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A convenient one-pot two-step synthesis of pyrazolylphosphonates from ethynylphosphonate

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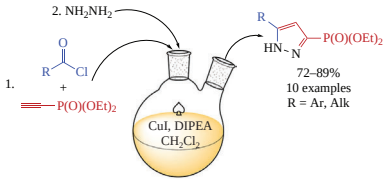
A convenient one-pot preparation of pyrazol-3-ylphosphonates involves Cu-catalyzed cross-coupling of acyl chlorides with diethyl ethynylphosphonate followed by heterocyclization with hydrazine.



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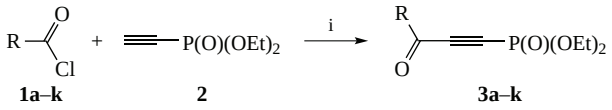
The pyrazole ring is a constituent of various biologically active compounds used as drugs, pesticides, *etc*. Hence, the development of new methods for their synthesis is an urgent problem.[1] Phosphorus-containing pyrazoles obtained recently[2–10] are also of interest due to their biological activity (for examples, see Online Supplementary Materials, Figure S1).

Conjugated ynones are actively used in the synthesis of numerous heterocyclic compounds, including pyrazoles.[11] They can react with nucleophiles according to 1,2- or 1,4-addition mechanism, which in the case of binucleophiles would lead to heterocyclic compounds in general as two regioisomers, while often this addition proceeds selectively. Ynones can also undergo various cycloaddition reactions. In general, ynones were used in the synthesis of pyrazoles, pyrimidines, pyridines, quinolines, benzodiazepines, triazoles, *etc*.[11–13]Among them, conjugated ynones bearing phosphoryl group are hardly investigated due to their low availability based on existing methods.[14–16]

During our work on the development of syntheses of new heterocyclic phosphonates,[17–20] we proposed that conjugated ynones of (3-oxoprop-1-yn-1-yl)phosphonate type could be convenient starting compounds to access various heterocyclic phosphonates, including pyrazoles. In this work, we have developed a new convenient method for the preparation of (3-oxoprop-1-yn-1-yl)phosphonates using Cu-catalyzed cross-coupling of available acyl chlorides and diethyl ethynylphosphonate, and utilized it for the one-pot synthesis of pyrazolylphosphonates.

First, we optimized the conditions for the preparation of (3-oxoprop-1-yn-1-yl)phosphonates using model benzoyl chloride **1a** and diethyl ethynylphosphonate **2** (Scheme 1). When CuI is used as the precatalyst in the presence of ligands (Table 1, entries 1–3), the reaction proceeds in CH_2Cl_2 at room temperature giving diethyl (3-oxo-3-phenylprop-1-yn-1-yl)phosphonate **3a** only in moderate yields, with significant formation of oxidative homocoupling product. However, in the absence of ligands homocoupling did not occur, and the desired phosphonate **3a** was formed in 90% analytical yield (^{31}P NMR) and was isolated in 80% yield (entry 4). Interestingly, inorganic bases were found to be ineffective (entries 5, 6), while DIPEA was the best choice of base. Among solvents, dichloromethane proved to be the most suitable one (entries 7–9).

The conditions developed for **3a** were used for the synthesis of a series of phosphoryl-substituted ynones **3b–k** (see Scheme 1). The benzoyl chlorides containing either electron donating or electron withdrawing group reacted with ethynylphosphonate **2** providing the corresponding ynones **3b–h** in good yields. The best yields were observed in the cases of



1a–k **2** **3a–k**

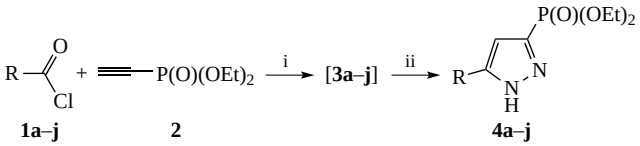
a R = Ph, 80%
b R = 4-MeOC$_6$H$_4$, 71%
c R = 2-MeOC$_6$H$_4$, 71%
d R = 4-MeC$_6$H$_4$, 73%
e R = 4-FC$_6$H$_4$, 70%
f R = 4-ClC$_6$H$_4$, 81%
g R = 4-BrC$_6$H$_4$, 79%
h R = 4-F$_3$CC$_6$H$_4$, 75%
i R = Bu^t, 90%
j R = adamantan-1-yl, 90%
k R = Me, 24%

Scheme 1 *Reagents and conditions*: i, **1**/**2**/DIPEA (1 : 1 : 1 molar ratio), CuI (10 mol%), CH_2Cl_2 (4 ml mmol^{-1}), room temperature, 16 h. Yields are given for 0.25 mmol scale, the yield for **3a** in 6 mmol scale was 83%.

Table 1 Optimization of conditions for the reaction between diethyl ethynylphosphonate **2** and benzoyl chloride **1a**.[a]

Entry	Ligand (mol%)	Solvent	Base	Yield[b] (%)
1	phen (10)	CH_2Cl_2	DIPEA	45
2	TMEDA (10)	CH_2Cl_2	DIPEA	50
3	PPh_3 (20)	CH_2Cl_2	DIPEA	63
4	–	**CH_2Cl_2**	**DIPEA**	**90 (80)**
5	–	CH_2Cl_2	Cs_2CO_3	0
6	–	CH_2Cl_2	K_2CO_3	0
7	–	toluene	DIPEA	15
8	–	THF	DIPEA	34
9	–	MeCN	DIPEA	25

[a] Reaction conditions: CuI (4.8 mg, 0.025 mmol), ligand (0.025–0.05 mmol), ethynylphosphonate **2** (40.5 mg, 0.25 mmol), benzoyl chloride **1a** (32 μl, 0.25 mmol), base (0.25 mmol), solvent (1 ml), room temperature, 16 h. [b] From ^{31}P NMR data, isolated yield is given in parentheses.



1a–j **2** **4a–j**

a R = Ph, 80%
b R = 4-$MeOC_6H_4$, 74%
c R = 2-$MeOC_6H_4$, 73%
d R = 4-MeC_6H_4, 72%
e R = 4-FC_6H_4, 72%
f R = 4-ClC_6H_4, 78%
g R = 4-BrC_6H_4, 73%
h R = 4-$F_3CC_6H_4$, 73%
i R = Bu^t, 89%
j R = adamantan-1-yl, 85%

Scheme 2 *Reagents and conditions*: i, **1**/**2**/DIPEA (1 : 1 : 1 molar ratio), CuI (10 mol%), CH_2Cl_2 (4 ml $mmol^{-1}$), room temperature, 16 h; ii, $N_2H_4 \cdot H_2O$ (1.5 equiv.), room temperature, 1 h. Yields are given for 0.25 mmol scale.

aliphatic acyl chlorides **1i**,**j**. However, acetyl chloride **1k** gave the corresponding product **3k** only in 24% yield. Importantly, the procedure was good for scaling up as ynone **3a** was obtained by application of 24-fold amount of reactants in 83% yield (1.32 g).

We also studied the possibility of using the conditions, developed for the synthesis of (3-oxoprop-1-yn-1-yl)-phosphonates **3**, in the synthesis of phosphonylpyrazoles without preliminary isolation. In fact, when the reaction between acyl chlorides **1a**–**j** and diethyl ethynylphosphonate **2** was complete, the futher addition of hydrazine hydrate to the reaction mixture provided quantitative (^{31}P NMR data) formation of the corresponding pyrazoles **4a**–**j** (Scheme 2).†

In conclusion, a convenient procedure for the preparation of (3-oxoprop-1-yn-1-yl)phosphonates by the Cu-catalyzed cross-coupling of acyl chlorides with diethyl ethynylphosphonate was developed. On this basis, a one-pot two-step synthesis of pyrazol-3-ylphosphonates has been proposed. Further study of the possibility of the application of (3-oxoprop-1-yn-1-yl)-phosphonates to the synthesis of other heterocyclic phosphonates is now underway.

† *General procedure for the synthesis of (3-oxoprop-1-yn-1-yl)-phosphonates* **3a**–**k** *and pyrazol-3-ylphosphonates* **4a**–**j**. A 8 ml glass vial was charged with diethyl ethynylphosphonate **2** (40.5 mg, 0.25 mmol), CuI (4.8 mg, 0.025 mmol), DIPEA (40 μl, 0.25 mmol), dry dichloromethane (1 ml) and acyl chloride **1a**–**k** (0.25 mmol) under Ar. The vial was closed with Teflon cap, and the mixture was stirred at room temperature for 16 h. For the preparation of **3a**–**k**, the mixture was evaporated, and the residue was purified by column chromatography on silica gel using EtOAc–hexane as the eluent. For the preparation of **4a**–**j**, when the first reaction was complete (16 h), hydrazine hydrate (18 μl, 0.375 mmol) was added, and the mixture was stirred for more 1 h. The solvent was evaporated, and the residue was purified by column chromatography on silica gel using CH_2Cl_2–MeOH as the eluent. Known compounds **3a**,**d**–**i**,[15] **3k**[16] and **4a**–**h**[21] gave satisfactory spectroscopic data being in agreement with previously reported ones. New compounds were fully characterized (see Online Supplementary Materials).

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.07.033.

References

1 S. Fustero, M. Sánchez-Roselló, P. Barrio and A. Simón-Fuentes, *Chem. Rev.*, 2011, **111**, 6984.
2 N. S. Goulioukina, N. N. Makukhin and I. P. Beletskaya, *Russ. Chem. Rev*., 2016, **85**, 667.
3 M. F. Jamali, N. K. Vaishanv and K. Mohanan, *Chem. Rec.*, 2020, **20**, 1394.
4 N. S. Goulioukina, N. N. Makukhin, E. D. Shinkarev, Y. K. Grishin, V. A. Roznyatovsky and I. P. Beletskaya, *Org. Biomol. Chem.*, 2016, **14**, 10000.
5 R. M. N. Kalla and I. Kim, *Mol. Catal.*, 2019, **473**, 110396.
6 X. Peng, X. Zhang, S. Li, Y. Lu, L. Lan and C. Yang, *Org. Chem. Front.*, 2019, **6**, 1775.
7 L. Imen and T. Soufiane, *Heterocycles*, 2017, **94**, 894.
8 E. Yu. Levashova, D. D. Zhukovsky, D. V. Dar'in and M. Yu. Krasavin, *Chem. Heterocycl. Compd.*, 2020, **56**, 806 (*Khim. Geterotsikl. Soedin*., 2020, **56**, 806).
9 M. Dhameja and J. Pandey, *Asian J. Org. Chem*., 2018, **7**, 1502.
10 S. F. Malysheva, V. A. Kuimov, N. A. Belogorlova, N. K. Gusarova, I. V. Taydakov, A. I. Albanov, I. L. Eremenko and B. A. Trofimov, *Mendeleev Commun*., 2019, **29**, 683.
11 C. Nájera, L. K. Sydnes and M. Yus, *Chem. Rev.*, 2019, **119**, 11110.
12 D. Bag and S. D. Sawant, *Chem. – Eur. J*., 2021, **27**, 1165.
13 E. F. Sagitova, D. N. Tomilin, O. V. Petrova, A. B. Budaev, L. N. Sobenina, B. A. Trofimov, G. Q. Yang and R. Hu, *Mendeleev Commun*., 2019, **29**, 658.
14 E. Öhler and E. Zbiral, *Monatsh. Chem*., 1984, **115**, 493.
15 L. Liao, H. Zhang and X. Zhao, *ACS Catal*., 2018, **8**, 6745.
16 Y. Moglie, E. Mascaró, V. Gutierrez, F. Alonso and G. Radivoy, *J. Org. Chem*., 2016, **81**, 1813.
17 A. Mitrofanov, A. Bessmertnykh-Lemeune, C. Stern, R. Guilard, N. Gulyukina and I. Beletskaya, *Synthesis*, 2012, **44**, 3805.
18 A. V. Murashkina, A. Yu. Mitrofanov, Y. K. Grishin, V. B. Rybakov and I. P. Beletskaya, *ChemistrySelect*, 2018, **3**, 6810.
19 A. Yu. Mitrofanov, Y. Rousselin, V. N. Khrustalev, A. V. Cheprakov, A. Bessmertnykh-Lemeune and I. P. Beletskaya, *Eur. J. Inorg. Chem.*, 2019, 1313.
20 A. Yu. Mitrofanov, V. A. Bychkova, S. E. Nefedov and I. P. Beletskaya, *J. Org. Chem*., 2020, **85**, 14507.
21 R. Kumar, D. Verma, S. M. Mobin and I. N. N. Namboothiri, *Org. Lett*., 2012, **14**, 4070.

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