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New cascade reactions starting from acetylenic ω-ketoesters: an easy access to electrophilic allenes and to 1,3-bridgehead ketones

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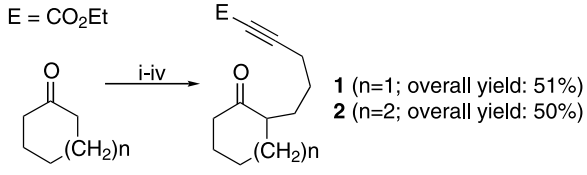
Abstract—Acetylenic ω-ketoesters bearing a three carbon–carbon bond spacer reacted smoothly with tetra-*n*-butylammonium fluoride and with potassium *tert*-butoxide to afford either electrophilic allenes or 1,3-bridgehead ketones, the latter being potentially useful molecules for the synthesis of biologically active compounds like Garsubellin A and Hispidospermidin.

The emergence of complex polycyclic natural products induces new challenges in organic synthesis. One of them is the development of new cascade reactions which enables a very fast access to complex molecules starting from easily available compounds. In this context, we recently reported that acetylenic ω-ketoesters bearing a four carbon–carbon bond spacer arm located between the cycloalkanone moiety and the electrophilic triple bond led either to electrophilic allenes or to electrophilic oxetanes depending on whether tetra-*n*-butylammonium fluoride (TBAF) or potassium *tert*-butoxide (*t*-BuOK) was used as a base.[1]

To further extend the utility of our cascade reactions, we focused our attention on the influence of the spacer length. For that purpose, the acetylenic ω-ketoesters **1** and **2** bearing a three carbon–carbon bond spacer were synthesized starting, respectively, from the corresponding cycloalkanones. After formation of the *N*,*N*-dimethylhydrazones and subsequent treatment with *n*-BuLi,[2] the addition of 5-iodopentyne[3] followed by an acidic hydrolysis yielded the corresponding ketones which were protected as dioxolanes. The latter were treated with *n*-BuLi and the acetylides were quenched with ethyl chloroformate followed by an acidic deprotection to afford the desired acetylenic ω-ketoesters **1** and **2** (Scheme 1).

When the acetylenic ω-ketoesters **1** and **2** were treated with TBAF, the reaction proceeded smoothly. Indeed, the allene derivatives **3** and **4** bearing a *cis* ring junction were isolated as major compounds[4] along with the spiro derivatives **5** and **6** as minor products.[5] In all cases, starting material was recovered and the increase of the reaction time led only to the formation of several unidentified side products. These results proved to be in good accordance with our previously reported observations (Scheme 2).[1]

However, when the acetylenic ω-ketoesters **1** and **2** were reacted with *t*-BuOK in THF, we never observed the formation of oxetane derivatives as previously.[1] Indeed, a new cascade reaction took place leading respectively to the tricyclic derivative **7** along with the diester **8** and to the tricyclic compound **9**. It has to be noted that the reaction occured very cleanly: indeed, according to TLC analysis, no other products were formed except the diester **8** (Scheme 3).



Scheme 1. *Reagents and conditions*: (i) $(CH_3)_2NNH_2$, CF_3COOH cat., C_6H_6 reflux; (ii) *n*-BuLi, THF, −5°C, 5-iodopentyne; (iii) diethyleneglycol, *p*TsOH cat., C_6H_6, reflux; (iv) *n*-BuLi, THF, −78°C, $ClCO_2Et$, HCl 10%.

Keywords: tetra-*n*-butylammonium fluoride; potassium *tert*-butoxide; intramolecular Michael addition; acetylenic ω-ketoesters; allenes; 1,3-bridgehead ketones.

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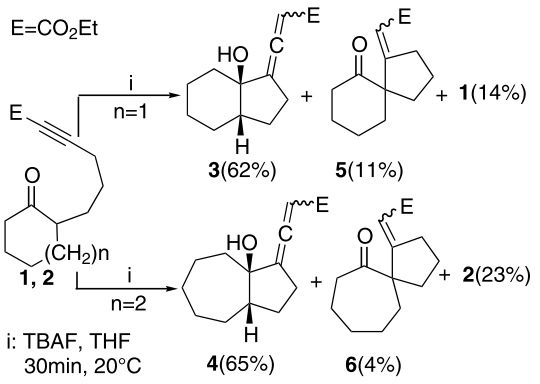
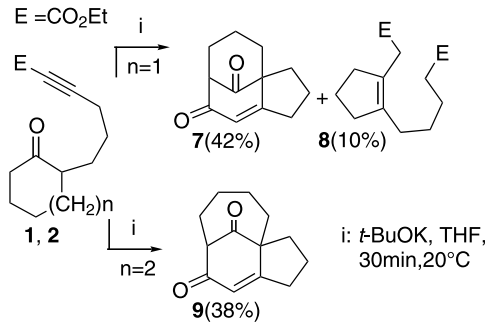
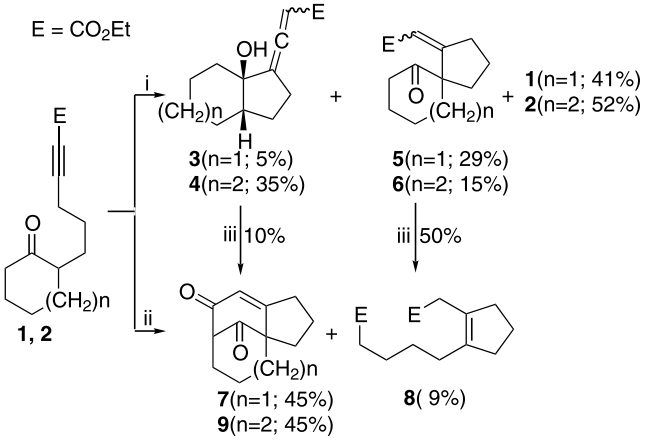


Scheme 2.



Scheme 3.

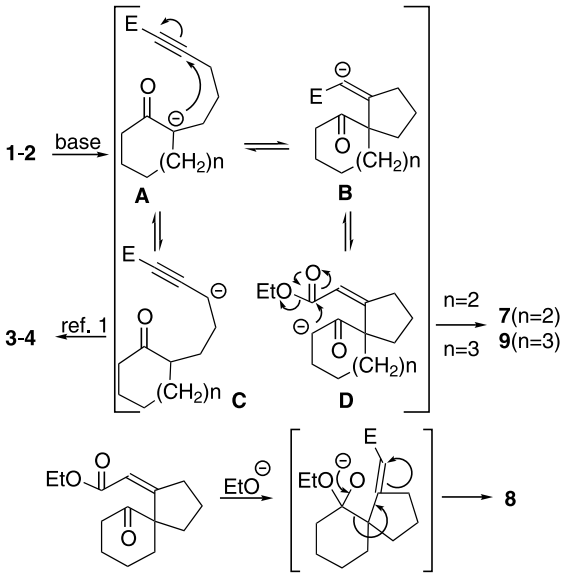


Scheme 4. *Reagents and conditions*: (i) *t*-BuOK, THF, −78°C, 30 min; (ii) *t*-BuOK, THF, 50°C, 30 min; (iii) *t*-BuOK, THF, 20°C, 30 min.

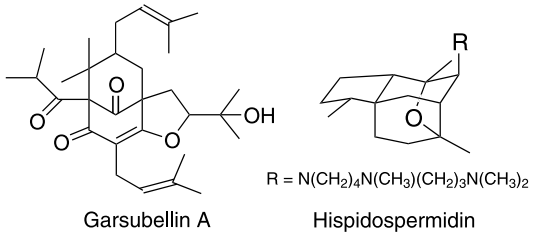
In order to increase the yield of the tricyclic derivatives **7** and **9**, a lot of different reaction conditions were tested. Thus, we observed that no tricyclic derivatives were formed when the reaction was carried out at −78°C. On the contrary, either the spiro derivative **5** or the allene **4** was isolated as major product, this being probably due to subtle conformation change. However, the tricyclic derivatives **7** and **9** were isolated as major products in 45% yield when the *t*-BuOK reaction was carried out at 50°C. On the other hand, when allene **3** was subjected to *t*-BuOK in THF at room temperature, a complex reaction mixture was obtained from which the tricyclic derivative **7** was isolated in 10% yield. Under the same reaction conditions, the spiro derivative **5** afforded diester **8**[6] as a major compound (Scheme 4).

Thus, the formation of these compounds could be explained as follows: the addition of *t*-BuOK to the acetylenic ω-ketoester **1** (**2**) could lead to carbanion A which evolves via an intramolecular Michaël addition toward carbanion B which is in equilibrium with carbanion D. The latter could then cyclize intramolecularly (Claisen condensation) to give the bridgehead ketone **7** (**9**). During that process, ethylate is formed and adds to the carbonyl group of the spiroketone to give E which evolves by a fragmentation reaction to afford the diester **8**. Of course, carbanion C could also be formed (either via an intra or intermolecular process) to afford the allene derivatives **3** (**4**) (Scheme 5).

So, the shortening of the tether between the reacting centers had virtually no effect on the TBAF catalyzed reaction. However, the *t*-BuOK reaction led to interesting tricyclic derivatives **7** and **9** isolated in 45% yield: these yields proved to be modest but one has to recall that not only the starting material are readily available but also that these reactions are very 'clean' reactions.[7] On the other hand, these polycyclic ring systems could be considered as useful molecules and potentially uti-



Scheme 5.



Scheme 6.

lized for the synthesis of biologically active natural products and analogs like for example Garsubellin A[8] and Hispidospermidin[9] which are respectively a potential Alzheimer's therapeutic and a potent inhibitor of phospholipase C (Scheme 6).

The scope and limitations of these cascade reactions as well as some applications, especially the development of new synthetic route toward Garsubellin A and Hispidospermidin are currently being further investigated and the results will be disclosed in the near further.

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3. Barbier, M.; Hügel, M. F. *Bull. Chem. Soc. Fr.* **1961**, *60*, 1324–1326.
4. Yields referred to isolated compounds. Allenes **3** and **4** were isolated as a mixture of *cis* isomers [**3**: 1 (less polar)/0.35 (most polar); **4**: 2.6 (less polar)/1 (most polar)]. Analytically pure isomers were obtained by successive medium pressure column chromatography.
5. The spiro derivatives **5** and **6** were, respectively, isolated as a single isomer and as a mixture of isomers (ratio: 2.6/1).
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7. Selected spectroscopic data: Allene **4**: less polar isomer; white crystals; mp 56–57°C; IR (CCl_4): 1962, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, $J=7.1$ Hz, 3H), 1.30–2.00 (m, 12H), 2.05–2.15 (m, 2H), 2.50–2.65 (m, 2H), 4.13 (ABX_3, $J_{AB}=10.8$ Hz, $J_{AX}=7.1$ Hz, $J_{BX}=7.3$ Hz, $\delta_A=4.10$, $\delta_B=4.17$, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.2, 22.9, 28.5, 28.8, 30.7, 31.7, 32.8, 38.8, 52.8, 60.6, 86.4, 90.8, 116.8, 166.0, 207.4.
   Allene **4**: most polar isomer; yellow oil; IR (CCl_4): 1960, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, $J=7.1$ Hz, 3H), 1.35–2.00 (m, 12H), 2.10–2.25 (m, 2H), 2.45–2.80 (m, 2H), 4.16 (q, $J=7.1$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.2, 22.9, 28.5, 28.7, 30.8, 31.9, 33.1, 38.7, 52.5, 60.8, 86.1, 91.0, 118.0, 166.4, 207.0.
   Spiro derivative **5**: isomer A, yellow oil; IR (CCl_4): 1709, 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, $J=7.1$ Hz, 3H), 1.50–1.90 (m, 8H), 1.95–2.15 (m, 2H), 2.25–2.65 (m, 2H), 2.90 (ddd, $J=2.5$ Hz, 6.7 Hz, 7.7 Hz, 2H), 4.14 (q, $J=7.3$ Hz, 2H), 5.67 (t, $J=2.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.3, 22.1, 22.8, 26.8, 33.0, 37.4, 38.1, 39.1, 59.6, 63.4, 114.3, 166.7, 168.3, 211.1. Spiro derivative **5**: isomer B, yellow oil; IR (CCl_4): 1739, 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, $J=7.1$ Hz, 3H), 1.50–2.15 (m, 8H), 2.20–2.50 (m, 4H), 3.04 (ABXYZ, $J_{A(B,\ C)X}=J_{A(B,\ C)Y}=J_{A(B,\ C)Z}=2.0$ Hz, $\delta_A=3.18$, $\delta_B=2.90$, 2H), 5.77 (h, $J=3.5$ Hz, 2.3 Hz, 1.5 Hz, 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 22.1, 26.4, 29.7, 34.4, 35.6, 35.8, 39.7, 60.5, 64.6, 130.3, 138.2, 171.7, 213.2.
   Diester **8**: colorless oil; IR (CCl_4): 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, $J=7.1$ Hz, 3H), 1.23 (t, $J=7.1$ Hz, 3H), 1.40 (q, $J=7.7$ Hz, 2H), 1.57 (quint, $J=15.9$ Hz, 7.6 Hz, 7.3 Hz, 2H), 1.77 (quint, $J=15.0$ Hz, 7.8 Hz, 7.5 Hz, 2H), 2.07 (t, $J=7.5$ Hz, 2H), 2.27 (t, $J=7.5$ Hz, 4H), 2.30–2.40 (m, 2H), 3.05 (s, 2H), 4.09 (q, $J=6.9$ Hz, 2H), 4.10 (q, $J=7.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.2, 14.3, 21.6, 25.0, 27.4, 28.1, 34.2, 34.4, 35.5, 36.3, 60.1, 60.4, 128.1, 139.3, 171.5, 173.6.
   Tricycle **9**: yellow crystals mp 45–46°C; IR (CCl_4): 1721, 1669 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.10–1.65 (m, 8H), 1.65–1.85 (m, 2H), 1.90–2.10 (m, 4H), 3.00–3.10 (m, 1H), 6.12 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.4, 23.1, 25.7, 28.2, 30.7, 33.9, 39.6, 57.9, 60.5, 123.0, 171.4, 201.0, 208.8.
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