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A Convenient Annulation Process Involving a Tandem Alkylation-Michael Addition Sequence

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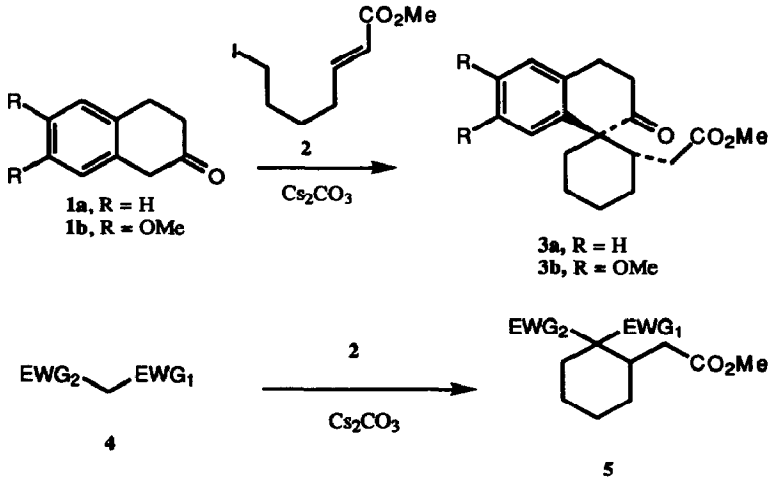
Abstract: *Malonic esters, β-keto-ester and other methylene-active compounds react with the 7-iodo-2-heptenoic acid methyl ester 2 in presence of cesium carbonate to give six-membered ring products 5, through a tandem alkylation-Michael addition reaction.*

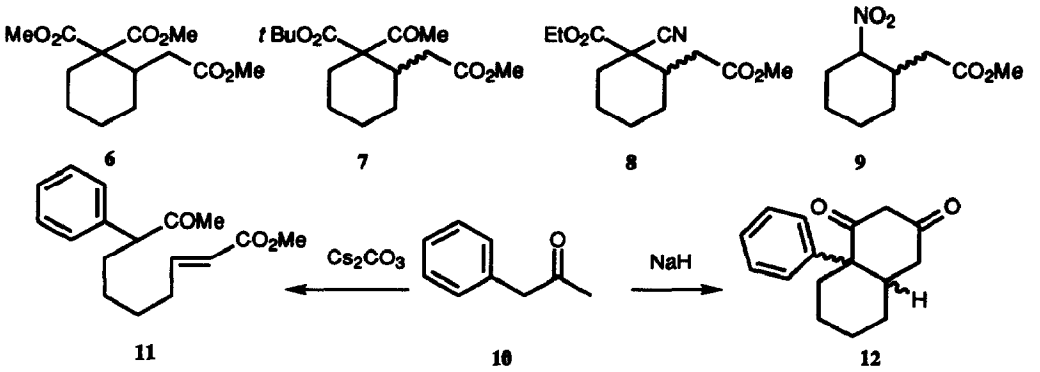
In connection with our efforts directed to the total synthesis of the Homoerythrina alkaloids, we recently reported a new spiroannulation reaction of 2-tetralone derivatives **1** by methyl (*E*)-7-iodo-2-heptenoate **2**, to provide keto-esters **3**, through a "one pot" tandem alkylation-Michael addition sequence.[1] As a further investigation of this useful quaternary carbon center formation, we now wish to report the extension of this reaction into a general synthetic method for the conversion of acidic methylene compounds **4** to six-membered derivatives **5**.



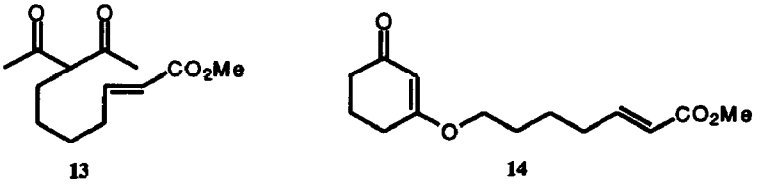
Based on our original findings, cesium carbonate was found to be the most convenient base to induced the cyclization. Thus, treatment of methyl malonate (2 eq.) with methyl (*E*)-7-iodo-2-heptenoate **2**[2] (1 eq.) in presence of cesium carbonate[3] (3 eq., DMF, 20°C, 12 h) afforded triester **6**[4] in 80 % yield. The results obtained

with other nucleophiles are summarized in Table 1. *tert*-Butyl acetoacetate, ethyl cyanoacetate and nitromethane gave similarly adducts **7**[5], **8**[6] and **9** respectively in good yields, as a mixture of diastereomers.

The use of cesium carbonate (3 eq., DMF, 20°C, 12 h) with the less acidic phenylacetone **10** led only to mono-alkylation product **11**; however changing Cs_2CO_3 for sodium hydride (3 eq., THF, 20°C, 12 h) gave diketone **12**, arising from a S_N2-Michael addition sequence, followed by a Claisen-type ring closure.[7]



The behavior of 1,3-diketones was also investigated. Acetylacetone led only to mono-alkylation product **13**; however in contrast to the phenylacetone case, we were unable to induce cyclization of the latter compound. Likewise, 1,3-cyclohexanedione gave a mono-alkylation product, but the process was further thwarted by a competitive O-alkylation reaction giving rise to keto-ester **14**.



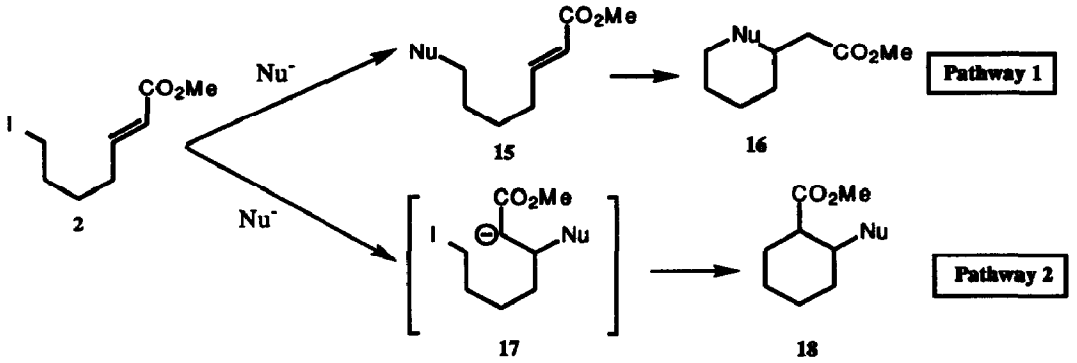
Condensation of 2-tetralone **1a** with iodo-ester **2**, in presence of Cs_2CO_3, gave good yield of spiro-adduct **3a**, however 6,7-dimethoxy-tetralone **1b** afforded keto-ester **3b** with a marking reduced yield (48 %). In order to improve the chemical yield we thought to use of stronger base, namely cesium *tert*-butoxide.[8] The choice of this base was directed considering that the stereochemical issue of the present spiroannulation is closely linked to the template effect of the cesium counterion.

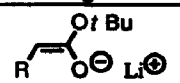
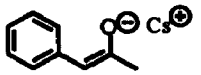
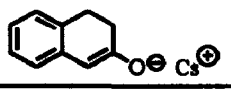
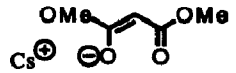
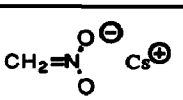
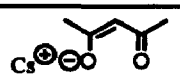
Nucleophile	base / solvant	product	yield, %
Methyl malonate	Cs_2CO_3 / DMF	**6**	80
t-Butyl acetoacetate	Cs_2CO_3 / DMF	**7**	78
Ethyl cyanoacetate	Cs_2CO_3 / DMF	**8**	85
Nitromethane	Cs_2CO_3 / DMF	**9**	65
Phenylacetone **10**	NaH / THF	**12**	52
2-Tetralone **1a**	Cs_2CO_3 / DMF	**3a**	66
1b	*t*BuOCs / *t*BuOH-THF	**3b**	80

Table 1

Thus treatment of **1b** with the ω-iodo-α,β–unsaturated ester **2** in presence of *t*BuOCs in *t*BuOH-THF gave spiro-adduct **3b** as the only diastereomer in 80 % yield. However it should be pointed out that the obtention of this yield required the use of a three-fold excess of **1b**, as a proton source.

We have previously shown that in such an annulation, the S_N2 alkylation occurs first, followed by the intramolecular Michael addition (pathway 1).[1] The same chronology of events as recently been reported for the reaction of neutral hetero-nucleophiles such as thiourea or benzylamine with ω-iodo-esters of type **2**.[9]



Nucleophile	pKa of NuH	Pathway 1 Tandem S_N2-Michael, %	Pathway 2 MIRC reaction, %	References
*i*Pr$_2$NLi	36	0	only	10
	25	0	only	11
	16	91 (S_N2)[a]	9	12
	16	only	0	c
	13	only	0	1
	13	only	0	c
$BnNH_2$	11	only	0	9
	10	only	0	c
	9	S_N2[b]	0	c

a) The Michael addition was not observed in this case. b) product **13** was obtained. c) this work.

Table 2

Such an order of reactivity is noteworthy, since ester enolates or lithium dialkylamides react according to a completely different scenario.[10,11] Indeed with the more basic nucleophiles, the Michael addition occurs in first place, followed by intramolecular halide displacement by the transient enolate **17** (pathway 2). This process usually known as Michael Initiated Ring Closure (MIRC) has received considerable applications for the stereoselective elaboration of five- and six-membered ring compounds.

Because nucleophiles could afford both type of products, it is of some importance to find a simple way to predict the outcome of the reaction of a given nucleophile with ω-iodo-α,β-unsaturated esters **2**.

It appeared that a mere look at the pKa of the nucleophile allows to find which process will take place (table 2). Thus, nucleophiles with a pKa of 16 and lower give S_N2 alkylation or tandem S_N2-Michael addition (depending either one or two acidic hydrogens are available), whereas more basic nucleophiles afford MIRC products.[12] Cyclopentadiene anion with a pKa of 16 is located on the borderline between the two groups, and affords a mixture of products arising of the two processes.[13]

Further efforts are underway to expand the scope of this reaction to functionnalized ω-iodo-α,β-unsaturated esters and to other ring sizes. The possibility to prepare optically active adducts is also currently under investigation.[14]

NOTES AND REFERENCES.

1. Le Dréau, M.-A.; Desmaële, D.; Dumas, F.; d'Angelo, J. *J. Org. Chem.* **1993**, *58*, 2933-2935.
2. Compound **2** was prepared from 2-hydroxy-tetrahydropyrane, by a three step sequence involving: Wittig olefination with $Ph_3P{=}CHCO_2Me$, mesylation, and sodium iodide displacement. The minor amount of (*Z*) α,β-unsaturated ester was removed by chromatography.
3. Cesium carbonate has been previously reported to be a exceptionally valuable reagent to induce intramolecular Michael addition. Deslongchamps, P.; Roy, B. L. *Can. J. Chem.* **1986**, *68*, 2068-2075. Lavallée, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 5117-5118.
4. **6**: Colorless oil, IR (film, cm^{-1}) 1737, 1378; ^1H NMR (200 MHz, $CDCl_3$) δ 3.65(s, 3H), 3.64(s, 3H), 3.58(s, 3H), 2.45(m, 3H), 2.13(dd, J = 12.9, 3.5 Hz, 1H), 1.95-1.18(m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.1(C), 171.9(C), 170.8(C), 58.4(C), 52.4(CH_3), 52.0(CH_3), 51.4(CH_3), 37.9(CH), 36.5(CH_2), 32.0(CH_2), 28.2(CH_2), 24.0(CH_2), 22.4(CH_2).
5. **7**: 3: 1 mixture of two diastereomers: colorless oil, IR (film, cm^{-1}) 1740, 1711; ^{13}C NMR (50 MHz, $CDCl_3$ only the major isomer is described) δ 205.5(C), 173.2(C), 170.8(C), 82.0(C), 64.4(C), 51.5(CH_3), 36.2(CH), 35.0(CH_2), 28.9(CH_2), 27.7(3CH_3), 27.2(CH_2), 26.8(CH_3), 22.3(CH_2), 22.2(CH_2).
6. **8**: 1.5: 1 mixture of two diastereomers: colorless oil, IR (film, cm^{-1}) 2234 (weak), 1743; ^{13}C NMR (50 MHz, $CDCl_3$ only the major isomer is described) δ 171.0(C), 168.2(C), 116.7(C), 62.6(CH_2), 5 1.6 (CH_3), 51.0(C), 38.5(CH), 37.5(CH_2), 34.2(CH_2), 28.4(CH_2), 24.5(CH_2), 21.8(CH_2), 13.8 (CH3)
7. The use of 1.2 eq. of NaH (the theoritical amount assuming a catalytic process for the Michael addition) give compound **12** in low yield.
8. Prepared by reaction of cesium metal with *t*BuOH in THF at 20°C.
9. Bunce, R. A.; Peeples, C. J.; Jones, P. B. *J. Org. Chem.* **1992**, *57*, 1727-1733.
10. Little, R. D.; Dawson, J. R. *Tetrahedron Lett.* **1980**, 2609-2612.
11. Yamaguchi, M.; Tsukamoto, M., Hirao, I. *Tetrahedron Lett.* **1985**, *26*, 1723-1726.
12. The use of a geminate doubly activated Michael acceptor shifts this scale since sodium malonate or *t*BuSLi have been reported to give MIRC type products upon reaction with ω-bromo-alkylidene. malonates. Little, R. D.; Verhé, R; Monte, W. T.; Nugent, S.; Dawson, J. R. *J. Org. Chem.* **1982**, *47*, 362-364.
13. Stille, J. R.; Grubbs, R. H. *J. Org. Chem.* **1989**, *54*, 434-444.
14. Di-*l*-menthyl malonate afforded cyclized product of type **5** ($EWG_1 = EWG_2 = CO_2$Menthyl) in good yield but with a low stereoselectivity.

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