 h reflux; NaH, DMSO, r.t.[4]; NaH, DME, 4 h reflux[5]). Intramolecular alkylation of a lithiated dithiane[6] could not be utilized since 6 was obtained from 5 only in very low yield. Cyclization of the γ,δ-unsaturated acid chloride[7] 7 to 8 was also unsuccessfull. Undoubtedly, conformational impediments and the high reactivity of the norbornadiene moiety towards radicals and electrophiles lay at the roots of these failures. Finally, we found that addition of the α-(ω-iodoalkyl) esters 9a,b to 2 equiv. of *t*-BuLi at -100°C[8] followed by hydrolysis at -50°C afforded pure 2a and 2b in satisfactory yields (60% and 45%, respectively; eq. 1)[9]:



(1)

Encouraged by these findings a number of other α-(ω-iodoalkyl) esters were subjected to the same reaction conditions. (Table I). Moderate to good yields are obtained for five- and six-membered ring systems (entries 1-5). The conversions of 9a,b into otherwise inaccessible 2a,b demonstrate the power of our method. Unfortunately in cases, where cyclization is expected to proceed more slowly (entries 6 and 7) other processes (e.g. protonation, intermolecular addition) prevail.

Table I Spiro ketones from lithium-iodine exchange[a] of α-(ω-iodoalkyl) esters[10]

Entry	Substrate	Spiro ketone (yield)[b]	Entry	Substrate	Spiro ketone (yield)[b]
1	9a	2a[c] (60)	5		 (66)
2	9b	2b[c] (45)			
3		 [d] (60)	6		– (0)
4		 (67)	7		 (<10[e])

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[a] Reactions were carried out in ether/pentane 2:1. The substrate was added to 2 eq. *t*-BuLi at $-100^{\circ}C$; the reaction mixture was then warmed up to $-50^{\circ}C$ in 45 min. and quenched with sat. NH_4Cl-solution. [b] Isolated yields. [c] Elemental analyses, mass and NMR-data are consonant with the structures assigned. [d] R.R. Sauers, T.R. Henderson, J. Org. Chem. 39, 1850 (1974). [e] Yield determined by GLC.

References and Notes

1) M.P. Cooke Jr. and I.N. Houpis, Tetrahedron Lett. 26, 4987 (1985).

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9) Pure products were obtained after short path distillation and column chromatography to remove minor amounts of side products 9 (X = H, n = 3,4) present in the crude reaction mixtures.

10) The iodides were prepared by alkylation of the esters with the appropriate dibromide (LDA, THF, -60° to $25^{\circ}C$) followed by bromine/iodine exchange (NaI, acetone).

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