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Base-Induced Cyclization of Derivatives of Bispropargylated Acetic Acid to *m*-Toluic Acid

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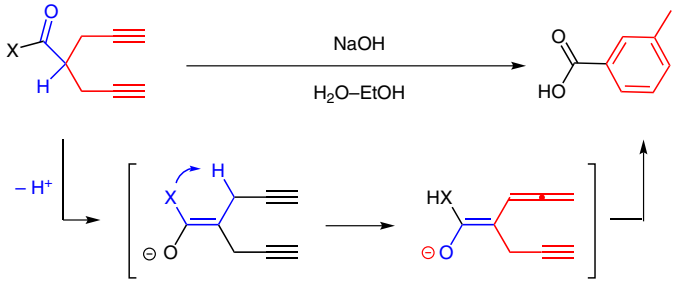

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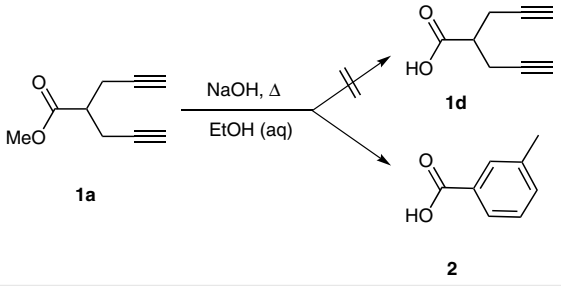
Abstract A base-induced cyclization reaction of 1,1-bispropargyls has been examined. Alkali treatment of 2,2-bispropynyl acetic acid derivatives in aqueous ethanol mostly provided 3-methylbenzoic acid. Investigations on substituent effects indicate the requirement of an electron-withdrawing group causing CH acidity and the center of the dipropargylic structure. Besides, an intramolecular hydrogen transfer causing the rearrangement of one terminal alkyne into a corresponding allene appears to be essential. Despite an unsatisfying conversion yield of below 40%, the reaction is interesting due to the mild cyclization conditions.

Key words alkyne–allene isomerization, vinylogous enolate, 6-*endo*-dig cyclization, bispropargyl, intramolecular proton transfer

The equilibrium of alkynes and allenes gives rise to various cyclizations, frequently involving aldol-type reactions. Many reactions are initiated by coordinating metals; this fits both intra-[1–4] and intermolecular reactions.[5] However, initiation can also apply basic conditions, if resonance effects drive the reaction.[6]

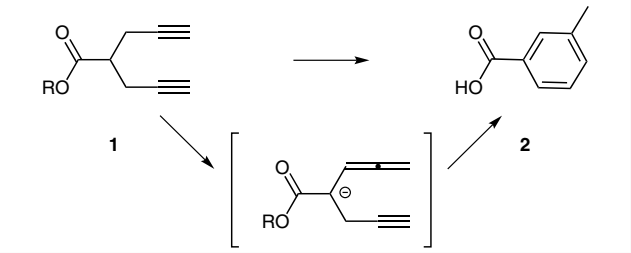
Based on a targeted synthesis of dendrimers by exploitation of 'click' chemistry, we synthesized various dipropargylic building blocks. The purification of some of these led to unexpected problems, due to the presence of aromatic compounds despite exclusive use of aliphatic reagents and solvents. This led to an investigation of the source of the aromatics, revealing an unexpected intrinsic reactivity for 1,6-heptadiynes with an electron-withdrawing substituent (EWG) on the central carbon.

Dipropargyl acetates, like **1a**, formed 3-methylbenzoic acid (**2**) upon treatment with strong base in aqueous alcohol at elevated temperature instead of the expected saponification product **1d**. The reaction is depicted in Scheme 1. This result is in line with a previous report on the aromatic isomerization of 1,6-heptadiyne-4-carboxylic acid **1d** under similar conditions.[7] Other reports indicate an identical isomerization of **1d** upon treatment with acid without heating.[8] However, the latter record has been previously rated as nonreproducible.[7] Despite the low reaction yield of below 40% for the transformation of methyl 2,2-dipropargyl acetate **1a** to 3-methylbenzoic acid (**2**), the process is interesting because of the unexpected reaction product and related mechanistic implications.



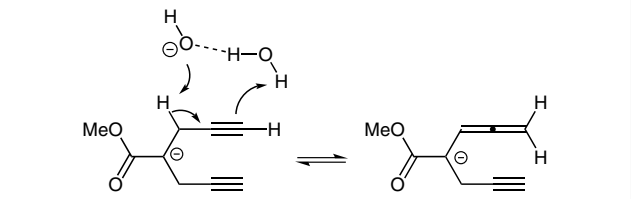
Scheme 1 Base-catalyzed cyclization of methyl 1,6-heptadiyne-4-carboxylate

It indicates an intrinsic reactivity of the 1,6-heptadiyne core for aromatic cyclization under moderate reaction conditions. The reaction is believed to pass through an initial alkyne–allene isomerization as shown in Scheme 2, probably driven by resonance stabilization of the enolate. Base-induced isomerizations of alkynes and allenes have been reported previously.[9–11] However, for these reactions stronger bases are normally applied.[6,11] Reaction mechanisms involving a cyclic proton transfer mediated by a deprotonated diamine[10,11] or an alkali amide[11] have been proposed. Both mechanisms propose a push–pull concept. The same may apply in water.



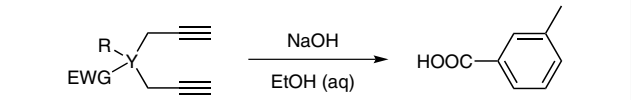
Scheme 2 Reaction pathway for cyclization of 1,6-heptadiyne-4-carboxylates

Based on the distance of the carbons for the proton transfer, a transition state involving a hydrated hydroxide is favored over an isolated hydroxide ion. Scheme 3 displays the isomerization of dialkyne **1** into the corresponding alkynyl allene. This reaction is likely driven by the conjugation of the enolate. Subsequent reaction of the allene with the second triple bond provides the aromatic ring. The concept of isomerization of alkenes and allenes through enolates with subsequent cyclization has been reported previously.[6]



Scheme 3 Solvent-mediated alkyne–allene isomerization

Although the isomerization of various diacetylenes to aromatics has been previously proposed as generic concept,[7] the reaction typically requires high temperatures (>160 °C), while the current reaction already enables the aromatization at temperatures below 100 °C. In order to rationalize the unexpected reactivity, a comparative study on various dipropargylic systems reflecting different substituent effects was performed.[12] The generic reaction scheme is displayed in Scheme 4, while specifications of the substrates and their respective reaction outputs are summarized in Table 1.



Scheme 4 Variation of substrates for attempted cyclization of 1,1-dipropargyls

Table 1 illustrates the importance of an acidic hydrogen atom at the central carbon of the starting material. Various dipropargyl acetic acid derived substrates (Table 1, entries **1a**,**b**,**d**,**f**) provided aromatic products in accordance with

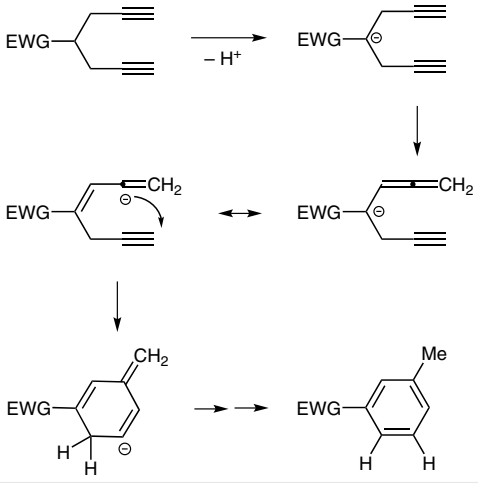
Table 1 Attempted Cyclization of 1,1-Dipropargyls

Entry	Compd	EWG	R	Y	Yield (%)[a]
1	**1a**	CO_2Me	H	C	37[b]
2	**1b**	CO_2Et	H	C	25[b]
3	**1c**	CO_2tBu	H	C	n.r.
4	**1d**	CO_2H	H	C	30[b]
5	**1e**	CN	H	C	45[b]
6	**1e**[c]	CN	H	C	n.r.
7	**1f**	$CONC_4H_8O$	H	C	>35[d,e]
8	**3**	COMe	H	C	ca. 60[d,f]
9	**3**[c]	COMe	H	C	complete[f]
10	**4**	CO_2Me	CO_2Me	C	n.r.[g]
11	**5**	CH_2OH	H	C	trace[h]
12	**6**	N/A	$C_{12}H_{25}$	N	n.r.

[a] n.r. = no reaction.
[b] Sole product: **2**.13
[c] Modified reaction conditions: anhydrous MeOH, NaOMe.
[d] No detection of leftover starting material, but diverse degradation products. Yield estimation based on integration of ^{1}H NMR (aromatic CH vs. propargylic CH).
[e] Instead of acid **2** the corresponding ethyl amide14 was obtained.
[f] NMR indicates complex mixture of products.
[g] No detection of aromatic compounds, but saponification of ester.
[h] NMR indicates no single product but mixture of aromatic products.

Scheme 5. Aromatic products were also observed for the base treatment of ketone **3**. The olefinic NMR signals in the range of aromatics for the latter may partially originate from aldol-type reactions. However, the simultaneous disappearance of propargylic signals strongly suggests a participation of the alkynes in the formation of aromatic compounds. On the other hand, substrates without a central hydrogen atom, referring to entries 4 and 6 (Table 1), did not form any aromatic products. The minor cyclization of alcohol **5**, despite missing CH acidity at the central carbon, is surprising. The NMR of the crude product indicated the presence of more than one aromatic product. It is assumed that an initial oxidation of the alcohol led to an aldehyde, which cyclized according to Scheme 5. Subsequent Cannizzaro reaction of the intermediate benzaldehyde gave rise to a mixture of aromatic compounds.

A more detailed analysis of reactions for dipropargylated acetic acid derivatives provided a surprising result: While esters with high sensitivity towards alkaline hydrolysis, like **1a** and **1b**, led to practically identical cyclization yields than those obtained for the corresponding carboxylic acid **1d** the *tert*-butyl ester **1c** failed to form aromatic products. Since *tert*-butyl esters commonly do not inhibit the α-CH acidity of carboxylic acids, it was concluded that the reaction starts with the saponification of the ester. This conclusion is in line with a solvent-dependent reactivity of nitrile **1e**, leading to benzoic acid **2** in the presence of water, whereas no reaction was observed under anhydrous condi-



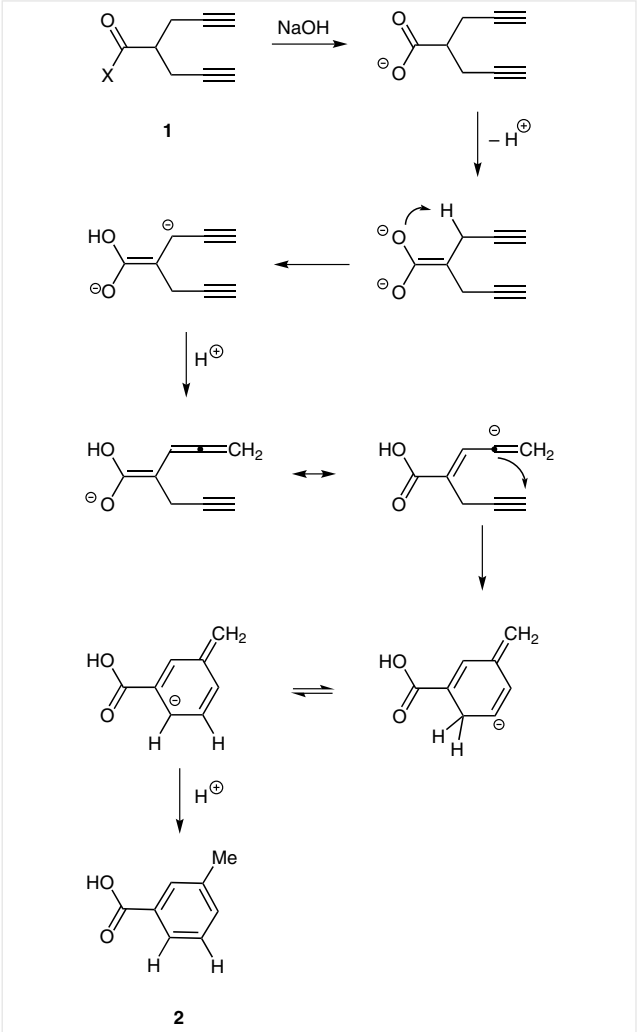
Scheme 5 Mechanism for base-induced cyclization of 1,6-heptadiynes with EWG at the central carbon

tions. As a consequence of these results, the basic mechanistic explanation in Scheme 5 requires adjustments.

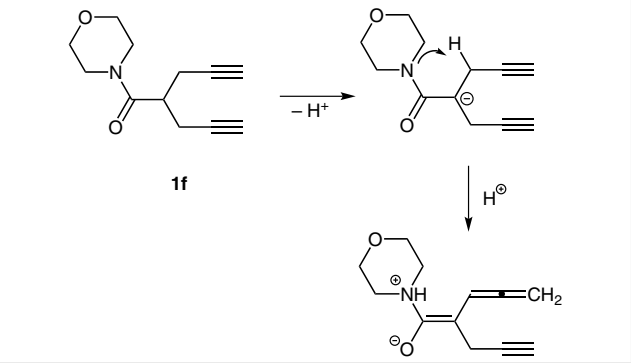
An intramolecular hydrogen transfer to initiate the alkyne–allene isomerization may explain the requirement for the saponification of carboxylic esters in **1** prior to the cyclization process. A possible mechanism is shown in Scheme 6. A cyclic proton transfer from the propargylic methylene group to a basic center at the carboxylic enolate replaces the previously suggested solvent-mediated push–pull mechanism displayed in Scheme 3. The five-membered-ring transition state, displayed in Scheme 6, cannot be achieved on stage of an ester, owing to the low basicity of both the enolate and the ester oxygen atoms. On the other hand, the enolate of a carboxylic acid, which requires double deprotonation, would be sufficiently alkaline to initiate the reaction. However, the formation of multiple anions is rather unfavored. Therefore, usually very strong bases are applied to produce enolates of carboxylic acid anions.[15,16] This requirement for strong basic conditions may explain why a substantial reduction of either base (12 equiv) or reaction temperature (ca. 90 °C) failed to induce the cyclization and rationalize the reaction time of several hours.

Following the initial alkyne–allene isomerization, the reaction continues as intramolecular nucleophilic addition of an allene enolate to an alkyne. It follows a 6-*endo*-dig route, which commonly is less favored compared to the competing 5-*exo*-dig cyclization.[17] However, Vasilevsky et al. reported a similar 6-*endo*-dig cyclization for an alkyne without enhanced electrophilicity.[18] Tautomeric rearrangement of the resulting vinyl anion through a formal 1,2-hydrogen shift provides a resonance-stabilized anion, which upon protonation readily leads to the substituted toluene derivative.

While most derivatives of 1,6-heptadiyne-4-carboxylic acid furnished 3-methylbenzoic acid (**2**) upon treatment with base, a different output was observed for morpholide **1f**. Instead of the carboxylic acid its ethyl amide was obtained. The different behavior may be understood based on an enhanced basicity of the morpholine nitrogen atom, which may enable the initial proton transfer on stage of the amide enolate, as shown in Scheme 7. While the conversion of the morpholide into an ethyl amide is not completely understood, an explanation may involve a thermoinduced elimination process of the protonated morpholide enolate. Unlike the morpholide **1f**, nitrile **1e** did not furnish an amide product based on a partial hydrolysis, but provided the carboxylic acid **2** instead. The reason for different reaction pathways for the morpholide and a primary amide can be found in the amide protons, which prevent the formation of an amide enolate owing to higher acidity of the nitrogen-bonded protons.



Scheme 6 Detailed mechanism for cyclization of 1,6-heptadiyne-4-carboxylates



Scheme 7 Base-induced alkyne–allene-tautomerization of tertiary 1,6-heptadiyne-4-carboxamides

We have rationalized the aromatization of 1,6-heptadiynes with electron-withdrawing groups at the central carbon based on a new reaction mechanism. The previously reported generic aromatization of diacetylenes[7] suggested a conjugated diene–allene intermediate. The current mechanism explains why certain derivatives of 1,6-heptadiyne-4-carboxylic acid exhibit a significant higher reactivity for the cyclization. The reaction starts with an intramolecular proton transfer initiating the alkyne–allene isomerization. The resulting allene enolate led to a nucleophilic addition following a 6-*endo*-dig cyclization, which finalized in a proton rearrangement resulting in benzene ring.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380513.

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(12) **General Cyclization Procedure**
The dipropargylic substrate (ca. 6.5 mmol) was dissolved in aq EtOH (24 mL, 75% v/v) and NaOH (12 equiv) was added, after which the reaction was heated to reflux overnight. The cooled reaction mixture was acidified with aq HCl and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was evaporated in vacuum to leave the respective product (mass recovery 85% and above). The conversion rate was determined based on relative ^{1}H NMR integrations of the aromatic product and remaining starting material. Details on the synthesis of starting materials are provided in the Supporting Information.
(13) **3-Methylbenzoic Acid (2)**
Purification applied chromatography using hexane–EtOAc (4:1) followed by crystallization. The conversion of **1a** (0.98 g, 6.5 mmol) provided **2** in 37% yield (0.33 g) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.3 (br s, OH), 7.94 (s), 7.93 (d), 7.42 (d), 7.42 (d), 7.36 (t), 2.42 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 138.3, 129.2, 134.6, 130.7, 128.4, 127.4, 21.2.
(14) ***N*-Ethyl-3-methylbenzamide**
Purification applied repeated (2×) column chromatography using hexane–EtOAc (3:1). The isolation of the conversion product of **1f** (200 mg, 1 mmol) only provided an analytical sample (ca. 30 mg, ca. 18%) as yellowisch oil. IR (ATR): 3304 (NH), 2923, 2852 (CH), 1644 (C=O), 1550 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (s), 7.46 (t), 7.22 (m, 2H), 6.13 (br s, NH), 3.42/3.41 (2 q, 2 H, Et-CH_2), 2.31 (s, 3 H, CH_3), 1.17 (t, 3 H, Et-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 138.38, 134.5, 132.1, 128.4, 123.6, 34.9, 21.3, 14.9. MS: 163, 162, 119, 91, in accordance with previously reported data.[19]
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