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An expedient approach to allenes and polycyclic structures using propargyl radicals

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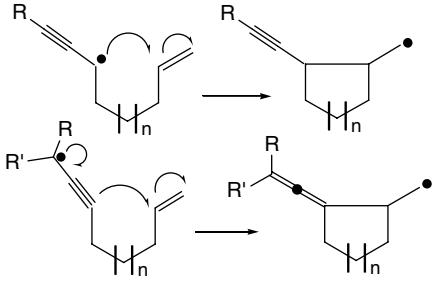
Abstract—A general approach to the synthesis of allenes and polycyclic structures has been developed, based on the addition of a xanthate to an enyne followed by ring-closure of the allenyl radical on to an internal olefin.

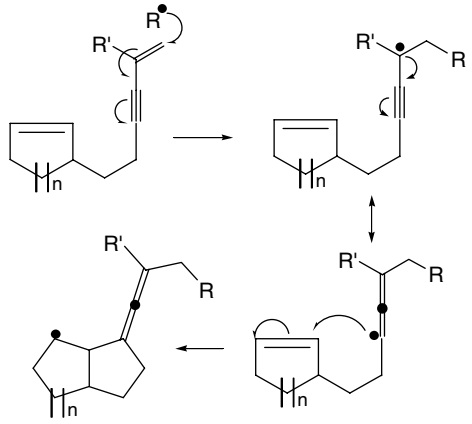
Propargyl radicals (or allenyl radicals, depending on which canonical form is drawn) have rarely been applied in organic synthesis, despite the popularity of radical based synthetic methods.[1] The underlying causes for such neglect may be linked to the relatively unknown nature of such species[2] and to the lack of convenient methods for generating them.

There are two methods for capturing a propargyl radical as outlined in Scheme 1. The first approach, which allows the introduction of an alkyne group, is of significant synthetic interest in view of the importance and richness of acetylene chemistry.[3] In the second, cyclisation of the allenyl radical provides the allene. Only four examples of the latter variation have been recorded, a few years ago, by Blechert and co-workers.[4] Furthermore, it was observed that an activated olefin was necessary for good yields, otherwise capture of the rather unreactive propargyl radical was very inefficient. The propargyl radical was generated from the corresponding bromide using stannyl radicals. One of the main limitations of this route is the tendency of stannyl radicals to add to terminal alkynes. In this letter, a new strategy for generating and capturing propargyl radicals by exploiting the advantages of the radical chemistry of xanthates is presented. Thus addition to an enyne would give a propargyl radical, which can cyclise to give the allene (Scheme 2).

The possibility of using an intermolecular addition in the first step, allows the introduction of different functionalities from various starting xanthates. Enynes systems **4**, **20** and **8**, which derive from (±)-isophorol and



Scheme 1. Different reactivities of propargyl radicals.



Scheme 2. Formation of an allene by a radical cascade.

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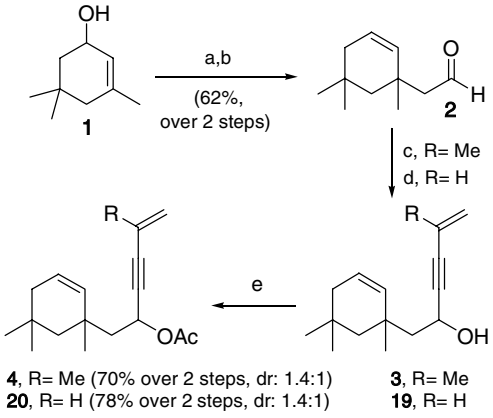
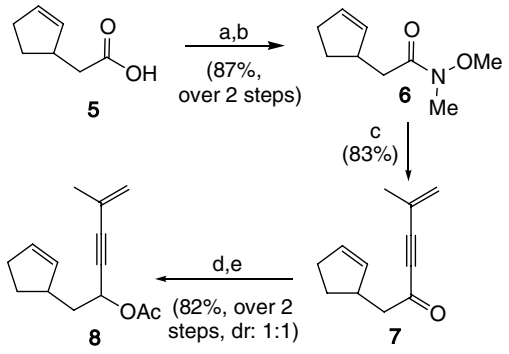


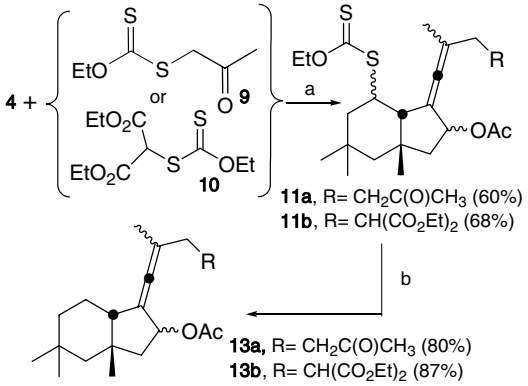
Scheme 3. Reagents and conditions: (a) butyl vinyl ether, $Hg(OAc)_2$, Δ, 18 h; (b) sealed tube, 215 °C, 45 min; (c) 2-methyl-1-buten-3-yne, *n*-BuLi, THF, −78 °C, 3 h; (d) 3-buten-1-yne, *n*-BuLi, THF, −78 °C, 3 h; (e) Ac_2O, DMAP, CH_2Cl_2, 0 °C, 2 h.

cyclopent-2-enyl-acetic acid, respectively, were chosen as model substrates. Treatment of (±)-isophorol **1** with butyl vinyl ether in the presence of mercuric acetate furnished the corresponding allyl vinyl ether, which was heated at 215 °C for 45 min in a sealed tube to afford aldehyde **2** by a Claisen rearrangement.[5] Treatment of the aldehyde with *n*-BuLi and either 2-methyl-1-buten-3-yne[6] or 3-buten-1-yne[7] furnished alcohols **3** and **19**, respectively. These were acetylated with acetic anhydride to afford compounds **4** and **20** in good overall yield (Scheme 3).

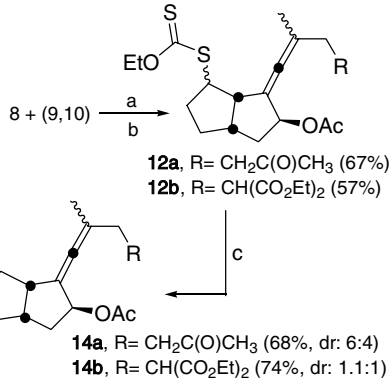
Successive treatment of cyclopent-2-enyl-acetic acid with oxalyl chloride and then with *N*,*O*-dimethylhydroxylamine hydrochloride afforded the corresponding Weinreb amide **6**.[8] Exposure of this amide to the action of *n*-BuLi and 2-methyl-1-buten-3-yne furnished ketone **7**, which was reduced to the alcohol with sodium borohydride and acetylated with acetic anhydride to afford finally compound **8** in good overall yield (Scheme 4). The reduction was undertaken to allow a more direct comparison with substrates **4** and **20**, but compound **7** is also an interesting partner for the radical sequence.



Scheme 4. Reagents and conditions: (a) oxalyl chloride, DMF, 0 °C, CH_2Cl_2, 1.5 h; (b) HN(OMe)Me·HCl, py, CH_2Cl_2, 0 °C, 3 h; (c) 2-methyl-1-buten-3-yne, *n*-BuLi, THF, −78 °C, 3 h; (d) $NaBH_4$, MeOH, 0 °C, 2 h; (e) Ac_2O, DMAP, CH_2Cl_2, 0 °C, 2 h.



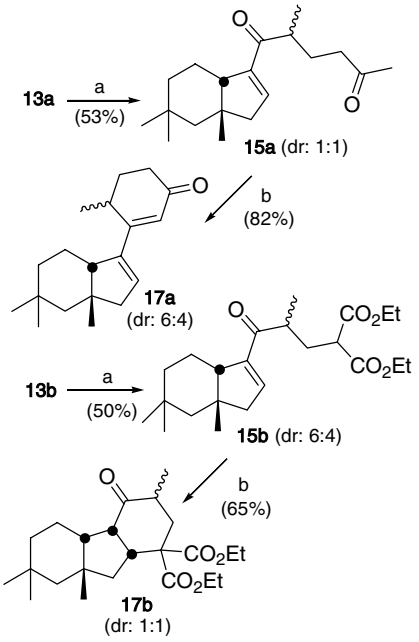
Scheme 5. Reagents and conditions: (a) lauroyl peroxide (DLP, 0.15 equiv/0.3 equiv), Δ, 1,2-dichloroethane; (b) nBu_3SnH, AIBN, PhMe, 100 °C, 1.5 h.



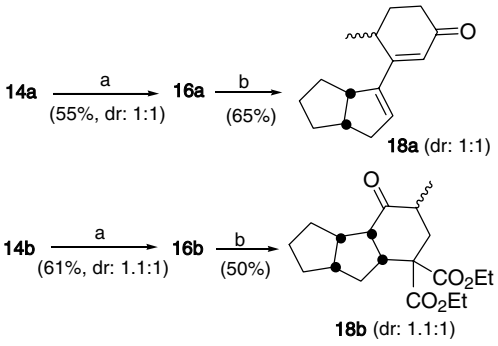
Scheme 6. Reagents and conditions: (a) xanthate **9**, lauroyl peroxide (DLP, 0.1 equiv), Δ, 1,2-dichloroethane; (b) xanthate **10**, lauroyl peroxide (DLP, 0.3 equiv), Δ, 1,2-dichloroethane; (c) nBu_3SnH, AIBN, PhMe, 100 °C, 1.5 h.

We were pleased to observe that enynes **4** and **8** successfully underwent the envisaged radical sequence of addition/cyclisation with α-xanthyl ketone **9** and α-xanthyl malonate **10**. These radical transformations led to the formation of *cis*-fused bicyclic compounds, **11a**,**b** and **12a**,**b**, respectively, as mixtures of diastereoisomers (Schemes 5 and 6). The xanthate function of allenes **11a**,**b** and **12a**,**b** was reductively removed with nBu_3SnH furnishing, respectively, **13a**,**b** and **14a**,**b** in good yields.

Heating allenes **13a**,**b** and **14a**,**b** in refluxing aqueous acetic acid caused their rearrangement to α,β-unsaturated ketones **15a**,**b** and **16a**,**b**, isolated as mixtures of diastereoisomers in moderate yields (trifluoroacetic acid and formic acid were tested but the best results were obtained with a mixture of acetic acid/water). Exposure of these ketones to DBU in methanol furnished the tricyclic structures **17a**,**b** and **18a**,**b**, respectively (Schemes 7 and 8) in an useful overall yield. Thus, the ketone adduct underwent a Robinson annelation whereas the malonate derivative could only evolve by a Michael addition to give a fused tricyclic structure. The relative stereochemistry was determined by NMR analysis (NOESY experiments).



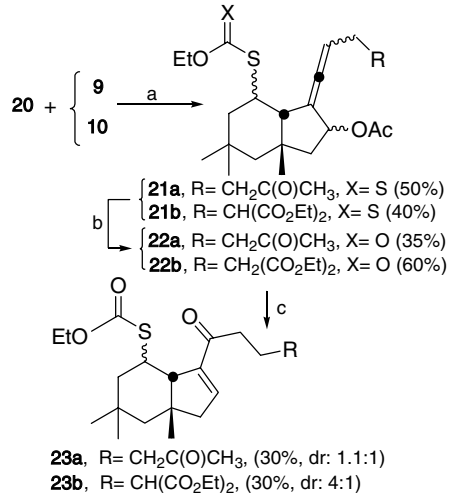
Scheme 7. Reagents and conditions: (a) $AcOH/H_2O$, Δ, 1.5 h; (b) DBU, MeOH/EtOH, Δ, 5 h.



Scheme 8. Reagents and conditions: (a) $AcOH/H_2O$, Δ, 1.5 h; (b) DBU, MeOH/EtOH, Δ, 5 h.

Enyne **20** underwent radical addition/cyclisation with xanthates **9** and **10**, to afford *cis*-fused bicyclic compounds **21a**,**b**, respectively (Scheme 9), as mixtures of diastereoisomers. Surprisingly, the xanthate group could not be cleanly reduced with stannane, presumably because of side reactions involving addition of stannyl radicals to the less substituted allene group.[9] Xanthates **21a**,**b** were therefore converted in moderate yield into thiocarbonates **22a**,**b** by oxidation of the thiocarbonyl group using phenylselenic acid.[10] Rearrangement by refluxing in a mixture of acetic acid/water afforded the desired α,β-unsaturated ketones, **23a**,**b** as a mixture of diastereoisomers. The yield was poor due to the formation of several unidentified side products.

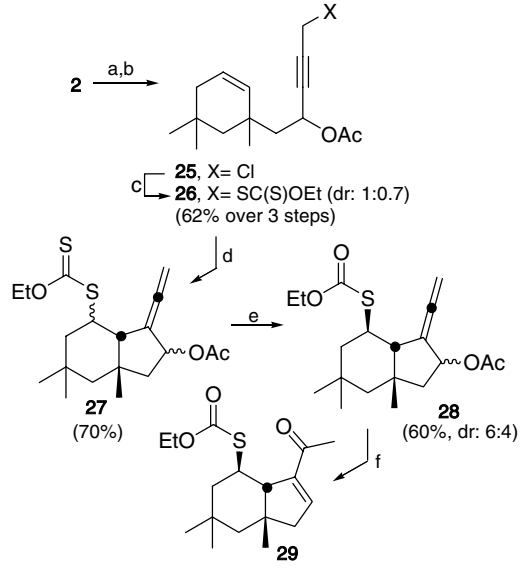
It was also possible to generate the desired propargyl radical by directly placing the xanthate in a propargyl position. Thus, successive treatment of aldehyde **2** with propargyl chloride/*n*BuLi and then acetic anhydride afforded compound **25**. Displacement of the chloride by reaction with the potassium salt of xanthic acid gave



Scheme 9. Reagents and conditions: (a) lauroyl peroxide (DLP, 0.15 equiv), Δ, 1,2-dichloroethane; (b) $PhSeO_2H$, THF, rt, 2 h; (c) $AcOH/H_2O$, Δ, 5 h.

compound **26**, which underwent intramolecular cyclisation to afford *cis*-fused bicyclic compound **27** as a mixture of diastereoisomers (Scheme 10). As in the case of compounds **21a**,**b**, the xanthate was oxidised with phenylselenic acid into thiocarbonate **28**. Rearrangement under acidic conditions afforded an inseparable mixture of the desired α,β-unsaturated ketone **29** and various impurities in undetermined but poor yield. The formation of these unidentified products might be the result of the fragility of the unsubstituted allene function under the conditions employed.

Other methods to rearrange cleanly the various allenes obtained into α,β-unsaturated ketones or other useful



Scheme 10. Reagents and conditions: (a) propargyl chloride, *n*-BuLi, THF, −78 °C, 3 h; (b) Ac_2O, DMAP, CH_2Cl_2, 0 °C, 2 h; (c) potassium salt of xanthic acid, CH_3CN, rt, 2 h; (d) lauroyl peroxide (DLP, 0.3 equiv), Δ, 1,2-dichloroethane; (e) $PhSeO_2H$, THF, rt, 2 h; (f) $AcOH/H_2O$, Δ, 1.5 h.

groups using transition metal based reagents[11] are currently under study.

In summary, these preliminary model studies demonstrate the feasibility and flexibility of the strategy for the synthesis of variously substituted allenes and polycyclic structures. Various combinations of rings can be constructed by modifying either the xanthate or the substrates. It is worth noting that in contrast to the earlier observations of Blechert and co-workers, there is no need for an activated olefin to capture efficiently the propargyl radicals.

Acknowledgements

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