Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2024, **34**, 581–583

Mendeleev Communications

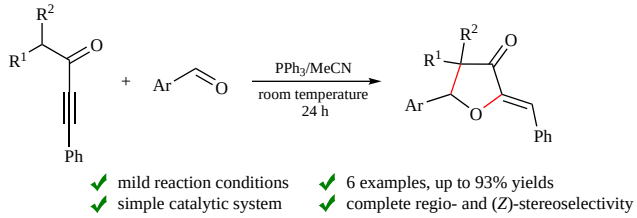
The reaction of 1-alkyl-3-phenylpropynones with aromatic aldehydes: an update

Sofia O. Karnakova and Dmitrii A. Shabalin*

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. E-mail: shabalin.chemistry@gmail.com

DOI: 10.1016/j.mencom.2024.06.037

1-Alkyl-3-phenylprop-2-yn-1-ones smoothly react with aromatic aldehydes in the presence of triphenylphosphine (acetonitrile, room temperature, 24 h) to regio- and stereoselectively afford (*Z*)-2-benzylideneoxacyclopentan-3-ones in yields up to 93%. The proposed mechanism for the transformation involves 1,3-*H* proton shift from the alkyl group at the intermediate β-phosphoniovinylide species.



Keywords: alkynones, acetylenic ketones, aldehydes, C–H active compounds, triphenylphosphine.

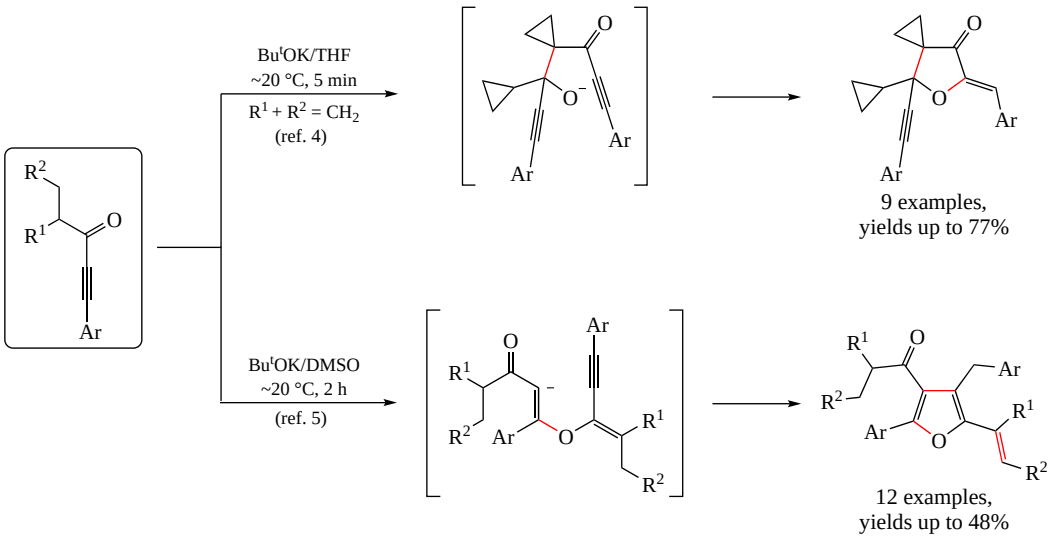
Conjugated alkynones are the substrates of outstanding importance for modern organic synthesis.[1–3] The synthetic utility of these compounds is further enhanced with alkyl substituents being attached to the carbonyl group which are prone to deprotonation and generation of reactive anionic intermediates. Recently, we discovered novel base-catalyzed dimerization pathways of such C–H active alkynones to assemble pharmaceutically relevant 6-methylene-5-oxaspiro[2.4]heptan-7-ones[4] or 3-acyl-5-alkenylfurans[5] depending on the nature of secondary alkyl substituent at the carbonyl group (Scheme 1).

On the example of the reaction between 1-cyclopropyl-3-phenylpropynone **1a** and 4-chlorobenzaldehyde **2a** in the presence of Bu^{t}OK/THF system it was shown that spiro[2.4]-heptanones with distinctly different substituent patterns may be obtained by adding competitive electrophilic reagents to the reaction mixture (Scheme 2).[4]

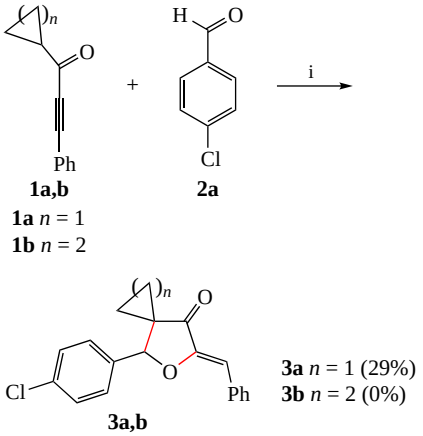
In this communication, we report preliminary observations on the effect of alkyl substituent nature on the reaction of C–H active alkynones with aromatic aldehydes. Thus, when the synthesis of 6-oxaspiro[3.4]octanone **3b** from 1-cyclobutyl-3-phenylpropynone **1b**, a homologue of **1a**, and aldehyde **2a** was attempted with the same Bu^{t}OK/THF system, the expected product was detected only in trace amounts at full conversion of starting alkynone **1b** (see Scheme 2).

Further optimization of the reaction conditions (Table S1, see Online Supplementary Materials), including base nature (Bu^{t}OK, Bu^{t}ONa, KOH·0.5H_2O, Cs_2CO_3) and its concentration (0.15–1.5 equiv.), solvent (THF, DMSO, DMF, DMA), reaction time and temperature, has revealed that the cyclization proceeds with poor efficiency when initial carbon-centered anionic intermediate is generated by direct deprotonation of alkynone **1b** with strong base. The best yield of spirocyclobutane derivative **3b** within this approach was 21% (^{1}H NMR of the crude material) after the reaction of alkynone **1b** with 2.0 equiv. of aldehyde **2a** in the presence of 0.25 equiv. of Bu^{t}OK in DMSO at room temperature for 5 min.

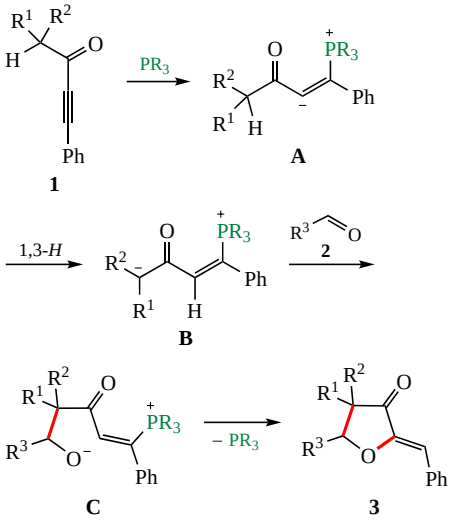
In a search for more efficient protocol, we have examined the reaction of alkynone **1b** with aldehyde **2a** in the presence of



Scheme 1



Scheme 2 *Reagents and conditions*: i, Bu^{t}OK (0.5 equiv.), THF, room temperature, 5 min.

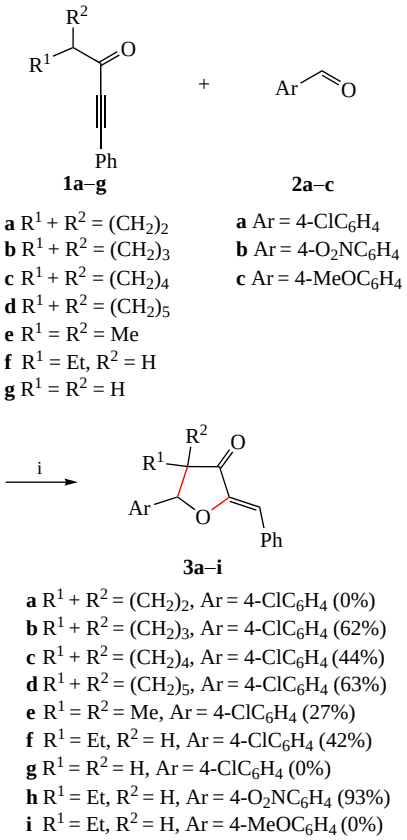


Scheme 3

nucleophilic catalyst, *i.e.* indirect deprotonation of alkynone **1b** was realized. In this case, the reaction was assumed to start from the addition of nucleophilic catalyst (typically, diverse triarylphosphines are used)[6–9] to the carbon–carbon triple bond of alkynone **1** giving zwitterionic intermediate **A** (Scheme 3). Further 1,3-prototropic shift should afford enolate **B** which upon the reaction with aldehyde **2** delivers linear intermediate **C**. The latter can undergo cyclization through addition/proton transfer/catalyst elimination sequence to finish the assembly of oxa cycle **3**.

After brief (but not exhaustive, Table S1) optimization of reaction conditions we found that cyclobutyl ynone **1b** readily reacted with 1.0 equiv. of 4-chlorobenzaldehyde **2a** in the presence of 1.0 equiv. of commonly used PPh_3 (MeCN, room temperature, 24 h) to give 6-oxaspiro[3.4]octanone **3b** in 62% NMR yield (Scheme 4).† Under the same conditions, alkynones **1c**–**f**, having at the carbonyl function cyclopentyl, cyclohexyl, isopropyl or *n*-propyl substituents, participated well in cyclization reaction (NMR yields of products **3c**–**f**, 27–63%), while methyl (**1g**) and cyclopropyl (**1a**) ynones did not give the corresponding oxa cycles (only tar formation was observed at the conversion of starting materials of *ca*. 50%). Apparently, the formation of product **3a** is prevented by low acidity of the cyclopropyl moiety of alkynone **1a** which hinders the formation of intermediate of type **B** finally causing polymerization of alkynone **1a** through intermediate of type **A**. In view of a good compatibility of methyl alkynone **1g** with other electrophiles under similar conditions,[6–9] additional theoretical studies are required to explain its low reactivity towards aromatic aldehyde **2a** at the **B** → **C** step (see Scheme 3). The influence of electronic nature of substituents in aldehyde component on the reaction outcome was more predictable: the replacement of chlorine with electron-withdrawing nitro group facilitated the formation of product **3h** (93% NMR yield), while the replacement with strong electron-donating methoxy group completely suppressed the studied reaction and formation of **3i**. It should be noted that in all cases, under the elaborated conditions, self-condensation products (see Scheme 1) were not observed.

The preparative yields of target compounds **3** in some cases were significantly lower than the NMR yields (see Scheme 4).



Scheme 4 *Reagents and conditions*: i, PPh_3 (1.0 equiv.), MeCN, room temperature, 24 h. For the products **3a**–**i**, NMR yields are given.

† *The reaction of alkynones* **1** *with aromatic aldehydes* **2** *(typical procedure)*. A 5 ml round-bottom flask with stir bar was sequentially charged with alkynone **1** (1 mmol), aldehyde **2** (1 mmol), dry acetonitrile (2 ml) and PPh_3 (262 mg, 1 mmol). The reaction flask was capped with a glass stopper, and the reaction mixture was stirred at room temperature (20–24 °C) for 24 h. After the reaction completion, the solvent was evaporated and the residue was purified by column chromatography over silica gel using hexane–diethyl ether (95 : 5, v/v) as eluent to afford product **3** as analytically pure sample or as a mixture enriched with the starting aldehyde **2**.

In the latter case, the sample was dissolved in methanol (5 ml), transferred into a separation funnel and mixed with saturated sodium bisulfite water solution (1 ml). The obtained mixture was vigorously shaken for 30 s. Then water (25 ml) and hexane–diethyl ether (9 : 1, v/v) mixture (25 ml) were added. After extraction, the organic layer was separated and dried over $CaCl_2$. The residue after solvent evaporation was purified by column chromatography over silica gel using hexane–diethyl ether (95 : 5, v/v) as eluent to afford product **3** as analytically pure sample.

For characteristics of all new synthesized compounds, see Online Supplementary Materials.

The reason of this is the need for additional purification step to remove traces of starting aldehydes[10] from fractions obtained after column chromatography of crude reaction mixture and enriched with product **3**.

In conclusion, it should be emphasized that here established novel features of the reaction between 1-alkyl-3-phenylpropynones and aromatic aldehydes, on the one hand, do not contradict the previously reported reactivity of methyl alkynone **1g** toward aldehydes of type **2a** whose carbonyl group is not additionally activated by the intramolecular hydrogen bonding with *ortho*-hydroxy or amino groups.[11] On the other hand, for the first time it is demonstrated that alkynones having at the carbonyl group alkyl substituents other than methyl and cyclopropyl may smoothly react even with unactivated aromatic aldehydes in the presence of PPh_3 as a catalyst to regio- and stereoselectively afford pharmaceutically prospective (*Z*)-2-benzylideneoxacyclopentan-3-ones **3**. In view of the revealed high reactivity of C–H active alkynones **1b**–**f**, future challenges in this field are the study of their reactions with aldehydes and related compounds (*e.g.*, imines or Michael acceptors), including detailed optimization of reaction conditions and purification protocols, evaluation of substrate scope, and theoretical rationalization of observed effect of alkyl substituent nature on the reaction outcome.

This work was supported within the state assignment of IrICh SB RAS (theme no. 122041100031-5). The spectral data were obtained with the equipment of the Baikal Analytical Center for collective use SB RAS.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.06.037.

References

1 C. Nájera, L. K. Sydnes and M. Yus, *Chem. Rev*., 2019, **119**, 11110.
2 Y. Li, J. Yu, Y. Bi, G. Yan and D. Huang, *Adv. Synth. Catal*., 2019, **361**, 4839.
3 J. C. Worch, C. J. Stubbs, M. J. Price and A. P. Dove, *Chem. Rev*., 2021, **121**, 6744.
4 S. O. Samultceva, M. Yu. Dvorko, D. A. Shabalin, I. A. Ushakov, A. V. Vashchenko, E. Yu. Schmidt and B. A. Trofimov, *Org. Biomol. Chem*., 2022, **20**, 5325.
5 M. Yu. Dvorko, D. A. Shabalin, I. A. Ushakov, E. Yu. Schmidt and B. A. Trofimov, *Eur. J. Org. Chem*., 2023, **26**, e202201464.
6 J.-H. Li and D.-M. Du, *Adv. Synth. Catal*., 2015, **357**, 3986.
7 L. Liang and Y. Huang, *Org. Lett.*, 2016, **18**, 2604.
8 K. Zhang, L. Cai, S. Hong and O. Kwon, *Org. Lett*., 2019, **21**, 5143.
9 L. Dutta, A. Chattopadhyay, N. Yadav and S. S. V. Ramasastry, *Org. Biomol. Chem*., 2023, **21**, 738.
10 M. H. Furigay, M. M. Boucher, N. A. Mizgier and C. S. Brindle, *J. Visualized Exp*., 2018, **134**, e57639.
11 Z.-X. Deng, Z.-Z. Xie, Y. Zheng, J.-A. Xiao, R.-J. Wang, H. Xiang and H. Yang, *Org. Biomol. Chem*., 2019, **17**, 2187.

Received: 28th February 2024; Com. 24/7407