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Oxidative C–O coupling as a new idea in the 'click-like chemistry': malonyl peroxides for the conjugation of two molecules

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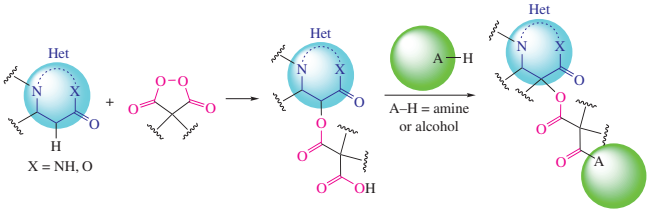
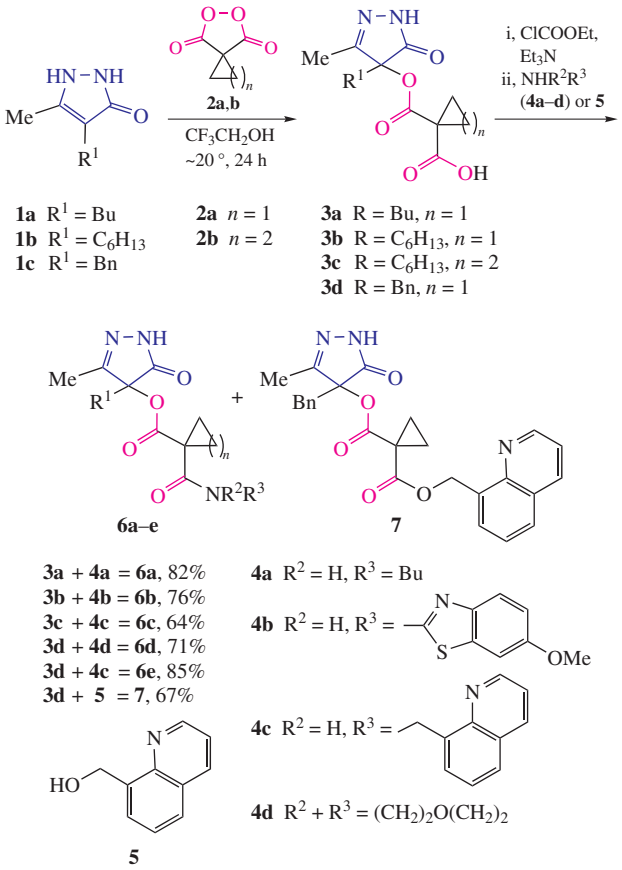
Malonyl peroxides were used for the one-pot construction of hybrid structures by conjugation of heterocycle (3*H*-pyrazol-3-one, isoxazol-5(2*H*)-one, pyrazolidine-3,5-dione, or barbituric acid) and amine or alcohol. The first stage represents oxidative C–O coupling with liberation of the carboxyl group which is functionalized at the second stage thus affording 'click-like' products with malonic linker.



In recent decades, the use of linkers in order to obtain structures with several pharmacophore groups has become a powerful tool for developing new lead compounds in the field of medicinal chemistry.[1,2] The demand for the quick, convenient and reliable synthetic approaches to hybrid structures and materials[3] resulted in the creation of 'click chemistry' concept.[4–8] 'Click chemistry'[4] implies pairs of functional groups reacting ('clicking') rapidly and selectively with one another under mild conditions and in good yields.

Examples of the most popular linkers in 'click chemistry' are triazole[9] and to a lesser extent dicarboxylic acids esters.[10] We suppose that the 'click chemistry' concept may involve oxidative processes along with well-recognized cycloaddition and condensation.[11] Oxidative coupling strategy includes the direct (without pre-functionalization) formation of new bonds, accompanied by abstraction of hydrogen atom from the substrate. However, the use of oxidation and especially oxidative coupling processes[12] in the design of structures with pharmacophore groups connected *via* linker has not been reported so far.

Here we proposed the idea of the hybrid molecule construction based on the oxidative C–O coupling of heterocyclic compounds with malonyl peroxides[13] for the connection of two heterocyclic moieties *via* malonate linker. Malonate type linker was applied to the construction of conjugates with anti-HIV,[14] antiangiogenic,[15] antibacterial,[16] including anti-tuberculosis,[17] activities. The known methods for the introduction of a malonate linker include successive functionalization of COOH groups in malonic acid in several steps using additional reagents: DCC[16(*a*)] and $SOCl_2$/pyridine.[14,15,16(*b*),17] The construction of the target hybrid structure in our study occurs *via* two successive one-pot stages: (i) oxidative C–O coupling of the heterocycle [3*H*-pyrazol-3-ones, isoxazol-5(2*H*)-one, pyrazolidine-3,5-dione, or barbituric acid] with malonyl peroxide, and (ii) reaction of formed carboxyl group in C–O coupling product with amines or alcohol (Schemes 1–4).†



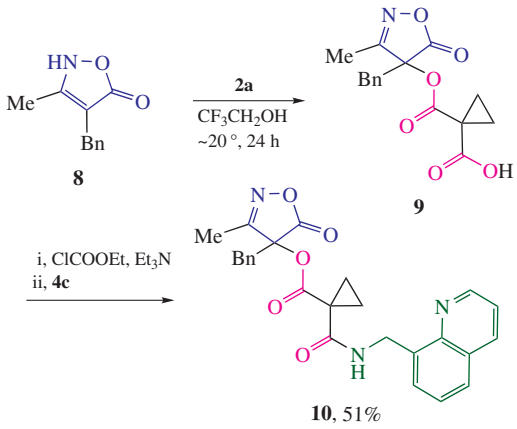
Scheme 1

† *General procedure*. Malonyl peroxide **2** (1.10 mmol) was added with stirring to a solution of heterocyclic substrate **1**, **8**, **11** or **14** (1 mmol) in CF_3CH_2OH (2 ml). The reaction mixture was stirred at 20–25 °C for 24 h and concentrated under water-jet vacuum. Subsequently, THF (2 ml) was added, the mixture was cooled to 0 °C, and ethyl chloroformate (173.6 mg, 1.6 mmol) and triethylamine (161.9 mg, 1.6 mmol) were added at stirring. After 30 min at 0–10 °C, amine **4** or alcohol **5** (2 mmol) was added to the reaction mixture. The mixture was stirred at 20–25 °C for 12 h and worked up, the yields of the conjugated products **6**, **7**, **10**, **13** and **16** refer to isolated material over both steps. For details, see Online Supplementary Materials.

The products thus obtained in view of multiple data[18–25] may be supposed to be useful.

In our hands, 3*H*-pyrazol-3-ones **1a–c** played the role of the first heterocycle component, malonyl peroxides **2a**,**b** were malonate linker precursors, and amines **4a–d** or alcohol **5** served as the second partner. The syntheses were carried out by a one-pot procedure and provided yields from good (**6c**, 64%) to high (**6e**, 85%) (see Scheme 1).

The one-pot synthesis of hybrid structure **10** from isoxazol-5(2*H*)-one **8** as first heterocycle, malonyl peroxide **2a** as malonate linker precursor and 1-(8-quinolinyl)methanamine **4c** was performed in good 51% yield (Scheme 2).

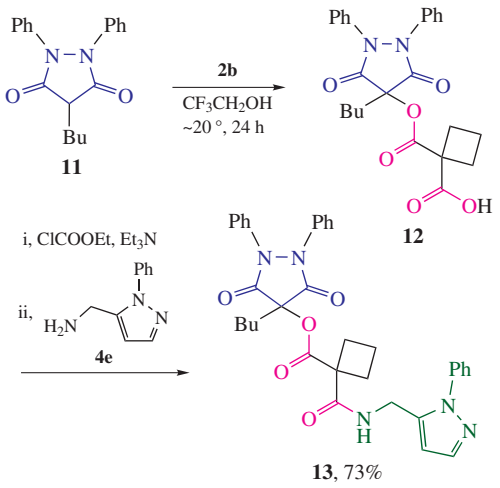


Scheme 2

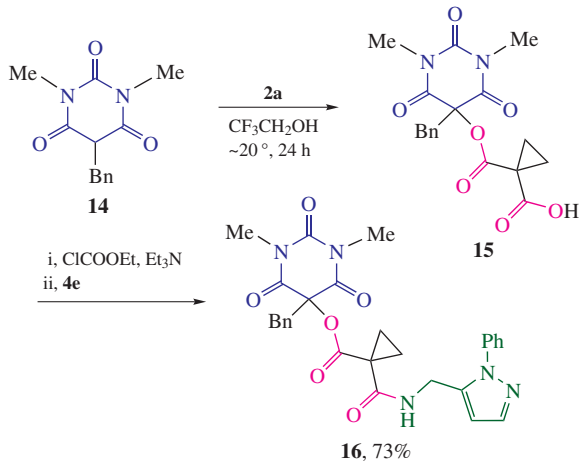
The use of phenylbutazone **11** as first heterocycle, malonyl peroxide **2b** as malonate linker precursor and (1-phenyl-1*H*-pyrazol-5-yl)methanamine **4e** as the second partner led to hybrid structure **13** in 73% yield (Scheme 3).

The conjugation of barbituric derivative **14**, malonyl peroxide **2a** and (1-phenyl-1*H*-pyrazol-5-yl)methanamine **4e** resulted in product **16** in 73% yield (Scheme 4).

Importantly, products **6**, **7**, **10**, **13** and **16** were prepared in respectable yields (51–85%) directly from the corresponding heterocyclic substrates **1**, **8**, **11** and **14**. The mechanism for the oxidative C–O coupling of the starting heterocycles with the malonyl peroxides was proposed.[13] Firstly, activation of the malonyl peroxide **2** with CF_3CH_2OH occurs. The formation of C–O coupling products **3**, **9**, **12** and **15** results from nucleophilic attack of the double bond or enol tautomer of the substrate on the activated malonyl peroxide, followed by proton reorganization. As chemical behavior of spiro peroxides **2a**,**b** in the oxidative



Scheme 3



Scheme 4

C–O coupling with heterocycles **1**, **8**, **11** and **14** is representative for various malonyl peroxides[13] and reactivity of the liberated carboxyl group in C–O coupling product **3**, **9**, **12** and **15** is common, it can be expected that the idea of using malonyl peroxides for the conjugation of two molecules is applicable to the preparation of a variety of hybrid structures. The employment of this method is not limited to conjugation of heterocycles. The proposed protocol can be extended to some biologically active natural compounds (*e.g.*, containing aromatic rings vitamins, terpenoids, steroids) which are known to react with malonyl peroxides.[26]

We believe that the suggested idea of conjugation of two heterocyclic moieties *via* a malonate linker with the use of oxidative coupling process is consistent with the concept of 'click chemistry'. Clearly, the herein reported strategy for the introduction of the linker based on oxidative coupling satisfies the main rules for a 'click' reaction: it is modular, broad in scope, gives high yields, generates no byproducts, uses simple reaction conditions, utilizes readily available starting materials and reagents, the solvents are easily removed, and product isolation is facile.

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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.2019.03.003.

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