Effective approach to 4,5-Diaryl-3(2H)-furanones – a promising inhibitors for COX-2

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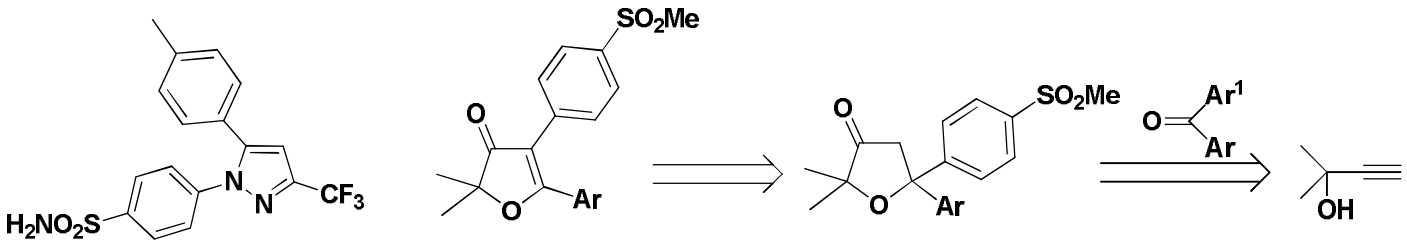
The efficiency of selective inhibitors for COX-2 in therapeutics of the arthritis, arthritis-associated disorders and postoperative pain strongly depends on the structure of a drugs employed [1-3]. Careful investigations on COX-1 and COX-2 structures had shown, that the key structural motif here is a secondary 'pocket' in the molecule of COX-2 [4,5], which allows 1,2-diarylsubstituted compounds to be localized within the space of this 'pocket' by one of the aryl group, that is impossible in the case of COX-1. An important role for coordination of such molecule in this area also plays hydrogen bonds, arising due to incorporation of SO_2NH_2 and SO_2Me groups in *p*-position of aryl ring. These bonds hold a molecule of inhibitor in the active region of a ferment thus increasing the efficiency of the drugs used.



1, Celecoxibe **2** **3** **4**

The initial testing of substituted 3(*2H*)-furanones for biological activity performed by scientists from South Korea [6,7] demonstrated that the derivatives of 4-(methylsulfo-nyl)phenyl-3(*2H*)-furanones **2**, similar in structure to Celecoxibe **1**, are also profitable selective inhibitors for COX-2 [6,7]. During the *in vivo* experiments on inhibition of carrageenan-induced rat paw edema and arthritis in Sprague-Darley rats, these compounds exhibited anti-inflammatory activity IC_{50} at the level of 0.05 - 1.00 μg/mL and ratio of selectivities COX-2 / COX-1 from 100 to 1000 depending on the nature of substituents in aryl rings of furanone **2**.

Therefore 3(*2H*)-furanones have aroused considerable interest as a potential high-active nonsteroid antiinflammatory drugs and elaboration of the effective methods for their synthesis presents an important task for organic chemists. A 6-stage scheme of their synthesis, which was developed earlier [6, 7], provided 3(*2H*)-furanones in the yields of up to 17%. The prime objective of our current research was to elaborable a new approach to potential NSAIDs with the structure of 4,5-diaryl 3(*2H*)-furanones **2** based on reactions of substituted tetrahydrofuranones **3** [8]. The developed 6-stage process for their synthesis from the commercially available Favorsky acetylene and *p*-substituted benzophenones enables one to prepare 3(*2H*)-furanones of the type **3** in 22-30% yields, with the reagent costs of $0.6 per 1g of a target product.

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