Tetrahedron Letters 51 (2010) 2218–2221

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Effect of fluorine or oxygen atom(s) in propargylic position on the reactivity in click chemistry

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ARTICLE INFO

Article history:
Received 23 January 2010
Revised 10 February 2010
Accepted 12 February 2010
Available online 18 February 2010

Keywords:
Fluorine
Click chemistry
Triazoles
1,3 Dipolar cycloadditions
ω-Diynes

ABSTRACT

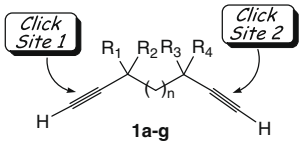
The use of especially designed ω-diynes allows to establish, through competitive reactions, the effect of C–F, C–OH, CF_2, C=O and $C(OMe)_2$ substituents on the reactivity of neighbouring triple bonds in click chemistry and this gives not only a reactivity scale but also a direct access to the difference in activation energies between the competitive reaction pathways.

Click chemistry is now being extensively studied, with many developments in various scientific fields.[1] In particular the reaction of azides on alkynes catalyzed, or not, by copper salts proved to be a very efficient reaction.[2] It is widely used in many areas but particular attention has been paid to bioorganic chemistry. Elegant applications of this copper-promoted Huisgen reaction have been reported already in medicinal chemistry,[3] for instance in the design of enzyme inhibitors at the femtomolar level,[4] for labelling of proteins[5] as well as for in vivo imaging.[6,7] In latter area, the use of cyclooctyne derivatives proved to be very important due to their high reactivity as dipolarophiles. Furthermore, adding a gemdifluoro substituent on such molecules increased their reactivity, allowing fast reactions even at room temperature.[6b] The high reactivity of such fluorinated molecules has been rationalized by extensive computational studies and the effect of the CF_2 group has been explained by the interaction of the two fluorine atoms with the triple bond.[8] This lowers the level of the frontier orbitals and increases the reactivity with a gain of 2.0 kcal mol^{-1} in the activation energy of the reaction corresponding to the difluorinated analogue.[8a] Extension of these effects to other substituents in propargylic position and other cycloalkynes has also been reported recently.[8b]

All previous studies have been performed on highly reactive cyclic systems and therefore the question remains to be studied what could be the effect of fluorine, as well as other atoms, on the reactivity of the neighbouring triple bond but on simple linear systems.[9,10] Towards this goal, we have designed novel model systems containing two differentially substituted ω-diynes as indicated in Figure 1. Each diyne has a different substitution pattern close to the triple bonds: CH_2 and CH(OH) for **1a**, CH_2 and CHF for **1b**, CH_2 and C=O for **1c**, CH_2 and $C(OMe)_2$ for **1d**, CH_2 and CF_2 for **1e**, CH(OH) and CHF for **1f** and CF_2 and C=O for **1g**.

The competition between the reactions on each independent triple bond will give useful informations on the reactivity of the two differentiated systems. This can be translated into quantitative data on the difference in activation energies between the two processes and therefore into the effect of the corresponding propargylic substituents on this click reaction.

The synthesis of diynes **1a–e** is reported in Scheme 1. It started from alkyne **2**, readily available through a zip reaction.[11] PCC oxidation, followed by the addition of ethynyl Grignard, afforded in 60% overall yield the first molecule **1a** which allows to study the competition between the CH_2 and CH(OH) groups.



a: R_1=R_2=R_3=H; R_4=OH; n=5
b: R_1=R_2=R_3=H; R_4=F; n=5
c: R_1=R_2=H; R_3,R_4=CO; n=5
d: R_1=R_2=H; R_3=R_4=OMe; n=5
e: R_1=R_2=H; R_3=R_4=F; n=5
f: R_1=R_3=H; R_2=OH; R_4=F; n=3
g: R_1=R_2=F; R_3,R_4=CO; n=3

Figure 1. The ω-diynes designed for studying, by competition between two different reacting sites, the effect of substituents in click chemistry.

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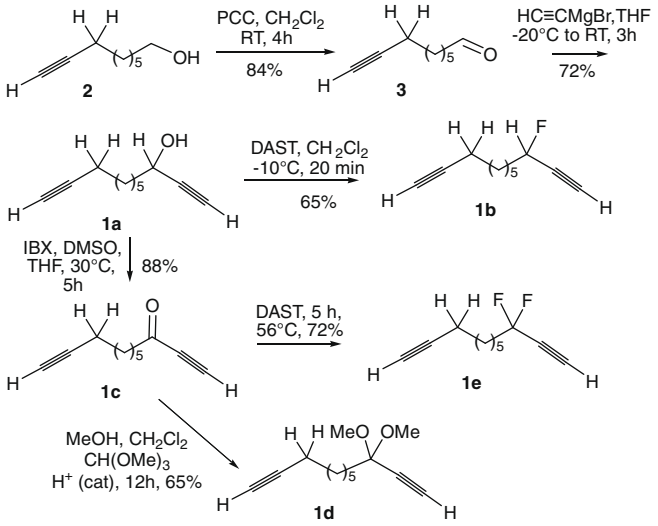
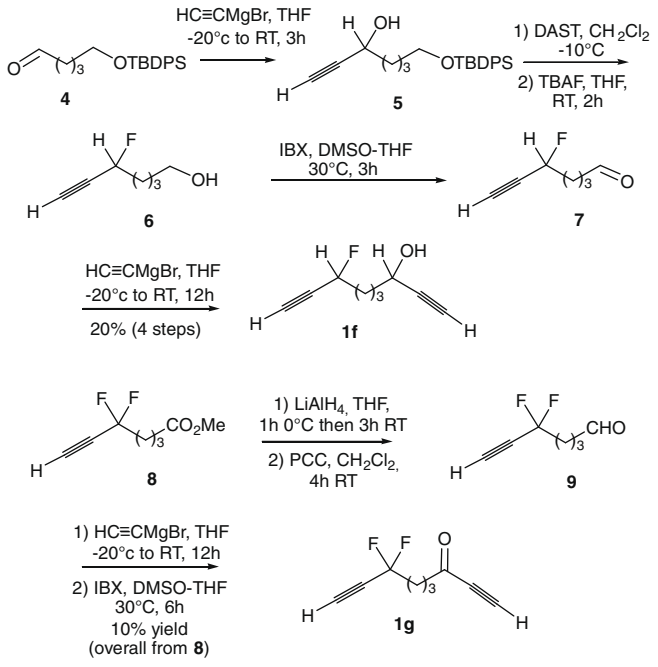
doi:10.1016/j.tetlet.2010.02.083



Scheme 1. Synthesis of ω-diynes **1a**–**e**.

Then, classical reactions were performed to obtain the next targets: dehydroxyfluorination using diethylaminosulfurtrifluoride (DAST) afforded the monofluorinated derivative **1b** in 65% yield. On the other hand, oxidation using 2-iodoxybenzoic acid (IBX) in a DMSO/THF mixture gave propargylic ketone **1c** in 88% yield. Protection of the latter derivative afforded ketal **1d** in 65% yield. The gemdifluoro propargylic derivative **1e** was obtained in 72% yield by reaction of **1c** with DAST (neat at 56 °C).

For the last two molecules **1f** and **1g**, other synthetic routes had to be followed, as indicated in Scheme 2. For **1f**, it started from known aldehyde **4**,[12] which reacted with ethynyl Grignard to afford intermediate **5**. DAST-mediated dehydroxyfluorination followed by deprotection afforded propargylic fluoride **6** which, after oxidation by IBX gave aldehyde **7**. A final addition of the Grignard reagent gave the targeted diyne **1f** in 20% overall yield. On the other hand, $LiAlH_4$ reduction of the known[13] difluoro propargylic derivative **8**, followed by PCC oxidation, gave aldehyde **9**. Grignard addition, followed by IBX oxidation afforded the last target molecule **1g** in 10% (unoptimized) overall yield from **8**.

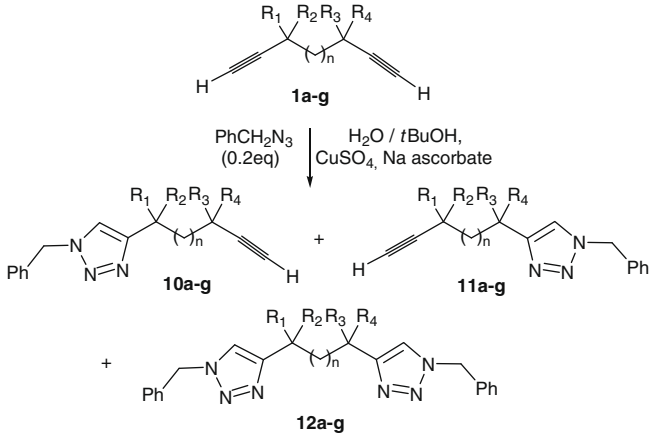


Scheme 2. Synthesis of ω-diynes **1f** and **1g**.

Having the desired diynes in hand, the stage was set for studying their reactivity in click chemistry. For this purpose we selected the classical reaction conditions, as described in the original publication by Sharpless and co-workers (benzyl azide with a catalytic system using copper sulfate and sodium ascorbate).[2] Starting from diynes **1a–g**, these cycloadditions can afford the monotriazoles **10a–g** and/or the monotriazoles **11a–g** as well as the bistriazoles **12a–g** (Scheme 3). All reactions were performed with a large excess of diyne (using 0.15–0.25 equiv of azide) in order to minimize the formation of bisadducts **12** and to take into account only the competition between the two triple bonds. All reactions have been performed at 25 °C for two hours and the results are reported in Table 1. Analysis of the crude reaction mixtures by ^1H and, when appropriate, by ^{19}F NMR gave the ratio of the different products obtained in the click reactions. The structures of the triazoles are easily established by NMR: the multiplicity of the remaining acetylenic proton, indicating the coupling with the R_1–R_2 or with the R_3–R_4 substituents is particularly relevant from the structure of the adduct (Table 2).

The reaction of diyne **1a** afforded a 22/78 ratio of monotriazoles **10a** and **11a** with only traces (<1%) of bistriazole **12a**. Triazoles **10a** and **11a** have been isolated by chromatography on SiO_2 and their structure was established unambiguously by NMR using the multiplicity of the acetylenic protons.

For **11a**, it appeared at 1.93 ppm as a triplet (with J = 2.6 Hz, by coupling with the propargylic CH_2). On the other hand, in the case of **10a**, the same proton appears at 2.46 ppm as a doublet only (with J = 2.1 Hz) by coupling with the CH(OH) proton. Therefore, the click reaction is 3.54 times faster on the triple bond bearing the CH(OH) substituent than on the other one with the CH_2 group. A similar sequence was followed starting with diyne **1b**, affording triazoles **10b** (18%), **11b** (80%) and a very small amount of bistriazole **12b**. Triazoles **10b** and **11b** were isolated by chromatography and their structures were established by NMR, as previously (Table



Scheme 3. Click reactions of ω-diynes **1a**–**g**.

Table 1
Click chemistry on ω-diynes **1a**–**1g**

Diyne	**10**	**11**	**12**	Ratio **11**:**10**	$\Delta E^{\neq}$(**11**)−$\Delta E^{\neq}$(**10**)
1a	22	78	Traces	3.54	−0.76 kcal mol^{-1}
1b	18	80	2	4.35	−0.89 kcal mol^{-1}
1c	2	97	1	48.5	−2.31 kcal mol^{-1}
1d	45	45	10	1	0 kcal mol^{-1}
1e	5	90	5	18	−1.72 kcal mol^{-1}
1f	45	55	0	1.22	−0.12 kcal mol^{-1}
1g	25	75	0	3	−0.65 kcal mol^{-1}

Table 2
Selected key NMR data on triazoles **10** and **11**

Triazole	*H*–C≡C–C (R_3)(R_4)–	*H*–C≡C–C (R_1)(R_2)–
10a	2.46 (d, J_{HH} = 2.1 Hz)	—
11a	—	1.93 (t, J_{HH} = 2.6 Hz)
10b	2.66 (dd, J_{HH} = 2.1 Hz, J_{HF} = 5.5 Hz)	—
11b	—	1.95 (t, J_{HH} = 2.7 Hz)
10c	3.22 (s)	—
11c	—	1.93 (t, J_{HH} = 2.7 Hz)
10d	2.53 (s)	—
11d	—	1.92 (t, J_{HH} = 2.6 Hz)
10e	2.75 (t, J_{HF} = 5.0 Hz)	—
11e	—	1.86 (t, J_{HH} = 2.7 Hz)
10f (2 dias)	2.44 (d, J_{HH} = 2.0 Hz) 2.45 (d, J_{HH} = 2.0 Hz)	—
11f (2 dias)	—	2.66 (dd, J_{HH} = 2.1 Hz, J_{HF} = 5.6 Hz) 2.67 (dd, J_{HH} = 2.1 Hz, J_{HF} = 5.5 Hz)
10g	3.22 (s)	—
11g	—	2.77 (t, J_{HF} = 5.0 Hz)

2). Therefore, the click reaction is 4.35 times faster on the triple bond with the CHF substituent than the CH_2 group. This shows that the CHF substituent is a slightly better activator for the click reaction than the CH(OH) group. The next step was the comparison of the CH_2 substituent with a carbonyl group. Not surprisingly the reaction of diyne **1c** afforded almost exclusively reaction on the activated triple bond to give **11c** (97%) with a small amount of **10c** (2%) and bisadduct **12c** (1%). Triazoles **10c** and **11c** were isolated by chromatography and their structures were established by the same NMR method. Therefore the reaction of the propargylic ketone is 48.5 times faster than the addition on the triple bond with the CH_2 group. Next was the comparison with the dimethylacetal group. The reaction of diyne **1d** afforded a 1:1 mixture of monotriazoles **10d** and **11d** together with **12d** (10%). So, in that case, the reactivity of the triple bonds with CH_2 and $C(OMe)_2$ groups is equal. On the contrary, in the case of **1e**, the reaction was strongly in favour of **11e** (90%) with small amounts of **10e** (5%) and **12e** (5%). Therefore the reactivity of the triple bond with the CF_2 substituent is 18 times faster than the addition on the triple bond with the CH_2 group. Finally, as a cross check for this study, the click reaction was performed on diynes **1f** and **1g**. The first reaction afforded a 45:55 mixture of monotriazoles **10f** and **11f** without bistriazole **12f**. This result confirms previous data obtained with **1a** and **1b**, indicating that the triple bond with CHF group has a slightly higher reactivity (ratio 1.22) than the triple bond bearing a CH(OH)substituent. On the other hand, the reaction of **1g** afforded a 25:75 ratio of **10g** and **11g**. This indicates that the carbonyl group activates the click chemistry by a threefold ratio as compared to the CF_2 moiety. Therefore for this azide-type click reaction, the reactivity order is:

$$C{=}O > CF_2 \gg CF \sim C(OH) \gg CH{=}C(OMe)_2$$

An important aspect of such a method using ω-diynes is that the ratio of the two monotriazoles can be used to access directly the difference in the activation energies for the two competitive pathways and corresponding results are given in Table 1.[14] It is interesting to remark that the results obtained with these linear systems appear in good agreement with the literature data obtained with the cyclooctyne derivatives and several interesting remarks can be made:[15]

- For the CF_2 group we observe a decrease of 1.72 kcal mol^{-1} in activation energy as compared to the CH_2 unit. This appears to be consistent with the 1.9 kcal mol^{-1} obtained by high level DFT calculations in the case of difluorocyclooctyne.[8b] On the other hand, we can compare the same CF_2 with the strong electron-withdrawing carbonyl group. The 1:3 ratio obtained in the case of **1g**, translates in an activation energy difference which is only 0.65 kcal mol^{-1} and this clearly establishes the strength of the effect of the CF_2 group.
- A single fluorine also accelerates significantly this reaction with a $\Delta\Delta E^{\neq}$ of −0.89 kcal mol^{-1} to be compared with the −1.4 kcal mol^{-1} obtained by computational studies for monofluorocyclooctyne.[8b] For cyclooctynes introduction of a fluorine atom increased the rate of click reaction by a 3.6 factor,[6,8b] which is also consistent with the 4.35 increase observed with **1b**.
- It is a common practice in fluorine chemistry to emphasize the similarity between a fluorine atom and an hydroxyl group. Our data confirm that this is correct in the case of the click reaction since the 1.22 ratio of triazoles obtained starting with **1f**, translates into a very small $\Delta\Delta E^{\neq}$ (−0.12 kcal mol^{-1}).
- The results obtained with alcohol **1a** are also consistent with the twofold increase in the reaction rate on a benzyloxycyclooctyne derivative,[6,8b] while computational studies gave a $\Delta\Delta E^{\neq}$ value of −1.7 kcal mol^{-1} for a methoxycyclooctyne.[8b]
- Finally, possibly for a combination of steric and electronic contributions, the dimethylacetal had no global effect on this reaction since a 1:1 mixture of regioisomers was obtained starting from **1d**.

In conclusion, we have demonstrated that ω-diynes **1** are useful models to study the effect of substituents in click chemistry, through the competition between the two reactive sites. This method allows to establish not only a reactivity order for the selected substituents but also allows to quantify the differences in the activation energies for the corresponding click reactions.

Acknowledgements

We thank CNRS and MESR for support of this research. We thank A. Lancou for preliminary studies on the click reactions of propargylic fluorides. We thank Professor A. Boucekkine for fruitful discussions and CRMPO (Rennes) for the MS studies.

Supplementary data

Supplementary data (experimental procedures, spectral and analytical data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.083.

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14. For reaction of molecules **1**, the difference in the activation energies for the competitive processes leading to **10** and **11** is given by: $\Delta E^{\neq}(\mathbf{11}) - \Delta E^{\neq}(\mathbf{10}) = \Delta\Delta E^{\neq} = -RT\,\mathrm{Log}[\mathbf{11}]/[\mathbf{10}]$.
15. High level computational studies are ongoing in order to analyze in more depth the effects of substituents on the reactivity in these linear systems.