Month 2012  Efficient Synthetic Approach to Substituted Benzo[b]furans and Benzo[b]thiophenes by Iodine-Promoted Cyclization of Enaminones

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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 enaminoles, 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 enaminoles 3 and 4 as their precursors, respectively (Scheme 1).

RESULTS AND DISCUSSION

2-Alkoxy carbonyl-1, 2-acyl-, and 2-aryloxy-carbonyl 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 aryloxycarbonyl, 5a–j [38,39], and the arylthiocarbonyl, 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-haloketones (9a–h) or ζ-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 brominated by the corresponding acetophenones, 10a–h, with bromine in

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