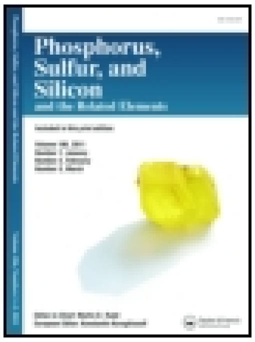

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SHORT COMMUNICATION

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Synthesis of 1,2,3-triazolyl-5-diethylphosphonate by domino reaction

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ABSTRACT

The synthesis of 1,2,3-triazolyl-5-diethylphosphonate was studied by the domino reaction of benzyl azide, phenylacetylene and diethyl phosphite. The effect of the reaction stoichiometry, the atmosphere and the amount of the catalyst were investigated.

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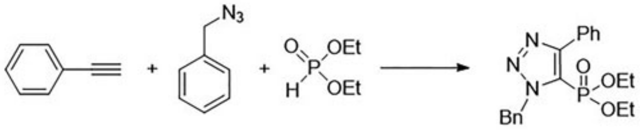
KEYWORDS
1,2,3-triazolyl-5-diethylphosphonate; domino reaction; Cu(I) catalyst; triazole ring

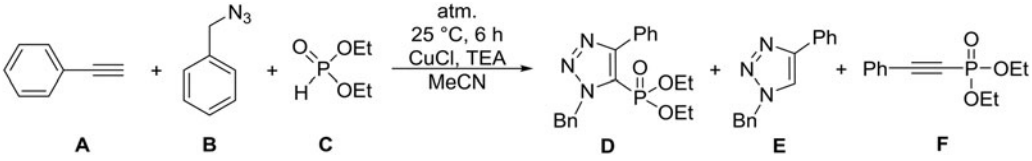
GRAPHICAL ABSTRACT



Over the last years, the chemistry of heterocyclic aminophosphonates has received an intense interest due to their versatile bioactivities.[1] Some triazolylphosphonate derivatives have been used for protein binding studies[2] and their analogs were suitable for bioconjugation.[3] One of the most effective tools for the preparation of heterocyclic aminophosphonates is multicomponent reactions (MCR). These transformations have several benefits, such as high atom economy, fast and simple accomplishment, ability to save time and energy and being environmentally-friendly.[4,5] The domino reaction belongs to the group of MCR but despite its outstanding properties, only one example can be found for the synthesis of triazolylphosphonates by domino reaction.[6]

In this work, the synthesis of 1,2,3-triazolyl-5-diethylphosphonate was investigated (Table 1). Preliminary experiments were carried out for the domino reaction of benzyl azide, phenylacetylene and diethyl phosphite in the presence of CuCl as a catalyst and trimethylamine as a base, at room temperature in acetonitrile. The effect of the reaction stoichiometry, the atmosphere and the amount of the catalyst were studied. First, the domino reaction was performed under a nitrogen atmosphere, and instead of the desired triazolylphosphonate (**D**), 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (**E**) was the main product (68%), which was formed by the click reaction of benzyl azide and phenylacetylene (Table 1/Entry 1). Carrying out the reaction in an open-air flask, the ratio was reversed, and the triazolylphosphonate (**D**) was formed in 53%, along with 7% of diethyl (phenylethynyl)-phosphonate (Table 1/Entry 2). Increasing the amount of the diethyl phosphite to two equivalents, the proportion of

Table 1. Domino reaction of benzyl azide, phenylacetylene and diethyl phosphite.



	A	B	C	Catalyst		Product composition* [%]		
Entry	Equiv.				Atmosphere	D	E	F
1	1	1.1	1.1	0.1	N_2	32	68	1
2	1	1.1	1.1	0.1	air	53	39	7
3	1	1.1	2	0.1	air	71	26	3
4	1	1.1	2	0.1	air bubbling	**83**	14	3
5	1	1.1	3	0.1	air bubbling	54	43	3
6	1	1.1	2	0.15	air bubbling	65	31	4

*Based on HPLC (222 nm).

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product **D** was 71%, which was further increased (83%) using continuous air bubbling (Table 1/Entries 3 and 4). Applying a larger excess of diethyl phosphite or catalyst increased the ratio of triazole (**E**) instead of the ratio of product **D** (Table 1/Entries 5 and 6). The best result was obtained by using two equivalents of diethyl phosphite and 10% of CuCl, applying continuous air bubbling. Extension of the reaction for the synthesis of various new triazolylphosphonates is being investigated.

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