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Vicinal alkylation–carboxymethylation of electron-poor alkenes by radical-chain reactions with *O*-alkyl *O*-silyl ketene acetals and their [3+2] annulation by reaction with *O*-cyclopropylcarbinyl *O*-silyl ketene acetals

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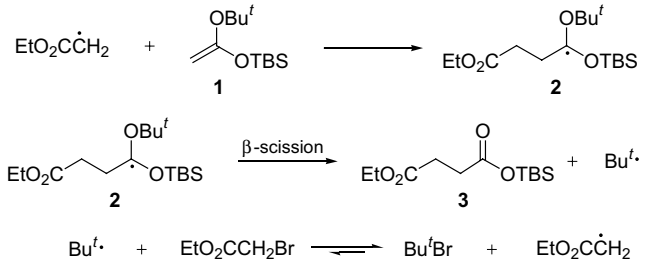
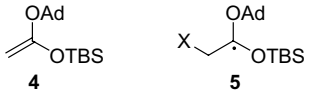
Abstract—*O*-Silyl ketene acetals of the type $H_2C{=}C(OR)OSiMe_2Bu^t$, in which R is a tertiary or secondary alkyl group, react with electron-poor alkenes to bring about vicinal alkylation–carboxymethylation of the latter. When R is a cyclopropyldimethylcarbinyl group such reactions take a more complex course involving ring opening of the cyclopropylcarbinyl radical and lead ultimately to [3+2] annulation of the alkene.

We have reported recently that 1-*tert*-butoxy-1-(*tert*-butyldimethylsiloxy)ethene **1** reacts with α-bromo esters to bring about their α-carboxymethylation.[1] This radical-chain reaction proceeds by the addition–fragmentation mechanism illustrated in Scheme 1 for ethyl bromoacetate and, in order to facilitate product isolation, the initially formed silyl esters are conveniently converted to methyl or ethyl esters by treatment with tetrabutylammonium fluoride (TBAF) and the appropriate alkyl iodide.[2] For example, the reaction of **1** with 2 equiv of ethyl bromoacetate, in refluxing cyclohexane containing 2,4,6-collidine (0.10 equiv) and dilauroyl peroxide (DLP, 0.05 equiv) as initiator, afforded the silyl ester **3** and thence diethyl succinate, which was isolated in 83% yield.



Scheme 1.

Because of the constraints imposed by its caged structure, the geometry at the radical centre in the tertiary 1-adamantyl radical (Ad·) is more strongly pyramidal than that in the *tert*-butyl radical and Ad· often behaves differently from a simple acyclic tertiary alkyl radical. It is generally more reactive and probably more nucleophilic[3] than Bu^t· and Ad–X bonds are stronger than the corresponding Bu^t–X bonds.[4] Therefore, we were led to explore the use of the *O*-adamantyl silyl ketene acetal **4** in place of the *tert*-butyl analogue **1**.[5] Although β-scission of an adduct radical of the type **5** to give Ad· is expected to be slower than cleavage of the corresponding *O*-*tert*-butyl adduct to give Bu^t·,[6] this propagation step may not necessarily be critical in determining the overall rate of the chain reaction, especially at higher temperatures. In the event, the ketene acetal **4** turned out to have increased thermal and hydrolytic stability compared with **1** and its radical reactions with α-bromo carbonyl compounds were found to proceed with somewhat greater facility than the corresponding reactions of **1**.[7]



Simple alkyl radicals are relatively nucleophilic and do not add readily to electron-rich alkenes, such as **1** or **4**,

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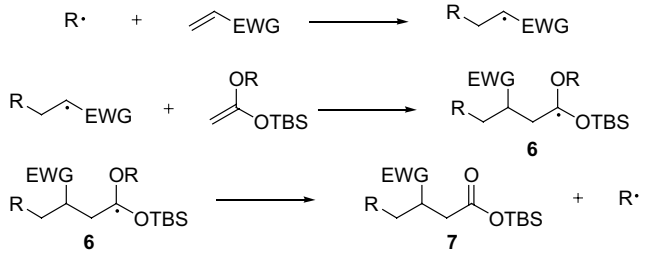
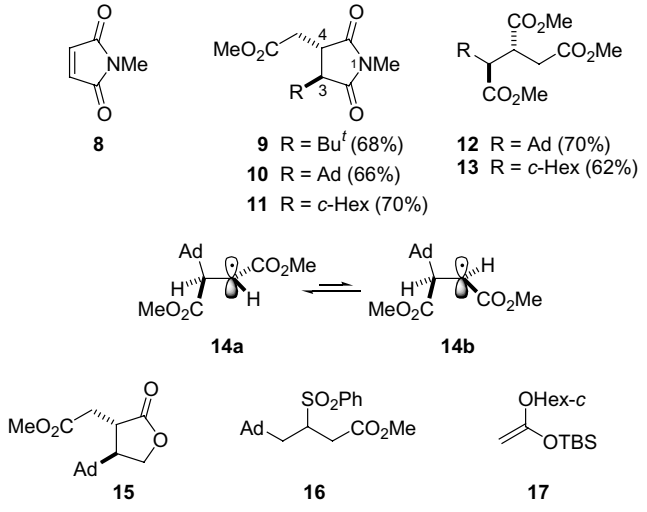
while their addition to electron-poor alkenes is comparatively rapid.[8] Therefore, we reasoned that *O*-*tert*-alkyl *O*-silyl ketene acetals should react with electron-poor alkenes to give compounds of the type **7** via the radical-chain pathway generalised in Scheme 2 (EWG, electron-withdrawing group). We were pleased to find that **1** reacted with *N*-methylmaleimide **8** (NMM, 1.2 equiv) in the manner predicted when heated for 3 h in refluxing benzene containing DLP (0.05 equiv); **4** reacted similarly with NMM in refluxing chlorobenzene using di-*tert*-amyl peroxide[1,9] (DTAP, 0.20 equiv) as initiator.[10] The initially produced silyl esters were converted to the methyl esters **9** and **10**, by treatment with TBAF and methyl iodide,[2] and the *trans* stereochemistry of the products (expected on steric grounds) was confirmed by NOE studies and by single-crystal X-ray diffraction.[11,12] The ketene acetal **4** reacted similarly with dimethyl maleate (1.2 equiv) in refluxing chlorobenzene containing DTAP initiator and the first-formed monosilyl ester was converted to the trimethyl ester, which was isolated in 70% yield as a single diastereoisomer, assumed to be the *anti* isomer **12**.[14] A small amount (ca. 5%) of the *syn* trimethyl ester was detected in the crude reaction product and dimethyl fumarate afforded the same mixture of diastereoisomers in similar yield.[15] This result implies that addition of the 1-adamantyl radical to the maleate or to the fumarate gives an adduct radical **14**, which is conformationally equilibrated before it adds to **4**. On steric and electrostatic grounds, the conformation **14a** should be preferred and this would be expected to add to **4** from its less shielded face *anti* to the bulky adamantyl group,[16] which would lead ultimately to the *anti* diastereoisomer **12** as the major product. The ketene acetal **4** also reacted with 5*H*-furan-2-one or with phenyl vinyl sulfone in refluxing chlorobenzene, using DTAP as initiator, to furnish the methyl esters **15** (61%) and **16** (55%), respectively.

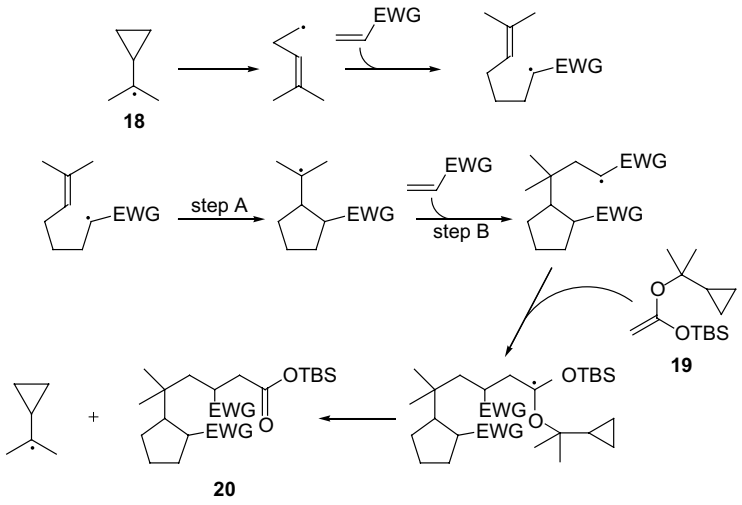


Scheme 2.



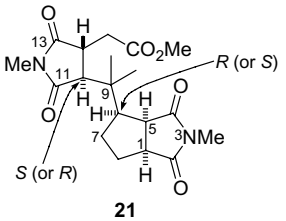
Next, we explored the possibility that *O*-secondary alkyl *O*-silyl ketene acetals, as typified by the *O*-cyclohexyl derivative **17**, might participate in analogous reactions with electron-poor alkenes, especially at relatively high temperature when the β-scission of the radical **6** (Scheme 2) should be sufficiently rapid to maintain the chain. In order to suppress oligomerisation of the alkene, NMM (1.2 equiv) in chlorobenzene was added by syringe pump over 2 h to a refluxing solution of the ketene acetal **17** and DTAP (0.20 equiv) in the same solvent. After heating for a further 2 h, the reaction mixture was worked up to yield the *N*-methylsuccinimide **11** (70%). A similar reaction of **17** with dimethyl fumarate afforded the *anti* trimethyl ester **13** as the major product (62% isolated) along with ca. 10% of the *syn* isomer.[15] The ketene acetal **17** was essentially unchanged after heating for 2.5 h in refluxing chlorobenzene, containing DTAP as initiator but no electron-poor alkene.

Encouraged by these results, we reasoned that the *O*-cyclopropyldimethylcarbinyl *O*-silyl ketene acetal **19** might react with electron-poor alkenes to bring about their [3+2] annulation, according to the mechanism generalised in Scheme 3 and involving the ring opening[17] of the cyclopropylcarbinyl radical **18** as a key step. Polar effects on the rates of radical addition reactions[8] are of crucial importance in directing the course of this complex chain process, which results in the formation of four new C–C bonds. As envisaged, when the ketene acetal **19** was heated for 3 h in refluxing benzene with NMM (2.2 equiv) and DLP (0.05 equiv), an annulated product of the type **20** was indeed formed and this was isolated as the diastereoisomerically pure methyl ester **21**.[18] However, under these conditions significant amounts of by-products analogous to **9**–**11** were formed via trapping by NMM of the undecyl radical (from DLP) and of the cyclopropylcarbinyl radical **18**; some oligomerisation of the NMM also took place. These complications could be minimised by slow addition over 2 h of the NMM (2.2 equiv) in benzene to a refluxing solution of **19** and DLP (0.10 equiv) in the same solvent. Now, the crystalline compound **21** could be isolated in 30% yield and its structure was confirmed by X-ray diffraction.[13] In the reaction of **19** with NMM, the 5-*exo* cyclisation (step A, Scheme 3) preferentially places the exocyclic dimethylcarbinyl radical centre in the *endo* position on the new bicyclic skeleton, in agreement with previous observations.[19] In the next stage of the propagation cycle (step B, Scheme 3), the addition of this tertiary alkyl radical to NMM takes place preferentially to generate a new chiral centre at C-10 with a configuration opposite (according to the Cahn–Ingold–Prelog rules) from that at C-6, which is separated from it by the dimethylcarbinyl group. Addition to form a radical (centred at C-14) in which C-6 and C-10 have the same configuration is predicted by molecular mechanics cal-



Scheme 3.

culations (MMX force field) to be less favourable thermodynamically by 4.5 kJ mol^{-1}.



21

Although the yield of **21** is so far only moderate, this type of metal- and halogen-free reaction is of significant interest in that it involves the formation, in a single pot from two readily obtained starting materials, of a cyclopentane ring and four new C–C bonds in a stereocontrolled manner. Moreover, the highly functionalised molecules that result from these alkylation–carboxymethylation and annulation reactions should be readily amenable to further elaboration, making this chemistry of potential use in the synthesis of complex molecules.

References and notes

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   The ketene acetals **4** and **19** have not been reported previously. Compound **4**: bp 98–100 °C/0.05 mm Hg; NMR (throughout, 500 MHz for ^{1}H, 125.7 MHz for ^{13}C; $CDCl_3$ solvent, *J* in Hz); δ_H 0.19 (6H, s, $SiMe_2$), 0.94 (9H, s, Bu^t), 1.62 (6H, m, Ad), 1.92 (6H, m, Ad), 2.16 (3H, br s, Ad), 3.51(8) (1H, d, *J* 1.1, =CH^AH^B), 3.52(4) (1H, d, *J* 1.1, =CH^AH^B); δ_C −4.8, 18.1, 25.7, 30.9, 36.2, 42.3, 74.6, 77.5, 156.9. Found: C, 69.9; H, 10.6. $C_{18}H_{32}O_2Si$ requires C, 70.1; H, 10.5. Compound **19**: bp 90–92 °C/1.0 mm Hg; δ_H 0.19 (6H, s, $SiMe_2$), 0.38 (4H, m, $2CH_2$), 0.93 (9H, s, Bu^t), 1.11 (1H, m, CH), 1.25 (6H, s, 2Me), 3.47 (1H, d, *J* 1.1, =CH^AH^B), 3.52 (1H, d, *J* 1.1, =CH^AH^B); δ_C −4.9, 1.8, 18.0, 21.0, 25.1, 25.7, 73.3, 79.7, 157.6. Found: C, 65.6; H, 10.9. $C_{14}H_{28}O_2Si$ requires C, 65.6; H, 11.0.
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9. Di-*tert*-butyl peroxide could also be used as initiator, but the yield was lower than with DTAP.
10. Representative procedure: 1-Adamantoxy-1-(*tert*-butyldimethylsiloxy)ethene **4** (616 mg, 2.0 mmol), *N*-methylmaleimide (267 mg, 2.4 mmol), di-*tert*-amyl peroxide (70 mg, 0.40 mmol) and dry chlorobenzene (4 mL) were added to a dry, argon-filled flask, containing a magnetic stirrer bar and equipped with a condenser. The flask was immersed in an oil bath, pre-heated to 140 °C, and the reaction mixture was stirred at reflux under argon for 3 h. The solvent was removed by rotary evaporation and methyl iodide (1.14 g, 8.0 mmol) and dry THF (2 mL) were added to the residue and the resulting solution was cooled in an ice-water bath before addition of tetrabutylammonium fluoride (1 M in THF, 2.2 mL). The solution was stirred at 0 °C for 2 h before saturated aqueous NH_4Cl solution (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3×10 mL), the combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel, using light petroleum (bp 40–60 °C)–diethyl ether–CH_2Cl_2 (16:4:5) as eluent, to give the methyl ester **10** (422 mg, 66%), which was recrystallised from hexane–CH_2Cl_2; mp 115–117 °C; δ_H 1.49 (3H, dd, *J* 12.0 and 1.8, Ad), 1.64 (3H, d, *J* 12.3, Ad), 1.71 (3H, d, *J* 12.3, Ad), 1.83 (3H, dd,

J 12.0 and 1.8, Ad), 2.00 (3H, br s, Ad), 2.21 (1H, d, *J* 4.6, H-3), 2.60 (1H, dd, *J* 17.0 and 4.9, C*H*^{A}H^{B}CO$_2$Me), 2.86 (1H, apparent q, *J* 4.8, H-4), 2.97 (3H, s, NMe), 2.99 (1H, dd, *J* 17.0 and 4.9, CH^{A}*H*^{B}CO$_2$Me), 3.66 (3H, s, OMe); δ_C 24.7, 28.2, 35.2, 35.8, 36.6, 37.4, 39.5, 52.0, 55.7, 171.2, 177.2, 178.4. Found: C, 67.6; H, 7.9; N, 4.4. $C_{18}H_{25}NO_4$ requires C, 67.7; H, 7.9; N, 4.4.

11. The structure of the ethyl ester corresponding to **10** was determined by X-ray diffraction.[13]
12. *N*-Phenylmaleimide reacted similarly with **1** in refluxing benzene to afford the *N*-phenylsuccinimide corresponding to **9** in 71% yield.
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14. We have not yet succeeded in obtaining crystals of **12** suitable for structure determination by X-ray diffraction. For a report of related radical reactions of an *O*-tributylstannyl enolate, in which similar stereochemical presumptions were made, see: Miura, K.; Fujisawa, N.; Saito, H.; Wang, D.; Hosomi, A. *Org. Lett.* **2001**, *3*, 2591–2594.
15. The *syn* isomers of **12** and **13** eluted after the *anti* compounds and were difficult to obtain pure; they were also contaminated with the corresponding adduct resulting from trapping of the ethyl radical (arising from the DTAP initiator). Identification of the *syn* isomers is based on comparison of their NMR spectra with those of **12** and **13**.
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18. Compound **21**: mp 182–184 °C (from hexane–CH_2Cl_2); δ_H 0.85 (3H, s, CMe), 0.89 (3H, s, CMe), 1.21 (1H, m, H-7A), 1.72 (1H, m, H-7B), 1.85 (1H, m, H-8A), 2.23 (1H, dd, *J* 13.0 and 6.1, H-8B), 2.78 (1H, dd, *J* 17.0 and 5.2, C*H*^{A}H^{B}CO$_2$Me), 2.82 (1H, apparent q, *J* 4.6, H-14), 2.87 (1H, m, H-6), 2.96 (3H, s, NMe), 3.01 (3H, s, NMe), 3.13 (1H, dd, *J* 17.0 and 3.6, CH^{A}*H*^{B}CO$_2$Me), 3.23 (1H, apparent t, *J* 8.7, H-1), 3.56 (1H, apparent t, *J* 8.4, H-5), 3.72 (3H, s, OMe), 4.09 (1H, d, *J* 4.9, H-10); δ_C 20.1, 24.4, 24.8, 25.1, 25.3, 28.4, 34.4, 36.8, 38.9, 45.3, 45.7, 50.3, 52.0, 53.2, 171.6, 178.6, 178.7, 180.1, 180.2. Found: C, 60.3; H, 6.9; N, 7.3. $C_{19}H_{26}N_2O_6$ requires C, 60.3; H, 6.9; N, 7.4.
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