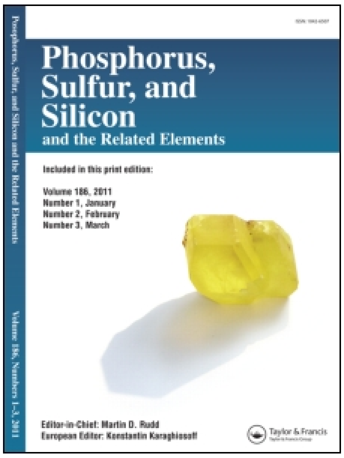

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A Rapid and Efficient Multicomponent Synthesis of Bi-Quinolines Under Solvent-Free Conditions

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A RAPID AND EFFICIENT MULTICOMPONENT SYNTHESIS OF BI-QUINOLINES UNDER SOLVENT-FREE CONDITIONS

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An efficient synthesis of substituted condensed quinolino-quinolines has been achieved in a one-pot reaction from 2-hydroxy/mercapto/seleno-4-methylquinoline and 2-mercapto/seleno-3-formyl quinolines using anhydrous ammonium hydroxide as the reductant by microwave irradiation under solvent-free conditions.

Keywords Ammonium hydroxide; microwave/solvent-free; quinolino-quinolines

INTRODUCTION

In recent years, interest in the chemistry of sulfur/selenium-containing compounds has increased remarkably due to their chemical properties,[1–5] biological activity, and pharmaceutical potential.[6–10] Some organoselenium compounds are known as effective insecticides, microbicides,[11] pro-oxidants,[12] and antimycobacterial agents.[13] Recent studies reveal that the intramolecularly stabilized organoselenium and sulfur compounds play an important role in the catalytic antioxidant activity.[13] Since, Se resembles sulfur (S) in many of its properties, it is isosteric.[14,15] The biological and pharmaceutical activities of different selenium compounds are of special interest, because it they are active sites of large selenium-dependent enzymes, such as glutathione peroxidase (GSHPx)[16,17] and prevention of cancer.[18] In the same field of research, the results of many studies[19,20] have related Se deficient bioavailability and intake to human cancer mortality. New synthetic selenium compounds may provide a way to minimize toxicity associated with higher selenium intake. Recently, several forms of organoselenium have been studied for their cancer preventive activities. Dietary *p*-methoxybenzeneselenol, a synthetic organoselenium compound, was

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found to inhibit azoxymethane-induced hepatocarcinogenesis in rats without clinical signs of toxicity.[21]

Quinolines and their derivatives are a very important class of compounds because of their wide occurrence in natural products[22] and biologically active compounds.[23] Furthermore, poly-substituted quinolines have been found to undergo hierarchical self-assembly into a variety of nano- and mesostructures with enhanced electronic and photonic functions.[24] In view of these points, a great deal of effort has been drawn to develop new and efficient synthetic routes to quinoline derivatives in both synthetic organic and medicinal chemistry.

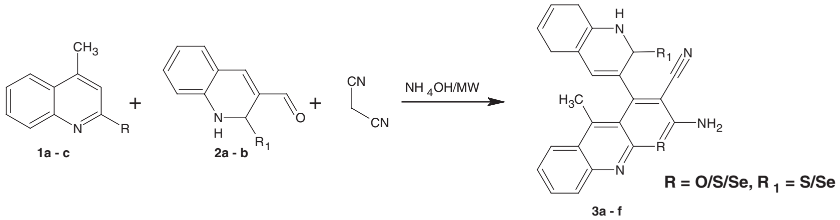
The use of scientific microwave apparatus in the development of efficient and selective greener methods has become a major focus of researchers worldwide, and selection of appropriate alternate eco-friendly reaction media has become an integral part of this paradigm shift.[25] Microwave (MW) irradiation as an alternative energy source in conjunction with water as reaction medium has proven to be a successful "greener" chemical approach.

Our approach is to develop a rapid and efficient scientifically based framework for greener preparation of these fused carbonitrile quinolino-quinolines in a manner that renders the materials less mobile in the environment and reduces or eliminates the use and generation of hazardous substances. The areas of opportunity are being exploited to engage green chemistry: (i) choice of solvent and (ii) the catalytic agent employed. We found microwave (MW) irradiation as an efficient and selective mode of activation in rapid and efficient synthesis of fused quinolino-quinolines-3-carbonitrile.

RESULTS AND DISCUSSION

Generally, planar fused quinolino-quinolines containing two or more hetero atoms are found to have valuable pharmacological activities as mentioned earlier, and therefore, they are useful compounds in medicinal research. Hence, in continuation of research on developing new fused quinoline-containing heterocycles due to their significant biological activities, it appeared expedient to synthesize a series of condensed and appropriately functionalized sulfur- and selenium-containing quinolino-quinolines in the present study. The starting compound 2-hydroxy/mercapto/seleno-4-methylquinoline (**1a–c**) 2-mercapto/seleno-3-formyl quinolines (**2a–b**) were prepared according to the method in the literature.[26] The desired compounds were obtained in one pot by the cyclization of 2-mercapto/seleno-3-formylquinolines and 2-hydroxy/mercapto/seleno-4-methylquinoline in the presence of anhydrous ammonium hydroxide–based microwave irradiation under solvent-free conditions with good yields. This method provides good yield of products in 10–13 min, making it a useful method for the synthesis of condensed quinolines.

The structure of the compounds was confirmed on the basis of elemental analysis and spectral data (see the Experimental section). The ^{1}H NMR (DMSO-d_6) spectrum in addition to aromatic protons resonated between δ 7.00–8.00 ppm (5–10 H) and exhibited a multiplet at δ 5.1–5.8 ppm corresponding to -CH protons, a broad singlet at δ 10.1–10.9 ppm for –SH/SeH proton indicating the attachment of the reactive partner to the quinoline substrate, and δ 4.1–4.7 corresponding to NH_2 protons along with CH_3 protons between δ 2.2–2.5. Finally, the structures were confirmed by the mass spectrum through the appearance of a molecular ion peak at m/z (M+) for all the synthesized compounds as presented in the Experimental section. The obtained elemental analysis values are in agreement with



Scheme 1 Synthetic pathway for the synthesis of desired molecules.

theoretical data. We synthesized four more title compounds, which exhibited similar spectral characteristics (Scheme 1).

CONCLUSION

In conclusion, we have developed a solvent-free, microwave-assisted, very facile protocol for the synthesis of fused quinolino-quinolines. This protocol offers scope for further work involving a variety of substrates with varied substituents. The microwave-facilitated version of quinoline synthesis is expected to be a viable alternative to the classic Friedlaender synthesis, owing to several advantages summarized herein.

EXPERIMENTAL

Chemistry

The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates using petroleum ether:ethyl acetate solvent. Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded in KBr pellets on a Perkin-Elmer 157 IR spectrophometer. ^{1}H NMR spectra were recorded in DMSO-d$_6$ on EM-390 (300 MHz) NMR spectrometer, and mass spectra were recorded on MASPEC low resolution instrument operating at 70 eV.

A dry, 50-mL flask was charged with 2-mercapto/seleno-3-formylquinoline (5 mmol), 2-hydroxy/mercapto/seleno-4-methylquinoline (5 mmol), malononitrile (5 mmol), and anhydrous ammonium hydroxide (10 mmol). The mixture was well mixed and then irradiated in a SANYOEM-350S microwave oven at 300 W or 150 W for a designated time as required for completing the reaction (determined by TLC). Then, after being cooled to room temperature, under these conditions, the reaction mass was poured onto crushed ice, the solid material was filtered off, and the crude product was purified by recrystallization from DMF. A similar reaction procedure has been followed for other derivatives.

2-Amino-5-methyl-4-(2-sulfanylquinolin-3-yl)-2*H*-pyrano[2,3-*b*]quinoline-3-carbonitrile (3a)

Pale red solid, yield 66%, 10 min, mp 187–189°C; ^{1}H NMR (DMSO d$_6$), δ 7.12–8.26 (m, 9H, Ar-H), 10.58 (s, 1H, S—H), 1.36 (s, 1H, C—H), 4.42 (s, 2H, NH$_2$), 2.24 (s, 3H, CH$_3$); m/z (%) [M]$^+$: [396]$^+$; Elemental analysis, Found: C, 69.59; H, 3.98; N, 14.02. Calculated for $C_{23}H_{16}N_4OS$: C, 69.68; H, 4.07; N, 14.13.

2-Amino-5-methyl-4-(2-selenoquinolin-3-yl)-2*H*-pyrano[2,3-*b*]quinoline-3-carbonitrile (3b)

Pale brown solid, yield 63%, 11 min, mp 196–198°C; ^{1}H NMR (DMSO d_6), δ 7.00–8.34 (m, 9H, Ar-H), 10.64 (s, 1H, Se-H), 1.22 (s, 1H, C—H), 4.56 (s, 2H, NH_2), 2.34 (s, 3H, CH_3); m/z (%) $[M]^+$: $[443]^+$; Elemental analysis, Found: C, 62.22; H, 3.58; N, 12.54. Calculated for $C_{23}H_{16}N_4OSe$: C, 62.31; H, 3.64; N, 12.64.

2-Amino-5-methyl-4-(2-sulfanylquinolin-3-yl)-2*H*-thiopyrano[2,3-*b*]quinoline-3-carbonitrile (3c)

Yellow solid, yield 59%, 10 min, mp 205–207°C; ^{1}H NMR (DMSO d_6), δ 7.12–8.38 (m, 9H, Ar-H), 10.52 (s, 1H, S—H), 1.25 (s, 1H, C—H), 4.68 (s, 2H, NH_2), 2.45 (s, 3H, CH_3); m/z (%) $[M]^+$: $[412]^+$; Elemental analysis, Found: C, 66.87; H, 3.85; N, 13.49. Calculated for $C_{23}H_{16}N_4S_2$: C, 66.96; H, 3.91; N, 13.58.

2-Amino-5-methyl-4-(2-selenoquinolin-3-yl)-2*H*-thiopyrano[2,3-*b*]quinoline-3-carbonitrile (3d)

Pale brown solid, yield 60%, 12 min, mp 221–223°C; ^{1}H NMR (DMSO d_6), δ 7.04–8.16 (m, 9H, Ar-H), 10.82 (s, 1H, S—H), 1.34 (s, 1H, C—H), 4.46 (s, 2H, NH_2), 2.68 (s, 3H, CH_3); m/z (%) $[M]^+$: $[459]^+$; Elemental analysis, Found: C, 60.21; H, 3.45; N, 12.08. Calculated for $C_{23}H_{16}N_4SSe$: C, 60.13; H, 3.51; N, 12.19.

2-Amino-5-methyl-4-(2-sulfanylquinolin-3-yl)-2*H*-selenopyrano[2,3-*b*]quinoline-3-carbonitrile (3e)

Brown solid, yield 61%, 13 min, mp 235–237°C; ^{1}H NMR (DMSO d_6), δ 6.95–8.06 (m, 9H, Ar-H), 10.72 (s, 1H, S—H), 1.44 (s, 1H, C—H), 4.58 (s, 2H, NH_2), 2.62 (s, 3H, CH_3); m/z (%) $[M]^+$: $[459]^+$; Elemental analysis, Found: C, 60.02; H, 3.46; N, 12.09. Calculated for $C_{23}H_{16}N_4SSe$: C, 60.13; H, 3.51; N, 12.19.

2-Amino-5-methyl-4-(2-selenoquinolin-3-yl)-2*H*-selenopyrano[2,3-*b*]quinoline-3-carbonitrile (3f)

Brown solid, yield 52%, 13 min, mp 247–248°C; ^{1}H NMR (DMSO d_6), δ 7.24–8.48 (m, 9H, Ar-H), 10.82 (s, 1H, S—H), 1.34 (s, 1H, C—H), 4.64 (s, 2H, NH_2), 2.38 (s, 3H, CH_3); m/z (%) $[M]^+$: $[506]^+$; Elemental analysis, Found: C, 54.48; H, 3.12; N, 11.00. Calculated for $C_{23}H_{16}N_4Se_2$: C, 54.56; H, 3.19; N, 11.07.

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