

Synthesis of 1,4-naphthoquinone derivatives using 1,3-dipolar cycloaddition and Sonogashira reactions

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ABSTRACT: Naphthoquinones are known according to their important bio-activities, such as their antitumoral and topoisomerase inhibition properties. From 2-azido (**3**) or 2,3-diacetylene-1,4-naphthoquinone (**4**) it was possible to obtain triazole derivatives (naphthoquinonic). This work describes the synthesis of two novel molecules, with triazole groups linked to 1,4-naphthoquinone using the 1,3-dipolar cycloaddition and Sonogashira reactions. The synthetic strategy followed two routes (Scheme 1). First, we synthesized the 2-bromo-1,4-naphthoquinone (**2**, yield 98%) by using Br_2 and $\text{CH}_3\text{CO}_2\text{H}$, and then used it to obtain 2-azido-1,4-naphthoquinone (**3**, yield 62%) from compound **1**, along with ethanolic solution (reflux) and NaN_3 . Finally, we prepared 1,2,3-triazole compounds (**4a**, **b**) by 1,3-dipolar cycloaddition, involving compound (**3**) and terminal acetylenes (phenylacetylene, **a**) and glycoside (**b**) using $\text{Cu}(\text{OAc})_2$ and ascorbate, under argon atmosphere. During the second step, 2,3-dibromo-1,4-naphthoquinone was prepared using $\text{Br}_2/\text{CH}_2\text{Cl}_2$ at room temperature. From compound (**5**) it was possible to synthesize (**6**), catalyzed by $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2/\text{CuI}/\text{Et}_3\text{N}$, under argon atmosphere, in 40% yield. The 1,3-dipolar cycloaddition reactions involving 2-azido-1,4-naphthoquinone (**3**) and alkynes (**a**, yield 23% and **b**, yield 30%) were conducted using the solvent system, (1:1) *tert*-BuOH/ $\text{H}_2\text{O}/\text{r.t.}$ 20 mol% of $\text{Cu}(\text{OAc})_2$ and sodium ascorbate, under stirring during 24 hours. The reaction involving 2,3-dibromo-1,4-naphthoquinone (**5**, yield 65%) and phenylacetylene was prepared using the solvent mixture (2:1) DMSO/ CHCl_3 and catalytic amount of $\text{CuI}/\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$. The final products were characterized by elemental analysis and spectrometric techniques (IR, NMR ^1H and ^{13}C). Two novel triazole compounds were synthesized from naphthoquinones by 1,3-dipolar cycloaddition from suitable 1,4-naphthoquinones obtained by Sonogashira couplings.

Keywords: 1,4-naphthoquinone; cycloaddition 1,3-dipolar; Sonogashira coupling

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