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Intramolecular alkynylogous Mukaiyama aldol type reaction mediated by TBSOTf/NEt_3

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ABSTRACT

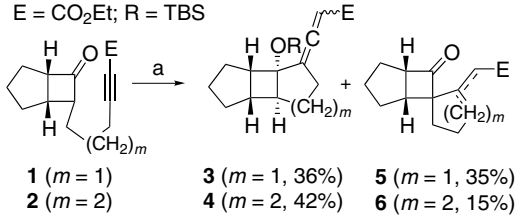
The treatment of propargylic esters tethered to bicyclo[3.2.0]heptanone, 2-methylindanone, 2-methyltetralone, or 2-methylsuberone led to fused tricyclic allenoates by an intramolecular alkynylogous Mukaiyama aldol type reaction promoted by TBSOTf/NEt_3, the key intermediates being silylalkynylketene acetals.

The aldol type reaction is a very efficient methodology for the construction of polyfunctionalized polycyclic compounds.[1] In general, aldehydes and ketones are reacting partners; however, the aldol type reaction was also extended to several other substrates. For example, the reaction of allenic esters with aldehydes in the presence of a base,[2] the reaction of ketene silyl acetals with aldehydes and ketones[3] as well as vinylogous aldol reactions[4] have been extensively studied. Very recently, an intermolecular alkynylogous aldol reaction was reported.[5] These results prompted us to report the first intramolecular alkynylogous Mukaiyama aldol type reactions, which take place under very smooth reaction conditions. The key intermediates are silylalkynylketene acetals generated in situ. Thus, polyfunctionalized allenic esters resulting from a dual activation of the starting acetylenic ω-ketoesters can be readily obtained with total diastereoselectivity for the ring junction.

Being currently involved in a program dealing with the synthesis of natural products bearing either a 5-4-5 tricyclic skeleton (Spatane family)[6] or an aromatic ring fused to a diquinane (Ar-5-5),[7] a hydrindane (Ar-5-6 or Ar-6-5),[8] or a decaline (Ar-6-6)[9] ring systems, we first studied the reactivity of acetylenic esters tethered to bicyclo[3.2.0]heptanones **1** and **2** toward Lewis acids like TBSOTf. The addition of excess TBSOTf to the latter in the presence of an excess NEt_3 afforded a mixture of two easily separable compounds: the tricyclic allenic esters **3** and **4**, respectively, isolated in 36% and 42% yield along with the spiroketoesters **5** and **6**, respectively, isolated in 35% and 15% yield. No trace of the corresponding silyl enol ether nor products resulting from a Michael-aldol reaction were observed[10] (Scheme 1).

To improve the yield of the tricyclic derivatives, compound **7** bearing a quaternary stereocenter in position 7 was chosen as the starting material. However, when TBSOTf/NEt_3 was added to **7**, the yield of the desired tricyclic allenic ester **8** was not improved. Amazingly, the strained tricyclic derivative **9** was isolated in 30% yield[10] (Scheme 2).

The formation of compounds **3**–**9** could be explained as follows: The addition of TBSOTf promotes the formation of the corresponding silyl enol ethers, which undergo an intramolecular Michael addition to the electrophilic triple bond yielding spiroketoesters **5**, **6**, and **9**. The formation of the α-allenic esters **3**, **4**, and **8** could result from a cascade reaction as follows: it is reasonable to state that the propargylic ester is in equilibrium with the allenic ester under our reaction conditions (NEt_3/TBSOTf). A 'first' TBSOTf activation of the allenic ester, in the presence of NEt_3, led to the silylalkynylketene acetal **A**. An intramolecular alkynylogous



Scheme 1. Reagents and condition: (a) TBSOTf, NEt_3, CH_2Cl_2 25 °C.

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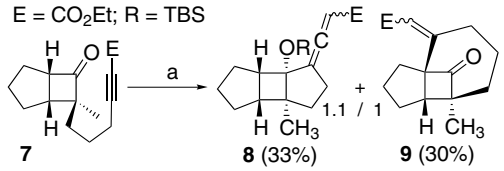
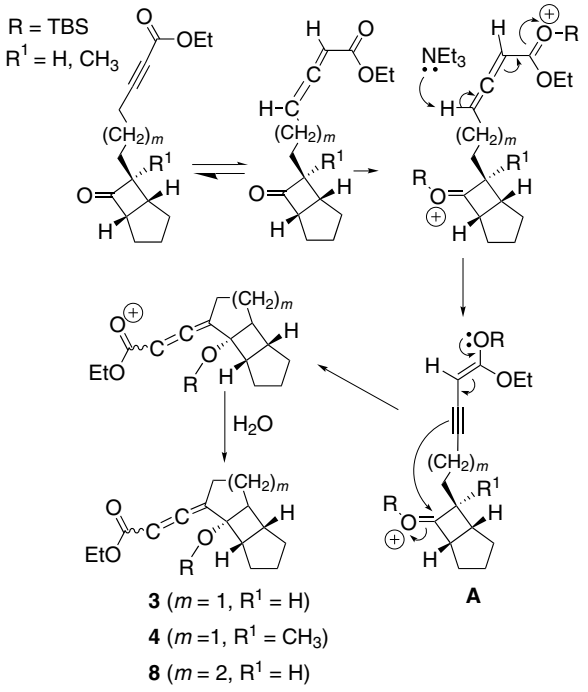


Scheme 2. Reagents and conditions: (a) TBSOTf, NEt_3, CH_2Cl_2, 25 °C.

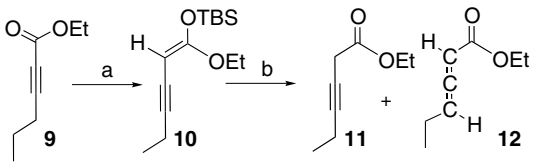


Scheme 3. Proposed mechanism for the formation of allenoates **3**, **4**, and **8**.

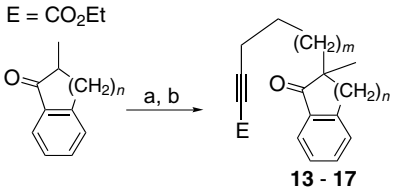
Mukaiyama aldol type reaction, induced by a 'second' Lewis acid activation of the cyclobutanone carbonyl group, then took place to afford the allenic esters **3**, **4**, and **8** (Scheme 3).

To confirm this mechanism, ethyl hexynoate **9** was treated with excess TBSOTf/NEt_3 leading to a new compound whose spectroscopic data fully agree with the silylalkynylketene acetal **10**.[11] Until now, the formation of this type of silylalkynylketene acetal always required the use of strong bases, this being sometimes incompatible with sensitive functionalities.[12] Moreover, the acidic hydrolysis of the latter using Conia's conditions[13] yielded unconjugated ester **11** along with the corresponding allene **12** (unseparable mixture of **11**/**12** in a 3/1 ratio) (Scheme 4).

Thus, confirmation of the structure of silylalkynylketene acetal **10** highly supports the mechanism proposed for the formation of allenes **3**, **4**, and **8**. Finally, it can be claimed that a dual–Lewis acid activation of the starting acetylenic ω-ketoesters took place to afford the corresponding allene derivatives via an alkynylogous Mukaiyama aldol reaction.[14]



Scheme 4. Reagents and conditions: (a) TBSOTf, NEt_3, CH_2Cl_2 25 °C, quant.; (b) SiO_2,$(CO_2H)_2$, CH_2Cl_2, 25 °C, 95%.



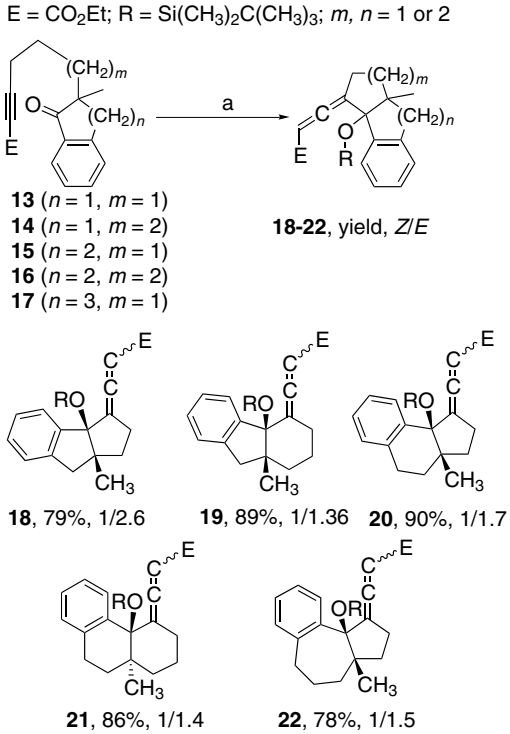
Scheme 5. Reagents and conditions: (a) 5-iodopentyne (or 6-iodohexyne), microwave, 30 s, DMF; (b) *n*-BuLi, $ClCO_2Et$, THF, −78 °C.

Table 1
Formation of compounds **13**–**17**

Entry	*n*	*m*	Product	Yield (%)
1	1	1	**13**	50
2	1	2	**14**	37
3	2	1	**15**	64
4	2	2	**16**	50
5	3	2	**17**	48

This TBSOTf methodology was extended to the acetylenic ω-ketoesters **13**–**17** derived, respectively, from 2-methylindanone, 2-methyltetralone, and 2-methylsuberone. The latter were obtained via a microwave-activated alkylation reaction of the starting ketones with 5-iodopentyne (or 6-iodohexyne) followed by the introduction of the carbethoxy group under usual conditions[15] (Scheme 5, Table 1).

The propargylic ω-ketoesters **13**–**17** were treated with excess TBSOTf in the presence of NEt_3 at room temperature to afford allenoates **18**–**22** as a mixture of *Z*/*E* isomers in 79–90% yields.[16] Total diastereoselectivity was observed for the formation of the ring junction. The cis ring junction for compounds **18**–**20** and **22** and the trans ring junction for compound **21** were confirmed by 2D COSY-NOESY NMR experiments (Scheme 6).



Scheme 6. Reagents and condition: (a) TBSOTf, NEt_3, CH_2Cl_2 25 °C.

In summary, a new intramolecular alkynylogous Mukaiyama aldol type reaction affording fused tricyclic allenoates is reported. The driving force of this reaction is a dual activation process employing TBSOTf/NEt_3. Further studies are currently underway to explore the scope and limitations of this novel reaction.

Acknowledgments

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11. Silylalkynylketene **9**: Yellow oil; IR (CCl_4): 2221, 1636 cm^{-1}. ^1H NMR (C_6D_6, 300 MHz): δ 3.86 (t, 1H, J = 2.10 Hz), 3.20 (q, 2H, J = 7.20 Hz), 2.31 (dq, 2H, J = 7.50 Hz, J = 2.10 Hz), 1.12 (t, 3H, J = 7.50 Hz), 1.08 (s, 9H), 0.83 (t, 3H, J = 6.90 Hz), 0.27 (s, 6H). ^{13}C NMR (C_6D_6, 125 MHz): δ 163.96, 90.52, 76.62, 63.67, 62.15, 25.84, 18.44, 14.90, 14.14, 13.96, −4.07. The double bond geometry of **9** most likely has the *E* configuration: the chemical shift of the vinylic proton is in agreement with the chemical shifts of similar *E* ketene silyl acetals (for the *Z* configuration, the chemical shift is at higher field); see: Ref. 3b.
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15. Microwave activation is an essential requirement for an effective alkylation reaction. Without activation, the yield decreased (50% instead of 70%) and the reactions were slower (24 h instead of 10 s). The microwave device we used is START SYSTEM from MILESTONE S.r.l. Via Fatebenefratelli, 1/524010 Sorisole (BG)—Italy. The reaction was runned in an open vessel in DMF (power: 400 W) for 30 s. For a leading reference concerning microwave activation, see: Perreux, L.; Loupy, A. In *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006; Vol. 1 pp 134–218.
16. An excess TBSOTf/NEt_3 has to be added to the starting acetylenic ω-ketoester to bring the reaction to completion. General procedure for the synthesis of allenoates: NEt_3 (5.26 mmol, 5 equiv) was added to a solution of ω-ketoester (1.05 mmol, 1 equiv) in CH_2Cl_2 (10 mL). The reaction mixture was stirred 30 min at room temperature. TBSOTf (3.16 mmol, 3 equiv) was added dropwise and the reaction mixture was stirred 3 h at room temperature. NEt_3 (2.63 mmol, 2.5 equiv) was added again and the reaction mixture was stirred 30 min at room temperature. TBSOTf (1.58 mmol, 1.5 equiv) was added again and the reaction mixture was stirred 30 min at room temperature, hydrolyzed with water (10 mL), extracted with CH_2Cl_2 (2 × 5 mL), and Et_2O (5 mL). The organic layers were washed with a saturated aqueous NaCl solution (10 mL) and dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure (10 mmHg/30 °C). The crude product was purified on a silica gel column (15 g SiO_2, EtOAc/hexane: 1/99) leading to the corresponding allenoates. Allenoate **3** (major isomer): pale yellow oil. IR (CCl_4): 1962, 1721 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.65 (dd, 1H, J = 4.92 and 2.37 Hz), 4.15 (ABX_3 syst, 2H, J_{AB} = 10.4 Hz, J_{AX} = 7.1 Hz, J_{BX} = 7.1 Hz, $\Delta\nu$ = 0.1 ppm, ∂_A = 4.1 ppm, ∂_B = 4.2 ppm), 2.78 (m, 2H), 2.64 (dd, 1H, J = 7.68 Hz), 2.07 (m, 4H), 1.52 (m, 6H, CH_2), 1.26 (t, 3H, J = 7.1 Hz), 0.86 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.49, 166.09, 117.07, 90.76, 82.35, 60.65, 52.19, 49.90, 37.65, 33.14, 31.61, 30.03, 26.92, 25.96, 25.63, 18.43, 14.46, −2.51, −3.47.