Sequential Free Radical Reactions with Xanthates: Cyclopentane Ring Annulation

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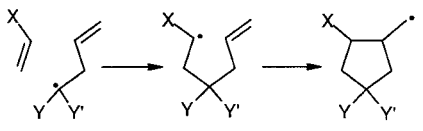
Abstract: In the presence of electron-rich alkenes, electro- and ambiphilic homoallylic radicals, generated by homolytic decomposition of the corresponding xanthates, undergo annulation with inverse electron-demand, and afford cyclopentane derivatives in moderate to good yields.

Free-radical reactions owe a significant part of their increasing popularity in the synthetic community to the possibility of sequencing, i.e. of performing multiple structural transformations via radical intermediates in a one-pot reaction.[1] A particularly useful application of this principle is a free radical annulation which allows for the construction of 5-membered carbocycles by an addition/cyclization tandem, starting from two acyclic, unsaturated fragments, and formally represents a synthetic equivalent of a homopolar 3+2 cycloaddition (Scheme 1).[2] However, due to the inherently nucleophilic character of simple alkyl radicals, sequential reactions of this type have mostly been restricted to electron-rich radicals and electron-deficient alkenes as the reaction partners. Radical additions with inverse electron demand (electron-deficient radicals with electron-rich alkenes) are possible, but incompatible with most widely used (rapid) chain transfer agents, like tributyltin hydride or thiohydroxamic esters: electron-withdrawing substituents at a radical centre stabilise the radical, decelerate intermolecular addition, and favour its direct reaction with a transfer agent instead. Annulations with inverse electron demand have been successfully performed when electrophilic 3-butenyl radicals were generated from vinylcyclopropanes (via the fragmentation of the corresponding cyclopropylmethyl radicals),[3] and also in the reactions of propargyl and allyl α-iodomalonates and malonodinitriles with electron-rich alkenes, under the conditions of iodine transfer, which afforded cyclopentane derivatives in good yields.[4] However, some of the aforementioned radical precursors are unstable and somewhat difficult to prepare and purify. We endeavoured to investigate the alternative methods of generation of carbon radicals for annulation reactions with reversed electronic requirements, using readily available and stable radical precursors, which would also be applicable to monosubstituted radicals. In that respect, group-transfer reactions of xanthates seemed promising.[5]

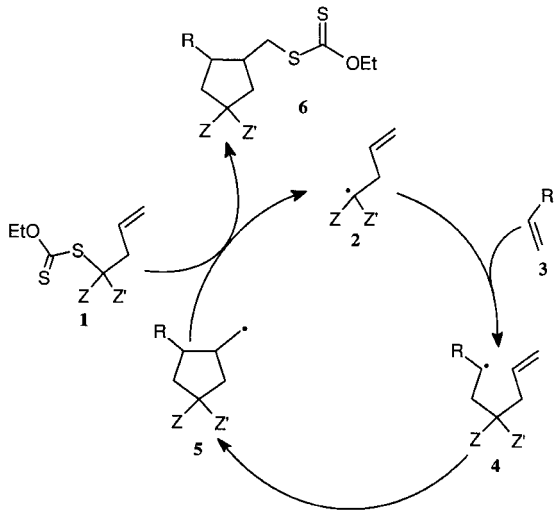


Normal electronic requirements:
X = electron-withdrawing group
Y, Y' = H, alkyl

Reversed electronic requirements:
X = alkyl
Y, Y' = electron-withdrawing group

Scheme 1

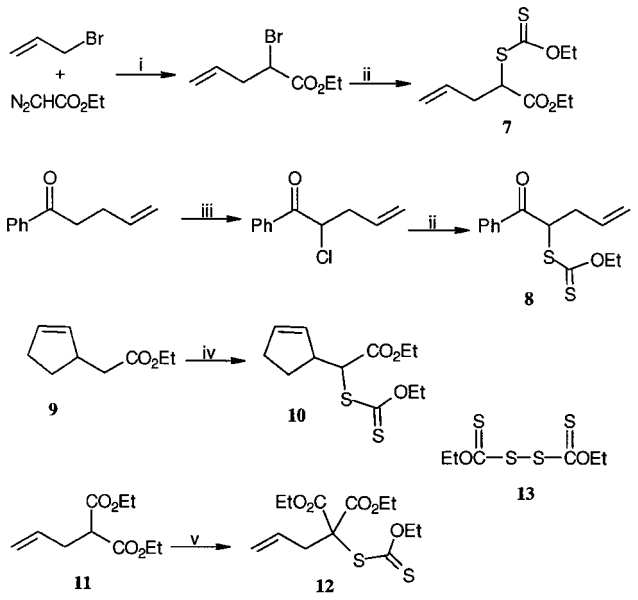
The principle of the envisaged annulation sequence is displayed in Scheme 2. In the presence of electron-rich alkene **3**, electron-deficient initial radical **2**, formed from **1** under homolytic conditions, should undergo addition/cyclization sequence giving rise to cyclopentylmethyl radical **5**. As the final radical **5** is non-stabilized and much more reactive than the initial one **2**, thermodynamically favourable group transfer reaction is expected to proceed efficiently, with the formation of the final product **6**, and regeneration of **2** which continues the chain. Starting compound **1** acts as both the radical precursor and transfer agent. The absence of an external transfer agent is essential for the success of the overall sequence, as the intermolecular addition of stabilized radical **2** is not expected to be very fast; however, the transfer step being reversible and degenerate, it does not compete with the addition, and gives the initial radical **2** long enough life-time to undergo even relatively slow reactions.



Scheme 2

To test the feasibility of this conception, four xanthate precursors, with one or two electron-withdrawing groups at the proradical carbon atom were prepared (Scheme 3). While **7** and **8** were obtained according to previously described methods,[6] ester and malonate xanthate derivatives **10** and **12** were synthesised directly from **9** and **11**, by the reactions of their enolates with diethyl dithiobis(thioformate) **13**.[7] This is a direct way of transforming carbanionic centres into proradical ones, resulting in the "umpolung" of active methylene compounds.

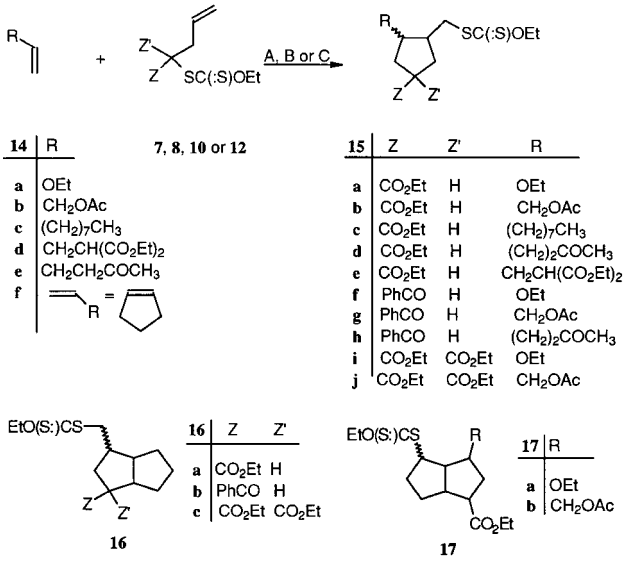
Given the known sensitivity of xanthates to UV light, the first annulation experiment was performed by simply irradiating a deaerated solution of **7** in 5 mol eq of allyl acetate, (in an NMR tube), by a 250 W high pressure mercury lamp (Method A). Under these conditions the consumption of the starting xanthate was complete within 45 min. Purification of the reaction mixture by column chromatography afforded the desired cyclopentane derivative **15b** in 59% isolated yield (Scheme 4, R= CH_2OAc, Z= CO_2Et).[8] The generality of this procedure was then tested by submitting various combinations of xanthate precursors **7**, **8**, **10**, **12**, and alkene acceptors **14a-f** to the same reaction conditions: in all cases cyclopentane derivatives were isolated in moderate to good yields. The results of these experiments are summarised in Table 1. The longest reaction times and the lowest yields were observed when cyclopentene **14f** was used as a radicophilic acceptor, which can be explained by the



i. Cu powder, reflux 4h (71%); ii KSC(:S)OEt, acetone, rt (**7**: 93%. **8**: 62%); iii. a) Me_3SiCl, Et_3N, DMF (78%); b) SO_2Cl_2, ether (85%); iv. a) LDA, THF, -78°C, b) **13**, 0°C (58%); v. a) NaH, DMSO, benzene, b) **13**, rt (50%)

Scheme 3

increased steric hindrance of 1,2-disubstituted alkene (entries 8, 9, 13, and 18). Annulation reactions could also be performed, with comparable efficiency, with chemical initiation (Method B),[9] but cleaner reactions and superior yields were obtained when the reactions were promoted by a visible light irradiation at room temperature (Method C).[10] With respect to radical annulations with normal electronic requirements, two features are of note: a) reactions can be run at high concentrations of reactants; b) no second addition of the final radical **4** to radicophilic alkene occurs (in "standard" annulation procedures preventing this step requires further sophistication of the reaction sequence, through the introduction of β-elimination as the final step, stabilization of the final radical, etc.).



Scheme 4. Radical annulation reactions: reactants and products

Table 1. Radical annulation reactions: conditions and yields

entry	radical precursor	alkene	method	time	product	yield (%)
1	**7**	**14a**	A	45 min	**15a**	50
2	**7**	**14b**	A	45 min	**15b**	59
3	"	"	B	6 h	"	72
4	"	"	C	45 min	"	76
5	**7**	**14c**	A	1 h	**15c**	49
6	**7**	**14e**	A	1 h	**15d**	44
7	**7**	**14d**	A	1 h	**15e**	38
8	**7**	**14f**	A	7 h	**16a**	30
9	"	"	B	10 h	"	38
10	**8**	**14a**	A	1 h	**15f**	46
11	**8**	**14b**	A	45 min	**15g**	64
12	**8**	**14e**	A	45 min	**15h**	53
13	**8**	**14f**	B	10 h	**16b**	17
14	**12**	**14a**	A	90 min	**15i**	50
15	"	"	C	90 min	"	72
16	**12**	**14b**	A	90 min	**15j**	51
17	"	"	B	6 h	"	36
18	**12**	**14f**	C	3 h	**16c**	36
19	**10**	**14b**	A	1 h	**17b**	71
20	**10**	**14a**	C	3 h	**17a**	60

Almost all cyclized products were obtained and isolated as inseparable mixtures of diastereoisomers. However, in some cases it was possible to separate a single diastereoisomer by careful column chromatography, and fully assign all signals in the NMR spectra. The lack of stereoselectivity observed in these reactions reflects the inherent reactivity of the corresponding Δ^6-hexenyl radicals **4**, and it is unlikely that the diastereoselectivity could be significantly improved by changing the reaction conditions. We hoped, however, that the reactions of cyclic precursors and/or cyclic alkene acceptors, leading to the formation of bicyclic frameworks, might proceed with a higher level of stereoselectivity, due to additional conformational constraints in transition states for both cyclization and group-transfer steps.[11] In that respect, it is noteworthy that the reaction of malonate derivative **12** with cyclopentene proceeded with complete stereoselectivity, and afforded a single isomer **16c** (tentatively assigned as "all *cis*")[12] in 30% isolated yield (entry 18). The reaction of **10** with allyl acetate afforded **17b** as a 1:1 mixture of diastereoisomers (entry 19; 8 diastereoisomers with *cis* ring junction are possible); other bicyclic products, however, were obtained as complex mixtures of diastereoisomers. Surprisingly, cyclic xanthate precursor **10** failed to react with cyclopentene, probably due to increased steric hindrance.

To summarise, homoallylic xanthates can serve as synthetically useful precursors of electrophilic alkyl radicals for annulation reactions with inverse electron demand. The ready availability of these compounds, very mild reaction conditions, and the simplicity of the experimental procedure make the described protocol a potentially useful complement to the already known methods for the construction of cyclopentane derivatives.

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8. ^{1}H-NMR: 4.65 (q, J=7 Hz, 2H); 4.2-4.0 (q+m, 4H); 3.5-3.0 (series of m, 2H); 2.82 (app. quint., J=8.8, 1H); 2.55-2.35 (m, 2H); 2.25-2.05 (m, 2H); 2.08 (s, 3H); 1.9-1.7 (m, 2H); 1.42 (t, J=7, 3H); 1.25 (t, J=7.2, 3H); ^{13}C-NMR: 214.5; 175.4; 170.8; 69.8; 64.2; 60.4; 41.9; 40.5; 40.3; 36.6; 34.7; 31.8; 20.8; 14.0; 13.6; IR_{film}: 2980; 1734; 1230; 1113; 1050; MS/CI (isobutane): 349 (M+1); Anal. Calcd. for $C_{15}H_{24}O_5S_2$: C: 51.70; H: 6.94; S: 18.40; Found: C: 51.56; H: 7.00; S: 18.37.

9. **Method B**: A deaerated solution of **7** (250 mg; 1 mmol) and **14f** (680 mg; 10 mmol) in benzene (5 ml) was heated to reflux under an argon atmosphere, while dilauroyl peroxide (20 mg) was added every 2 h. After 10 h the reaction was complete (TLC). The solvent was removed under reduced pressure and the product purified by column chromatography on SiO_2 (eluent: toluene) to afford 121 mg (38%) of **16a** as a light-yellow oil. ^{1}H-NMR: 4.63 (q, J=7, 2H); 4.1 (q, J=7, 2H); 3.24 (dd, J_1=13, J_2=7.2, 1H); 3.11 (dd, J_1=13, J_2=7.8, 1H); 2.77 (m, 1H); 2.6-2.2 (m, 5H); 2.12-2.0 (m, 3H); 1.8-1.62 (m, 3H); 1.42 (t, J=7, 3H); 1.26 (t, J=7, 3H); ^{13}C-NMR: 215.14; 170.18; 69.79; 60.36; 50.26; 47.94; 46.93; 40.19; 37.66; 34.44; 33.82; 27.2; 27.0; 14.27; 13.75; IR_{film}: 2953; 2866; 1729; 1217; 1181; 1051; MS/CI (isobutane): 317 (M+1).

10. **Method C**: In a Pyrex, external water-cooled reactor, a deaerated solution of **12** (180 mg; 0.56 mmol) and **14a** (720 mg; 5.6 mmol) in benzene (0.6 ml) was irradiated for 1.5 h with a 250W xenophot sun-lamp focalized light, with stirring, under an argon atmosphere. After the evaporation of solvent, the product was purified by column chromatography on SiO_2 (eluent: toluene) to afford 148 mg (72%) of **15i** as a light-yellow oil. ^{1}H-NMR: 4.63 (q, J=7.1, 2H); 4.2 (2 x q, 4H); 3.83 (m, 1H); 3.5 (m, 1H); 3.36-3.21 (dd+q, 3H); 2.65 (dd, J_1=14.4, J_2=1.6, 1H); 2.47-2.3 (m, 3H); 2.2 (dd, J_1=14.4, J_2=4.2, 1H); 1.42 (t, J=7, 3H); 1.32-1.21 (2 x t, 6H); 1.12 (t, J=7, 3H); ^{13}C-NMR: 215.2; 172.6; 171.7; 79.8; 69.8; 63.8; 61.6; 61.4; 58.6; 43.2; 38.6; 37.3; 34.7; 15.2; 13.9 (2 x CH_3); 13.7; IR_{film}: 3020; 2982; 1728; 1217; 1159; 1114; MS/CI (isobutane): 393 (M+1); Anal. Calcd. for $C_{17}H_{28}O_6S_2$: C: 52.02; H: 7.19; S: 16.34; Found: C: 52.29; H: 7.30; S: 16.29.

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