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Unveiling an underestimated potential of vanillin-derived alkynes: synthesis of highly functionalized 3(2*H*)-furanone with antiradical activity

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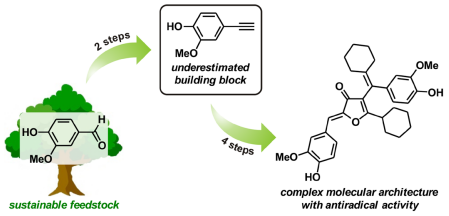
Target-oriented synthesis of highly functionalized 3(2*H*)-furanone from vanillin through several alkyne intermediates was realized in six steps. The title compound bearing two 4-hydroxy-3-methoxyphenyl moieties showed antiradical activity 1.54 times higher compared to Trolox.

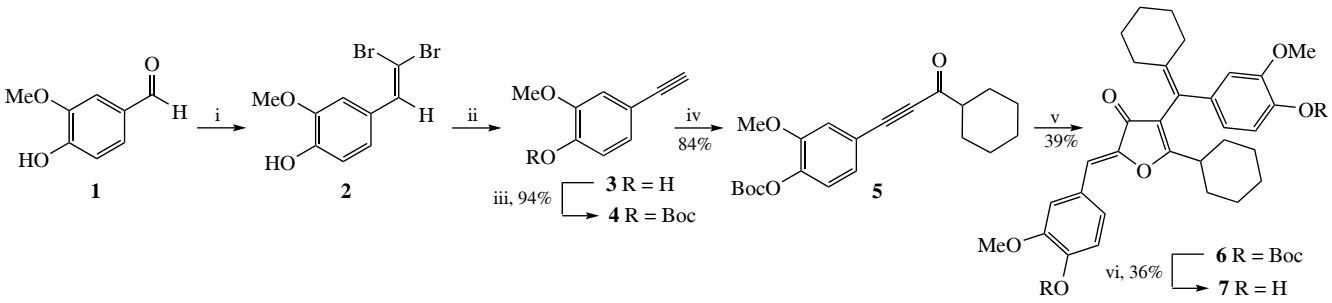


Keywords: vanillin, alkynes, acetylenic ketones, 3(2*H*)-furanones, radical scavenging activity.

An efficient replacement of fossil resources with environmentally friendly and sustainable feedstocks for the synthesis of high added-value compounds represents one of the most pressing challenges of modern organic chemistry. Due to its abundance and renewability, the forest biomass has been proposed as a promising source for the green production of diverse chemicals.[1] Notable among them is vanillin **1**, a product of lignin depolymerization,[2] having aromatic structure and three functional groups, which has already demonstrated great potential in all walks of chemistry, from drug discovery to materials science.[3] Particularly, the aldehyde group of vanillin could be readily modified by the Corey–Fuchs reaction[4] to afford a novel alkyne building block that was successfully employed in the synthesis of pharmaceutically prospective molecular architectures only *via* traditional cross-coupling[5,6] and cycloaddition reactions.[7–11] Meanwhile, in recent years alkynes with highly reactive carbon–carbon triple bond have become an ideal structural unit for a number of atom-economic and energy-saving processes[12–14] and, therefore, vanillin-derived alkynes can provide access to a much wider chemical space.

As a part of our long-standing research interest in the chemistry of acetylenes,[15–20] in this communication we report our first attempt to unveil an underestimated synthetic potential of vanillin-derived alkyne building blocks. Based on our recent experience,[18] we designed and realized the synthetic route from vanillin **1** to highly functionalized 3(2*H*)-furanone (Scheme 1). It is relevant to note here that the parent heterocyclic scaffold is widely met in natural products and biologically active compounds,[21] and its conjugation with vanillin moiety is undoubtedly of interest for medicinal chemistry.

According to the published protocols,[4] vanillin **1** was first converted to alkyne **3** by the Corey–Fuchs reaction through 1,1-dibromoalkene **2**. Next, to avoid difficulties in subsequent steps, the phenolic group was protected by the treatment of alkynylphenol **3** with Boc anhydride furnishing protected alkyne **4**. The cross-coupling of the latter with cyclohexanecarbonyl chloride in the presence of $Pd(PPh_3)_2Cl_2$/CuI/Et_3N catalytic system provided alkynone **5** in good yield (84%), which was further subjected to Bu^{t}ONa-catalyzed dimerization into Boc-protected 3(2*H*)-furanone **6**. The yield of the latter was 39% which is comparable to the yields previously reported for the dimerization of related alkynones.[18] It should be noted that the final deprotection step did not proceed at room temperature while at high temperature (100 °C) significant decomposition of the target 3(2*H*)-furanone **7** occurred, resulting in only moderate 36% yield. Obviously, with a proper choice of the protecting group, the outcome of this step should be improved.



Scheme 1 *Reagents and conditions*: i, CBr_4 (2.0 equiv.), PPh_3 (4.0 equiv.), CH_2Cl_2, 0 °C, 3 h (ref. 4); ii, BuLi (4.0 equiv.), THF, –60 °C, 2 h (ref. 4); iii, Boc_2O (1.5 equiv.), Et_3N (1.5 equiv.), DMAP (10 mol%), CH_2Cl_2, room temperature, 2.5 h; iv, CyC(O)Cl (1.5 equiv.), $Pd(PPh_3)_2Cl_2$ (1 mol%), CuI (3 mol%), Et_3N (1.25 equiv.), THF, room temperature, 14 h; v, Bu^{t}ONa (25 mol%), PhMe, room temperature, 2 h; vi, 10% aq. HCl, dioxane, 100 °C, 3 h.

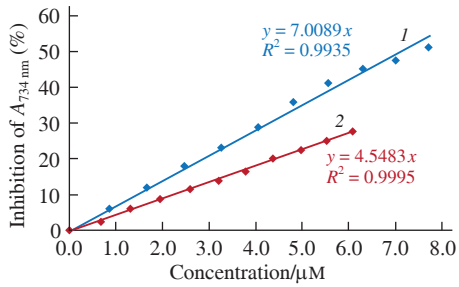


Figure 1 Degree of inhibition of the absorbance at 734 nm as a function of the concentration of (*1*) compound **7** and (*2*) Trolox.

Vanillin derivatives are an important class of antioxidants that inhibit oxidation reactions by neutralizing free radicals through the formation of stable phenoxy radicals. Since many diseases such as cancer, atherosclerosis, Alzheimer's and Parkinson's diseases, *etc.* are accompanied by a violation of redox processes and a subsequent damage of biomolecules, the study of the biological activity of drug candidates in these cases is usually preceded by measuring their antiradical activity *in vitro*. In this context, we have assessed the free radical scavenging activity of 3(2*H*)-furanone **7** using 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) radical cation ($ABTS^{\bullet+}$).[22] Briefly, an aliquot of ethanol solution of compound **7** was added to $ABTS^{\bullet+}$ working solution every 4 min, and the absorbance at 734 nm was measured. As follows from the obtained results (Figure 1), the title compound **7** showed 1.54 times higher activity than Trolox as a standard antioxidant.

In conclusion, we designed highly functionalized 3(2*H*)-furanone decorated with two 4-hydroxy-3-methoxyphenyl moieties utilizing available vanillin as the starting material. The $ABTS^{\bullet+}$-scavenging assay of the target compound confirmed the expected good antiradical activity with TEAC value of 1.54. Further studies to demonstrate a high synthetic potential of vanillin-derived alkyne building blocks in the target-oriented synthesis of pharmaceutically promising compounds are currently underway in our lab.

The spectral data were obtained with the equipment of the Baikal Analytical Center for collective use SB RAS. HRMS spectra were recorded at Shared Research Facilities for Physical and Chemical Ultramicroanalysis, Limnological Institute, SB RAS.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7727.

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