



Synthesis, characterization of novel benzothiophene

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Abstract

A library of novel benzo[*b*]thiophene have been synthesized regioselectively in good yields through the one-pot domino reactions of thiophenone, malononitrile and aromatic aldehydes in the presence of NaOEt. This transformation presumably involves Knoevenagel condensation–Michael addition–intramolecular Thorpe-Ziegler cyclization–Tautomerization–Elimination sequence of reactions.

Keywords

Benzothiophene, thiophene, malononitrile.

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Article History: Received 01 October 2020; Accepted 10 December 2020

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1. Introduction

benzo[*b*]thiophene derivatives are found within the structural core of several biologically active compounds, for example, raloxifeneTM is a selective estrogen receptor modulator for the prevention of osteoporosis in postmenopausal women [1] and zileutonTM is an active inhibitor of 5-lipoxygenase used to prevent difficulty in breathing, wheezing and coughing due to asthma and sertaconazole has several known mechanisms of action (Figure 1) [2].

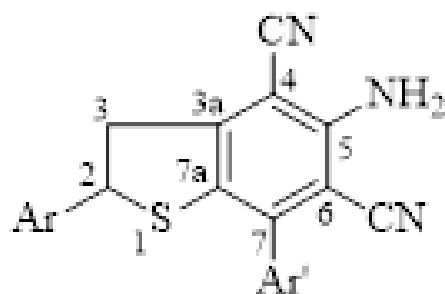


Figure 1. Benzo[*b*]thiophene derivatives synthesized in the present work

Other pharmacological applications of benzo[*b*]thiophene derivatives include estrogen receptor antagonists, [3] antifungal, [4] antiinflammatory [5] and antimetabolic [6] agents. The

above significance of benzo[*b*]thiophene derivatives has set path to several investigations leading to their synthesis and biological activity studies [7].

Several other molecular entities containing benzothiophene core are at various stages of development. They include **T588** [8] a cognition enhancing agent with potential application for treating Alzheimer's dementia; **LY353381** [9] an additional SERM from Lilly; **AP521** [10] with potent 5HT_{1A} receptor binding ability; **CI959** [11] an anti-inflammatory agent; and **B428** [12] a urokinase inhibitor. Another structurally interesting compound is **PD144795** [13] an endothelial cell activation inhibitor as a benzothiophene oxide (Figure 3).

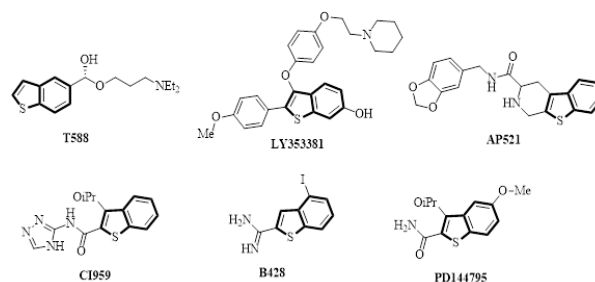
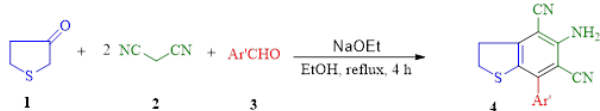


Figure 2. Benzothiophenes Various stages of development

In view of the importance of benzothiophene derivatives, herein we report a domino protocol for the regioselective synthesis of a library of highly functionalized novel 5-amino-2,7-diaryl-2,3-dihydrobenzo[*b*]thiophene-4,6-dicarbonitriles **4** in good yields through the one-pot four-component reactions of 5-aryldihydro-3(*2H*)-thiophenones **1**, malononitrile **2** and aromatic aldehydes **3** in the presence of morpholine (Scheme 1).



Scheme 1 Synthesis of 2,3-dihydrobenzo[*b*]thiophene-4,6-dicarbonitriles **4**

2. Structure elucidation

The structure of all the Benzo[*b*]thiophenes **4** were elucidated unambiguously with the help of one and two-dimensional NMR spectroscopy. As a representative case, the ¹H and ¹³C NMR chemical shift assignment of **4r** are discussed.

In the ¹H NMR spectra of **4r**, the 2-CH and the 5-NH₂ protons overlap and appear as a multiplet at 5.01–5.08 ppm. The D₂O exchange experiment reveals that the H-2 appears as a triplet at 5.04 ppm (*J* = 8.4 Hz) and the latter appears as a broad singlet at 5.08 ppm.

Table 1. Yield and melting point of Benzo[*b*]thiophene **4**

Entry	Comp	Ar'	Yield of 4 (%)	mp (°C)
1	4a	4-MeC ₆ H ₄	79	165-167
2	4b	4-MeOC ₆ H ₄	85	167-169
3	4c	4-ClC ₆ H ₄	72	175-177
4	4d	4-FC ₆ H ₄	73	157-1159

^a Isolated yield after purification by column chromatography

3. Conclusion

The present investigation reports a one-pot domino protocol for the regioselective synthesis of novel Benzo[*b*]thiophene via Knoevenagel condensation–Michael addition–intramolecular Thorpe-Ziegler cyclization–Tautomerization–Elimination sequence of reactions.

This four-component reaction results in the formation of four new C–C bonds in a single operation. The structure of all the Benzo[*b*]thiophene was elucidated with NMR and single crystal X-ray studies.

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ISSN(P):2319 – 3786

Malaya Journal of Matematik

ISSN(O):2321 – 5666

