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SHORT COMMUNICATION

A SPLENDID METHOD FOR SYNTHESIS OF 2-(BENZOTHIAZOLE)-3-PHENYL ACRYLONITRILE DERIVATIVES CATALYSED BY PIPERDINE

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ABSTRACT. A simple and efficient method is developed for the synthesis of 2-(benzothiazol-2-yl)-3-(substituted phenyl)acrylonitrile from 2-(benzothiazole-2-yl)-3-oxopentanedinitrile and aromatic aldehydes in the presence of a catalytic amount of piperdine into ethanol at reflux. Advantage of this procedure is relatively good yields (81-86%) with short reaction times (1.5-3 h), under moderate reaction conditions and simple workup procedure, plus easy preparation and handling of the catalyst.

KEYWORDS: 2-(Benzothiazole)-3-phenylacrylonitrile, One-pot synthesis, 2-(Benzo-thiazole-2-yl)-3-oxopentanedinitrile, Aromatic aldehydes, Piperdine

INTRODUCTION

Benzothiazole, a heterocyclic aromatic moiety with electron rich sulfur and nitrogen atoms, which is used as a pharmacological agent due its well known immunomodulatory, immunosuppressive, antitumor, and antiviral properties [1]. The benzothiazole skeleton constitutes an important template for a wide variety of biologically active compounds. This molecule and its derivatives are known to be powerful antitumour agents [2, 3], calmodulin antagonists [4], neurotransmission blocker [5], and neuroprotective agent [6]. Benzothiazole type compounds attracted considerable attention in anticancer drug development [7, 8]. Modified benzothiazole derivatives with additional functional groups can likely improve the biological potential of these compounds. 2-Aryl substituted benzothiazoles are studied as antimicrobial [9], antifungal agents [10] as well as imaging agents for β-amyloid [11], inhibition of enzymes such as cyclooxygenase [12], acetylcholine esterase [13] and plant growth regulation [14].

In view of importance of benzothiazole and their derivatives, many methods have been reported for the synthesis of benzothiazole, such as palladium-catalyzed Suzuki biaryl coupling of 2-bromobenzothiazole with arylboronic acids [15], coupling of benzothiazoles with aryl bromides [16] and the reaction between thiophenols and aromatic nitriles [17]. In the recent past, the reactions catalyzed by silica gel [18], iodine [19] and Backer's yeast [20] have also been reported for the synthesis of benzothiazole derivatives. However, many of these methods are associated with disadvantages such as long reaction time, drastic reaction conditions, expensive reagents, low yields and tedious work-up procedures. The disadvantage is that the catalyst is destroyed during the work-up procedure and cannot be recovered or reused [17-19]. Therefore, it is paramount to find a simple, inexpensive procedure for the synthesis of benzothiazoles, with provision of recoverable and reusable catalyst. Earlier we have reported a simple and one step method for synthesis of wide range of pyrimidine derivatives [21].

In this article we communicate the prospect to synthesize 2-(benzothiazol-2-yl)-3-(substituted phenyl)acrylonitrile derivatives by the reaction 2-(benzothiazole-2-yl)-3-oxopentanedinitrile with aromatic aldehydes, using piperdine as a catalyst (Scheme 1). Here, an

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efficient and simple method for the synthesis of target compounds is described. To the best of our knowledge, using piperdine as a catalyst, the synthesis of benzothiazoles has not been reported yet.

EXPERIMENTAL

All reagents were synthesis grade and were used without further purification. Melting points were determined on a Fisher–Johns melting point apparatus were uncorrected. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were obtained on a Perkin Elmer BX serried FT-IR 5000 spectrometer using KBr pellet. The NMR spectra were recorded on a Bruker 400 MHz spectrometer for ^{1}H NMR. The chemical shifts were reported as ppm down field using TMS as an internal standard. LCMS Mass spectra were recorded on a MASPEC low resolution mass spectrometer operating at 70 eV.

General procedure for the preparation of 2-(benzothiazol-2-yl)-3-(substituted phenyl)acrylonitrile. To a solution of 2-(benzothiazole-2-yl)-3-oxopentanedinitrile **1** (1 mmol) and aromatic aldehydes **2** (1 mmol) in ethanol (10 mL) was added a few drops of catalytic piperdine and the reaction mixture was refluxed for 2-3 hours. After completion of the reaction as indicated by TLC, The precipitate was filtered and washed with 50% EtOH (2×10 mL). The crude product was purified by recrystallization from ethonal (solid products) or by chromatography using silica gel and mixtures of hexane/ethyl acetate of increasing polarity.

*2-(Benzothiazol-2-yl)-3-phenylacrylonitrile (**3a**)*. M.p. 154–155 °C; ^{1}H NMR: δ 5.71 (s, 1H, CH), 6.34 (s, 1H, ═CH), 7.28–8.20 (m, 9H, Ar–H); IR (KBr, cm^{-1}): 2231 (CN), 1720 (C═O), 1625 (C=N), 1586 (C═C), 762 (C-S); MS (70 eV, EI): *m/z* (%): 263 (M+1); anal. calcd for $C_{16}H_{10}N_2S$: C, 73.26; H, 3.84; N, 10.68. Found: C, 73.33; H, 3.78; N, 10.59.

*2-(Benzothiazol-2-yl)-3-(4-methylphenyl)acrylonitrile (**3b**)*. M.p. 159-161 °C; ^{1}H NMR: δ 2.48 (s, 3H, CH_3), 5.68 (s, 1H, CH), 6.31 (s, 1H, ═CH), 7.20–8.15 (m, 8H, Ar–H); IR (KBr, cm^{-1}): 2236 (CN), 1722 (C═O), 1628 (C=N), 1590 (C═C), 769 (C-S); MS (70 eV, EI): *m/z* (%): 276 (M^+); anal. calcd for $C_{17}H_{12}N_2S$: C, 73.88; H, 4.38; N, 10.14. Found: C, 73.81; H, 4.43; N, 10.19.

*2-(Benzothiazol-2-yl)-3-(4-ethylphenyl)acrylonitrile (**3c**)*. M.p. 188-190 °C; ^{1}H NMR: δ 1.18 (t, 3H, Ar–CH_2–$\underline{CH_3}$), 2.52 (q, 2H, –CH_2), 5.72 (s, 1H, CH), 6.35 (s, 1H, ═CH), 6.90–8.10 (m, 8H, Ar–H); IR (KBr, cm^{-1}): 2233 (CN), 1718 (C═O), 1623 (C=N), 1585 (C═C), 760 (C-S); MS (70 eV, EI): *m/z* (%): 290 (M^+); anal. calcd for $C_{18}H_{14}N_2S$: C, 74.45; H, 4.86; N, 9.65. Found: C, 74.49; H, 4.92; N, 9.72.

*2-(Benzothiazol-2-yl)-3-(4-chlorophenyl)acrylonitrile (**3d**)*. M.p. 235–237 °C; ^{1}H NMR: δ 5.75 (s, 1H, CH), 6.38 (s, 1H, ═CH), 7.45–8.12 (m, 8H, Ar-H); IR (KBr, cm^{-1}): 2212 (CN), 1694 (C═O), 1610 (C=N), 1538 (C═C), 776 (C–Cl), 760 (C-S); MS (70 eV, EI): *m/z* (%): 297 (M+1); anal. calcd for $C_{16}H_9ClN_2S$: C, 64.75; H, 3.06; N, 9.44. Found: C, 64.81; H, 3.12; N, 9.37.

*2-(Benzothiazol-2-yl)-3-(4-bromophenyl)acrylonitrile (**3e**)*. M.p. 210–211 °C; ^{1}H NMR: δ 5.78 (s, 1H, CH), 6.43 (s, 1H, ═CH), 7.58–8.13 (m, 8H, Ar–H); IR (KBr, cm^{-1}): 2219 (CN), 1714 (C═O), 1616 (C=N), 1538 (C═C), 774 (C-S); MS (70 eV, EI): *m/z* (%): 341 (M+2); anal. calcd for $C_{16}H_9BrN_2S$: C, 56.32; H, 2.66; N, 8.21. Found: C, 56.39; H, 2.71; N, 8.29.

*2-(Benzothiazol-2-yl)-3-(4-methoxyphenyl)acrylonitrile (**3f**)*. M.p. 194–196 °C; ^{1}H NMR: δ 3.73 (s, 3H, OCH_3), 5.74 (s, 1H, CH), 6.40 (s, 1H, ═CH), 6.90–8.20 (m, 8H, Ar–H); IR (KBr, cm^{-1}):

2225 (CN), 1738 (C═O), 1618 (C=N), 1532 (C═C), 1221 (C–O–C), 761 (C-S); MS (70 eV, EI): *m/z* (%): 293 (M+1); anal. calcd for $C_{17}H_{22}N_2OS$: C, 69.84; H, 4.14; N, 9.58. Found: C, 69.77; H, 4.23; N, 9.42.

*2-(Benzothiazol-2-yl)-3-(4-(dimethylamino)phenyl)acrylonitrile (**3g**)*. M.p. 201–203 °C; ^{1}H NMR: δ 3.01 (s, 6H, $N(CH_3)_2$), 5.73 (s, 1H, CH), 6.38 (s, 1H, ═CH), 6.68–8.16 (m, 8H, Ar–H); IR (KBr, cm^{-1}): 2219 (CN), 1679 (C═O), 1623 (C=N), 1528 (C═C), 1340 ($N(CH_3)_2$), 764 (C-S); MS (70 eV, EI): *m/z* (%): 306 (M+1); anal. calcd for $C_{18}H_{15}N_3S$: C, 70.78; H, 4.95; N, 13.76. Found: C, 70.91; H, 5.03; N, 13.87.

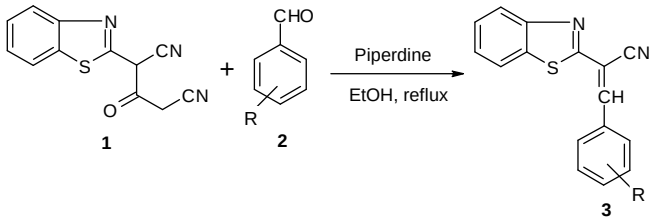
*2-(Benzothiazol-2-yl)-3-(2,4-dichlorophenyl)acrylonitrile (**3h**)*. Mp 149–151 °C; ^{1}H NMR: δ 5.78 (s, 1H, CH), 6.51 (s, 1H, ═CH), 7.28–8.09 (m, 8H, Ar–H); IR (KBr, cm^{-1}): 2218 (CN), 1682 (C═O), 1637 (C=N), 1545 (C═C), 748 (C-S); MS (70 eV, EI): *m/z* (%): 331 (M+2); anal. calcd for $C_{16}H_8Cl_2N_2OS$: C, 58.02; H, 2.43; N, 8.46. Found: C, 58.19; H, 2.39; N, 8.53.

*2-(Benzothiazol-2-yl)-3-(2,4,6-trimethylphenyl)acrylonitrile (**3i**)*. M.p. 157–159 °C; ^{1}H NMR: δ 2.36 (s, 3H, Ar–CH_3), 2.52 (s, 6H, Ar–CH_3), 5.70 (s, 1H, CH), 6.36 (s, 1H, ═CH), 6.90–8.24 (m, 6H, Ar–H); IR (KBr, cm^{-1}): 2208 (CN), 1650 (C═O), 1606 (C=N), 1548 (C═C), 758 (C-S); MS (70 eV, EI): *m/z* (%): 304 (M^+); anal. calcd for $C_{19}H_{16}N_2S$: C, 74.97; H, 5.30; N, 9.20. Found: C, 75.07; H, 5.38; N, 9.14.

*2-(Benzothiazol-2-yl)-3-(4-isopropylphenyl)acrylonitrile (**3j**)*. M.p. 181–183 °C; ^{1}H NMR: δ 1.16 (d, 6H, $CH(CH_3)_2$), 2.93 (q, 1H, CH), 5.72 (s, 1H, CH), 6.41 (s, 1H, ═CH), 7.18–8.15 (m, 8H, Ar–H); IR (KBr, cm^{-1}): 2200 (CN), 1690 (C═O), 1600 (C=N), 1533 (C═C), 762 (C-S); MS (70 eV, EI): *m/z* (%): 304 (M^+); anal. calcd for $C_{19}H_{16}N_2S$: C, 74.97; H, 5.30; N, 9.20. Found: C, 75.07; H, 5.38; N, 9.14.

*2-(Benzothiazol-2-yl)-3-(4-tert-butylphenyl)acrylonitrile (**3k**)*. M.p. 171–172 °C; ^{1}H NMR: δ 1.28 (s, 9H, $3CH_3$), 5.70 (s, 1H, CH), 6.40 (s, 1H, ═CH), 7.20–8.22 (m, 8H, Ar–H); IR (KBr, cm^{-1}): 2237 (CN), 1691 (C═O), 1618 (C=N), 1539 (C═C), 763 (C-S); MS (70 eV, EI): *m/z* (%): 319 (M+1); anal. calcd for $C_{20}H_{18}N_2S$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.53; H, 5.79; N, 8.94.

RESULTS AND DISCUSSION



Scheme 1. The synthetic route of 2-(benzothiazole)-3-phenylacrylonitrile.

The synthesis of 2-(benzothiazol-2-yl)-3-(substituted phenyl)acrylonitrile derivatives (**3a-k)** was achieved through the versatile and efficient synthetic route outlined in Scheme 1. All the synthesised compounds were obtained in good to high yields. Products were purified and characterized by various spectroscopic techniques. The IR spectra of compounds (**3a-k**) showed characteristic absorption bands at 2237–2200 cm^{-1}, 1738–1682 cm^{-1}, 1637–1600, 1590–1528 and 774–748 cm^{-1} corresponding to the $C{\equiv}N_{str}$, $C{=}O_{str}$, $C{=}N_{str}$, $C{=}C_{str}$ and $C–S_{str}$ functions in the structures. Similarly the ^{1}H NMR spectra showed peaks due to in the range of δ 5.68–5.78

for –CH, δ 6.31–6.51 for =CH, and δ 6.68–8.24 for Ar–H. The mass spectrum of all the compounds showed molecular ion peak at M^+, M+H, at M+2H corresponding to its molecular formula, which confirmed its chemical structure. The IR, ^{1}H NMR, LCMS mass spectra and elemental analysis showed the structure of various novel 2-(benzothiazol-2-yl)-3-(substituted phenyl)acrylonitrile derivatives (**3a–k**).

CONCLUSIONS

In conclusion, we have developed a novel and efficient method for the synthesis of 2-(benzothiazole)-3-phenylacrylonitrile by treatment of 2-(benzothiazole-2-yl)-3-oxopentane-dinitrile with aromatic aldehydes using piperdine as an effective catalyst. The noteworthy advantages of this procedure are good yields (81-86%), short reaction times (1.5-3 h), moderate reaction conditions, simple workup procedure and finally easy preparation and handling of the catalyst. This methodology may find wide applications in organic synthesis for preparation of the 2-(benzothiazole)-3-phenylacrylonitrile.

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