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Efficient Synthetic Approach to Substituted Benzo[*b*]furans and Benzo[*b*]thiophenes by Iodine-Promoted Cyclization of Enaminones

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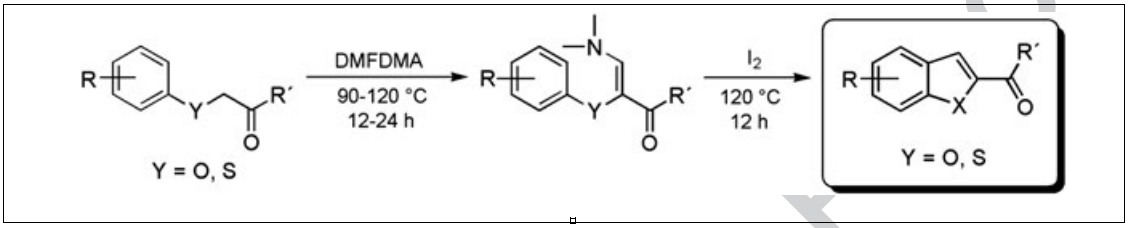

An efficient synthetic approach to the substituted benzo[*b*]furan and benzo[*b*]thiophene scaffolds by iodine-mediated cyclization of the corresponding enaminones is described. This protocol was applied to a large series of these latter precursors to afford the respective benzoheterocycles substituted at the C-2 position by a carbonyl group functionality. A study of the factors that control this process reveals that the reactivity depends on the presence of electron-donor groups in the aryl ring of the aryloxycarbonylic and arylthiocarbonylic moieties.

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INTRODUCTION

An intense effort has been made to synthesize benzo[*b*]furans [1–8] and benzo[*b*]thiophenes [1–3,9–11], because of their biological activity as potential pharmacological agents, and to their occurrence in nature [12,13]. Different substitution patterns in these heterocycles have provided new opportunities for drug discovery and novel applications in material science. Consequently, a strong demand exists for the design of new structures of these heterocycles, as well as new or improved methodologies for their efficient synthesis.

Benzo[*b*]furans and their derivatives exhibit a broad range of biological activities, such as antineoplastic [14–17], antioxidant [18,19], and anti-inflammatory [20]. As a result, a number of routes of synthesis have been described in the literature, in particular those leading to 2-substituted benzo[*b*]furans [1–11,21]. As pharmaceutical agents, benzo[*b*]thiophene derivatives are used as estrogen receptor modulators [22], mitotic inhibitors [23,24], multidrug resistance modulators [25], angiogenesis inhibitors [26–28], and antimicrobial [29], antidepressant [30], and anti-inflammatory [31–33] agents. Moreover, the 2-substituted benzo[*b*]-thiophene moiety is present in various drugs on the market today, such as zileuton, a potent and selective inhibitor of 5-lipoxygenase [34], and raloxifene [22,35], an agent for treating osteoporosis. Therefore, several synthetic approaches have been developed to construct their benzene-fused heterocyclic skeleton, commonly starting from a benzene ring with the appropriate substituents, on which the five-membered heterocyclic ring is built [36].

Recently, we reported a novel straightforward synthesis of benzo[*b*]furans [37–39], through an intramolecular cyclization of properly functionalized enaminones, which was successfully extended to the preparation of indoles [40] and coumarins [41]. With the aim of optimizing and extending our methodology to other kinds of benzo[*b*]-heterocycles, we hereby describe the development of alternative conditions for the preparation of benzo[*b*]furans **1**, and the synthesis of benzo[*b*]thiophenes **2**, by using enaminones **3** and **4** as their precursors, respectively (Scheme 1). **S1**

RESULTS AND DISCUSSION

2-Alkoxycarbonyl-, 2-acyl-, and 2-aroyl-benzo[*b*]-fused five-membered heterocyclic rings **1a–j** and **2a–n** were synthesized according to the sequence of reactions illustrated in Schemes 2 and 3 and Tables 1–3. Thus, the aryloxycarbonylic, **5a–j** [38,39], and the arylthiocarbonylic, **6a–n**, compounds were prepared in moderate to good yields (41–99%) by a reaction between the substituted phenols **7a–f** or thiophenols **8a–e** with the corresponding α-haloesters (**9a–b**) or α-haloketones (**9c–k**), in the presence of potassium carbonate in acetone at reflux for 12 h (Scheme 2). 2-Bromoacetophenones **9d–k** are commercially available or can be prepared by bromination of the corresponding acetophenones, **10a–h**, with bromine in **S2 S3 T1 T2 T3**