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Synthesis of 1-methyl-4-alkyl-1,3-diacetylenes. Prototropic rearrangement in 1-alkyl-1,3-diacetylenes

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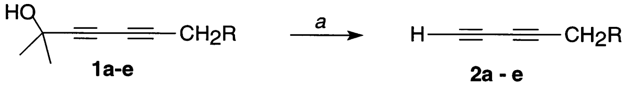
Abstract—Treatment of 2-methyl-2-hydroxy-6-alkyl-3,5-diacetylenes with powdered NaOH was used for the synthesis of terminal 1-alkyl-1,3-butadiynes that can be isolated (54–97%) or used in situ. In an attempt to increase the yields of some of the obtained products, different experimental conditions were studied and we found that by using CTAB as a catalyst, a prototropic rearrangement was promoted to afford the 1-methyl-4-alkyl-1,3-diacetylenes in the 62–94% yield range. © 2001 Published by Elsevier Science Ltd.

The reaction of propargylic monoacetylenic alcohols with NaOH, KOH or NaH is known as retro-Favorskii reaction.[1–4] This reaction permits the deprotection of terminal acetylenes with generation of acetone as a by-product and has been very useful in organic synthesis.[4,5]

Compounds of type **1** can have the terminal triple bond deprotected to afford the terminal 1-organyl-1,3-butadiynes **2** by the retro-Favorskii reaction as depicted in Scheme 1. During the last decade, terminal 1-organyl-1,3-butadiynes **2a–e** have been used by our group as intermediates in the synthesis of compounds like enynes, dienes and enediynes,[6–9] but no systematic studies regarding the transformation of **1** into **2** or full experimental details have been reported to date.[5,6]



Scheme 1. *a*. NaOH/hydrocarbon (solvent), reflux.

In most cases, the required acetylenic alcohols of type **1** were prepared[10–12] by the Cadiot–Chodkiewicz unsymmetrical cross-coupling reaction of 2-methyl-3-butyn-2-ol with 1-bromo acetylenes.[10–13] However, more recently and with the same purpose, we began to use the 4-bromo-2-methyl-3-butyn-2-ol[14] in reactions with commercially available terminal alkynes. This last approach is more practical and convenient than the previous one[6] because the synthesis of several different bromo acetylenes needed for reaction with 2-methyl-3-butyn-2-ol is not necessary.

In the present study, to perform the retro-Favorskii reaction on compounds of type **1** we always used powdered sodium hydroxide with a non-polar solvent (xylene or toluene) under reflux and compounds of type **2a–d** were obtained in most cases with more than 99% purity after purification, as determined by GC and ^{1}H NMR (Scheme 1, Table 1), but the yields obtained in some specific cases were only moderate (entries 5 and 6; Table 1). For example, the 1,3-undecadiyne **2d** was isolated in only 54% yield. For **2e** the yield obtained was 58% and the highest purity 90% (GC, ^{1}H NMR), as shown in Table 1, entry 6. The study of new experimental conditions was desirable in order to improve the obtained yields, particularly for **2d** and **e**. With this in mind, we decided to test different solvents (polar and non-polar) and the use of catalysts such as cetyltrimethylammonium bromide (CTAB) or dibenzo-18-crown-6-ether, and to compare the use of powdered NaOH and KOH as bases.

In the first experiment, we added a catalytic amount of CTAB to the reaction of compound **1d** with NaOH in xylene under reflux. However, an unexpected result was observed because the reaction did not stop at the formation of compound **2d**. Under the new experimental conditions developed in the present study, no improvement in yields of compounds **2** were obtained but the complete isomerization to the 1-methyl-4-alkyl-

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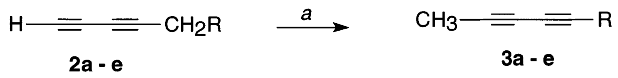
1,3-butadiynes **3** occurred in good yields (Scheme 2, Table 1). Although the reaction of compounds **1** with NaOH in xylene or toluene was previously known,[5,6] the use of a phase transfer catalyst or the prototropic rearrangement with NaOH in non-polar solvents was never mentioned before.

Considering this new and interesting result, we decided to isolate[15] the terminal 1-alkyl-1,3-butadiynes **2** and to study systematically this prototropic rearrangement by determining the optimal experimental conditions for the complete transformation of **1** or **2** into compounds **3** and our preliminary results are described herein.



Scheme 2. *a*. NaOH/hydrocarbon (solvent), reflux, catalyst (CTAB or crown ether).

The best results for this transformation were obtained[16] using the CTAB as a catalyst (0.17 equiv.) and sodium hydroxide (1.25 equiv.) as the base (Scheme 2). Dibenzo-18-crown-6-ether was alternatively used as a catalyst, but longer reflux time and 0.35 equiv. were necessary to obtain yields similar to those obtained with CTAB (0.17 equiv.), while $Me_4N^+Br^-$ appeared to be less efficient, affording low yields and longer reaction times. The solvent choice depends on the boiling point of the obtained product to avoid losses in the purification and solvent removal steps. Thus, it was determined that xylene and toluene are the best solvents to be used for the isomerization of the 1-alkyl-1,3-butadiynes **2a**, **c** and **d** because the complete reaction is a temperature-dependent process. As can be observed in Table 1 (entry 2), the 1,3-decadiyne **2a** was completely transformed into the 2,4-decadiyne **3a** in 71% yield, after 25 min under reflux, using toluene as a solvent. On the other hand, when using xylene as a solvent the reaction was completed after 15 min and even when the reaction was continued for 1 h and 40 min under reflux, the 2,4-decadiyne yield was not higher than 75% (entry 1, Table 1).

In the case of the more volatile 2,4-diacetylenes **3b** and **e** the solvent of choice was hexane. The solvent was carefully removed and both the 2,4-octadiyne **3b** and the 2,4-heptadiyne **3e** were obtained in good yields (Table 1, entries 3 and 6). In both of these examples, intermediates **2b** and **e** were generated in situ from the acetylenic alcohols **1b** and **e**, respectively. By performing these reactions in one pot, yield losses during purification and during the solvent removal steps (particularly under reduced pressure) can be minimized. However, it is important to note that when hexane is used as solvent, the employed base needs to be the more reactive KOH because when using NaOH no reaction is observed at the hexane reflux temperature. By contrast, in the other examples, using xylene or toluene as the solvent, NaOH was used because it affords cleaner reactions than KOH. Interestingly, all

Table 1. 1-Alkyl-1,3-diacetylenes and 1-methyl-4-alkyl-2,4-diacetylenes obtained

Entry	1-Alkyl-1,3-diacetylene $1 \rightarrow 2$	1-Methyl-4-alkyl-2,4-diacetylene 1 or $2 \rightarrow 3$	Solvent (Purity of **2**)[a]	reaction time (min)[b]	Yield (%)[b,c,d]
1	$H{-}\equiv{-}\equiv{-}C_6H_{13}$ **2a**	$CH_3{-}\equiv{-}\equiv{-}C_5H_{11}$ **3a**	Xylene (> 99%)	**8** (100)	**74** (75)
2	$H{-}\equiv{-}\equiv{-}C_6H_{13}$ **2a**	$CH_3{-}\equiv{-}\equiv{-}C_5H_{11}$ **3a**	Toluene (> 99%)	**15** (25)	**83** (71)
3	$H{-}\equiv{-}\equiv{-}C_4H_9$ **2b**[e,f]	$CH_3{-}\equiv{-}\equiv{-}C_3H_7$ **3b**	Hexanes (> 95%)	**90** (10)	**69** (71)
4	$H{-}\equiv{-}\equiv{-}C_{10}H_{21}$ **2c**	$CH_3{-}\equiv{-}\equiv{-}C_9H_{19}$ **3c**	Xylene (> 99%)	**10** (72)	**97** (94)
5	$H{-}\equiv{-}\equiv{-}C_7H_{15}$ **2d**	$CH_3{-}\equiv{-}\equiv{-}C_6H_{13}$ **3d**	Xylene (> 99%)	**90** (25)	**54** (62)
6	$H{-}\equiv{-}\equiv{-}C_3H_7$ **2e**[f,g]	$CH_3{-}\equiv{-}\equiv{-}C_2H_5$ **3e**	Hexanes (> 90%)	**10** (5)	**58** (72)

[a] Determined by GC and ^1H NMR. [b] Bold for **2**, in parenthesis for **3**. [c] Purified by flash chromatography (SiO_2). [d] CTAB (0.17 equiv.) used as catalyst. [e] Generated *in situ* from **1b**. [f] KOH (0.9 equiv.) used instead of NaOH. [g] Generated *in situ* from **1e**.

the observations discussed here about the solvents and bases used can be applied to the transformation of **1** into **2** and of **2** into **3**.

The isomerization rates were higher with KOH than with NaOH; however, the formation of a second product was observed, particularly when the reaction was performed with KOH at higher temperatures (reflux of xylene). In one experiment, when **2d** was reacted under these conditions (KOH, CTAB, xylene), this second product was identified as the corresponding 1-ethyl-4-alkyl-1,3-butadiyne. Its formation was explained by a second prototropic rearrangement, although this second rearrangement occurred only partially and compound **3d** was still the major product (15:85 ratio by GC and ^{1}H NMR), even with longer reaction times under reflux or when larger amounts of KOH (up to 14 equiv.) were used. In a similar reaction of compound **2d** with KOH in the absence of the catalyst and employing ethanol as solvent, only 18% of **2d** underwent isomerization to **3d** after 3 h under reflux.[17] In this case, most of the starting material remained untouched and the formation of three new products was detected by GC and ^{1}H NMR (300 MHz) as being the prototropic rearranged product **3d**, the 1-ethyl-4-alkyl-1,3-butadiyne and the corresponding ethylvinyl ether formed by the addition of potassium ethoxide to the terminal triple bond of **2d**.

It should be noted that the use of the Cadiot–Chodkiewicz reaction[11,12] is not the best option to obtain compounds **3a–e** because it would require the highly volatile and explosive propyne or the volatile and pyrophoric 1-bromopropyne.[13] Thus, one can state that our methodology for the synthesis of the 1-methyl-4-alkyl-1,3-butadiynes **3a–e** will be very important and interesting in organic synthesis.

In summary, we described here the previously unknown prototropic rearrangement of 1,3-butadiynes and established the first highly efficient synthesis of 1-methyl-4-alkyl-1,3-butadiynes from 2-methyl-2-hydroxy-6-alkyl-3,5-diacetylenes (or from the corresponding terminal 1-alkyl-1,3-butadiynes) using NaOH or KOH as base in the presence of a phase transfer catalyst (CTAB) in xylene, toluene or hexanes.

Acknowledgements

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15. **Typical procedure for the retro-Favorskii reaction**: To a solution of the 2-methyl-2-hydroxy-6-alkyl-3,5-diacetylene **1** in 2 mL of xylene (for **1c**) or toluene (for **1a** and **d**), powdered NaOH (0.10 g, 2.5 mmol) was added at rt. The mixture was refluxed for the time indicated in Table 1 (monitored by TLC and/or GC). After this time, the deep yellow–brown solution was allowed to reach rt and was then diluted with hexanes (2 mL). The 1-alkyl-1,3-diacetylene **2** was purified by flash column chromatography on silica gel (hexanes).
16. **Typical procedure for the prototropic rearrangement on 2**: To a 15 mL flask, containing a solution of the 1-alkyl-1,3-diacetylene **2** or the 2-methyl-2-hydroxy-6-alkyl-3,5-diacetylene **1** (1 mmol) in the hydrocarbon solvent (1.5 mL, Table 1), powdered NaOH (0.05 g, 1.25 mmol) or KOH (0.05 g, 0.9 mmol) and CTAB (0.07 g, 0.17 mmol) was added at rt. The mixture was refluxed for the time indicated on the Table 1. Then, the deep yellow–brown solution was allowed to reach rt and was then diluted with hexanes (**2a**, **c** or **d**) or pentane (**1b** and **e**). The 1-methyl-4-alkyl-1,3-diacetylene **3** was purified by flash column chromatography on silica gel (hexanes or pentane).
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