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Efficient synthesis of new pyrano[3,2-*b*]pyran derivatives via Fe_3O_4@SiO_2-IL-Fc catalyzed three-component reaction

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Abstract: Ferrocene-containing ionic liquid supported on silica-coated Fe_3O_4 magnetic nanoparticles (nano Fe_3O_4@SiO_2-IL-Fc), a novel heterogeneous nanocatalyst, was synthesized. The structure of the catalyst was characterized by Fourier-transform infrared spectroscopy (FT-IR), X-ray diffraction patterns (XRD), energy-dispersive X-ray spectroscopy (EDX) and field emission scanning electron microscopy (FE-SEM). The novel nanomagnetic catalyst was used in the one-pot synthesis of pyrano[3,2-*b*]pyran derivatives by the three-component reaction of various aldehydes, malononitrile and kojic acid or chlorokojic acid at room temperature under ultrasonic irradiation. This new method has many advantages such as simplicity, short reaction times, high yields, easy workup and easy purification. Also, the nanocatalyst can be separated on an external magnet and reused for at least six consecutive runs without any significant loss of its catalytic activity.

Keywords: ferrocene; heterogeneous catalysis; multicomponent reaction; nanostructures; pyrano[3,2-*b*]pyran; supported ionic liquids.

Introduction

Synthesis of efficient and recyclable catalysts has been an increasingly important goal for chemists and material scientists for both economic and environmental reasons [1, 2]. In this regard, magnetic nanoparticles (MNPs) have been widely used as catalysts due to their high surface area, easy synthesis and functionalization, good stability, low toxicity and facile separation by an external magnetic force [3–6]. Recent investigations have revealed that MNPs can act as excellent supports for various homogeneous catalysts, and diverse organic transformations catalyzed by supported MNPs have been reported [7]. Besides, supported ionic liquids (SILs) are an important class of heterogeneous catalysts and have many advantages over free ILs, including a higher number of accessible active sites on the catalyst, reduction in the amount of required IL and improved recyclability of catalysts [8]. Ferrocene containing SILs have been synthesized and used in some organic reactions [9, 10], but the development and expansion of these types of catalysts needs more attention.

Pyran derivatives are important structural units of many natural products and synthetic compounds which possess a wide range of pharmacological and biological activities such as anti-HIV [11], anticancer [12, 13], antimicrobial [14], antifungal [15], antidiabetic [16], antiviral and anti-inflammatory [17] and antioxidant [18] properties, among others [19–22]. Pyrano[3,2-*b*]pyrans are of great interest in organic synthesis, and various methods using different homogeneous and heterogeneous catalysts have been reported for the preparation of these compounds and analogues [23–29].

In continuation of our research on the synthesis and applications of ferrocene derivatives [30, 31] and the development of multicomponent reactions [32–35], herein we report the design and synthesis of novel ferrocene labeled ionic liquid supported on MNPs as an efficient catalyst for the synthesis of a series of pyrano[3,2-*b*]pyran derivatives under ultrasound irradiation.

Results and discussion

The ferrocene functionalized ionic liquid supported on magnetic nanoparticle (Fe_3O_4@SiO_2-IL-Fc) as the catalyst was prepared according to Scheme 1. A chemical co-precipitation method was used for the preparation of nanomagnetite (Fe_3O_4). Subsequently, Fe_3O_4 nanoparticles were covered with silica (Fe_3O_4@SiO_2) using the Stober method [36]. The silica-coated MNPs were subsequently allowed to react with (3-chloropropyl)triethoxysilane to obtain the functionalized

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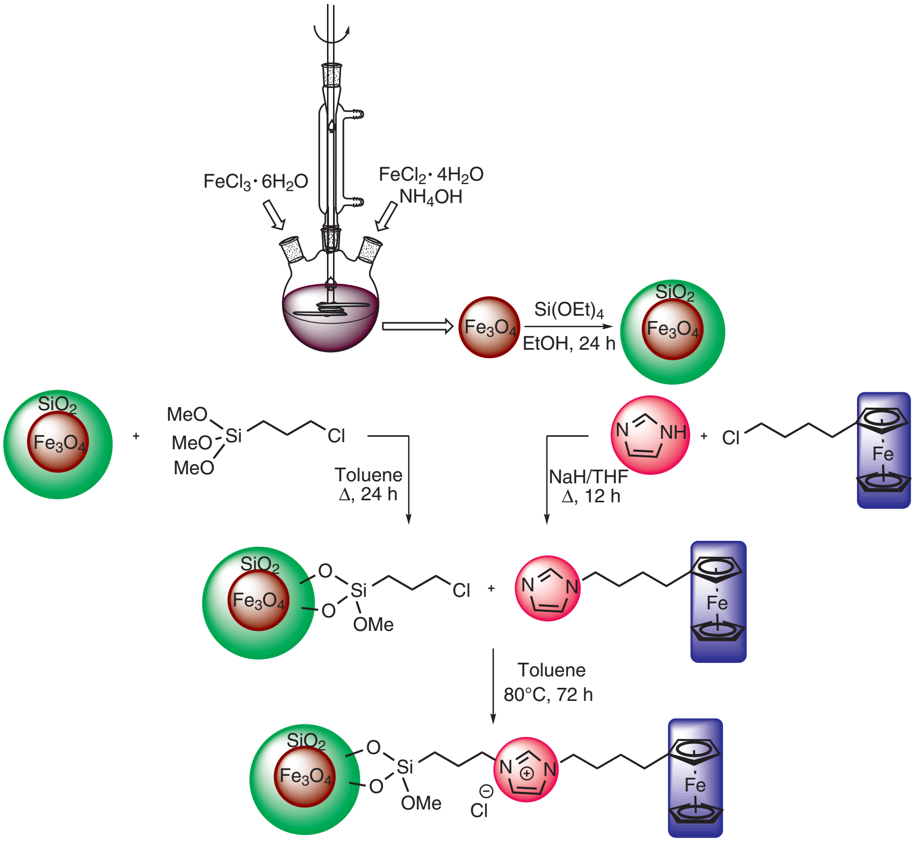


Scheme 1 Preparation of Fe_3O_4@SiO_2-IL-Fc nanocatalyst.

nanoparticles. Then, 1-(4-ferrocenylbutyl)-1*H*-imidazole was prepared by the reaction of imidazole with 4-chlorobutylferrocene. Finally, ferrocene containing ionic liquid supported on MNPs was synthesized by the reaction of chloropropyl functionalized silica-coated MNPs with 1-(4-ferrocenylbutyl)-1*H*-imidazole.

The nanomagnetic Fe_3O_4 particles show the IR absorption peak at about 572 cm^{-1} which is related to Fe-O bond vibrations. The Fe_3O_4@SiO_2-propyl chloride core-shell MNPs show the Fe-O and Si-O-Si bonds IR vibrations, and the absorption peak at 2925 cm^{-1} is related to the asymmetric stretching vibration of aliphatic C-H moieties. Finally, in the infrared (IR) spectrum of the Fe_3O_4@SiO_2-IL-Fc MNPs, absorption peak above 3000 cm^{-1} is related to the stretching vibration of aromatic C-H moieties of imidazole and ferrocene groups. The absorption peak at 1644 and 1385 cm^{-1} are linked to the stretching vibrations of C=N and C=C bonds of aromatic rings.

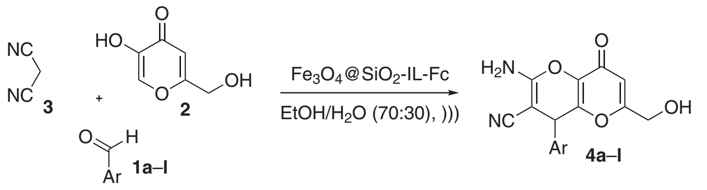
The energy-dispersive X-ray spectrum of the Fe_3O_4@SiO_2-IL-Fc nanocatalyst is consistent with the presence of the expected elements (Fe, Cl, Si, O, N and C) in the structure. The X-ray diffraction (XRD) analyses illustrate the degree of crystallinity of the synthesized Fe_3O_4@SiO_2-IL-Fc nanocatalyst. The XRD pattern of Fe_3O_4@SiO_2-IL-Fc is the same as that of Fe_3O_4 and shows diffraction peaks at $2\theta = 30.4°$, 35.7°, 43.3°, 53.9°, 57.3° and 63.0°. These results indicate that the functionalization process did not induce any phase change of Fe_3O_4. The surface morphology of the nanoparticles was investigated by field emission scanning electron microscopy (FE-SEM) analysis. The FE-SEM images show that the particles are uniformly distributed and the sizes of MNPs are under 60 nm.

For optimization of the catalyst and reaction conditions, the reaction of 4-methylbenzaldehyde (1 mmol), malononitrile (1.2 mmol) and kojic acid (1 mmol) was selected. Initially, the model reaction was examined with some catalysts including typical ILs, ferrocene labeled IL and newly synthesized Fe_3O_4@SiO_2-IL-Fc nanocatalyst under solvent-free conditions at 80°C. It was found that Fe_3O_4@SiO_2-IL-Fc shows the best catalytic activity. Different solvents including CH_2Cl_2, CH_3CN, EtOH and H_2O were examined in the presence of Fe_3O_4@SiO_2-IL-Fc as catalyst. For the reaction conducted in ethanol or aqueous ethanol the product **4a** is obtained rapidly and in high yield. However, the best yield of 95% is obtained in aqueous ethanol containing 30% of water under ultrasonic irradiation. The amount of the catalyst under optimized conditions is 6 mg per 1 mmol of the aldehyde. Different aromatic aldehydes were allowed to react under this optimal procedure with ultrasonic irradiation. The results are summarized in Scheme 2. The reactions of aromatic aldehydes with both electron-releasing and electron-withdrawing substituents furnish the corresponding 2-aminopyrano[3,2-*b*]pyrans **4** in good to high yields under the optimized conditions. Aldehydes with electron-withdrawing substituents react more rapidly, while electron donating substituents decrease the reactivity and the reactions are completed at longer reaction times.

Chlorokojic acid (**5**) was also subjected to this reaction under optimized conditions and the target compounds **6a–f** were synthesized in high yields (Scheme 3). All products **4** and **6** were characterized by melting points, IR, ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR and elemental analysis.

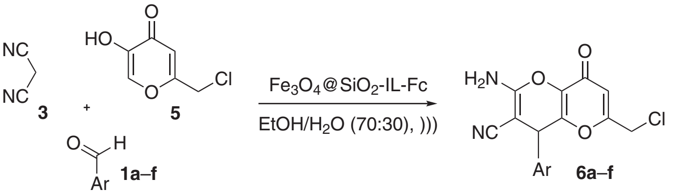
A possible mechanism for the Fe_3O_4@SiO_2-IL-Fc catalyzed condensation reaction is proposed in Scheme 4. The first step is the Knoevenagel condensation of aromatic aldehyde and malononitrile to generate the intermediate product (A). Then, the Michael addition of (chloro) kojic acid enolate (B) with (A) furnishes an intermediate product (C), which undergoes cyclization to (D). The intermediate product (D) is a direct precursor to the final pyrano[3,2-*b*]pyran product.

The reusability of the magnetic nanocatalyst was investigated using the model reaction leading to **4a**. After completion of the reaction, the catalyst was separated with an external magnet. The collected nanocatalyst was repeatedly washed with EtOH prior to use in the next round of catalysis. The catalyst exhibited a consistent activity up to the sixth consecutive cycle. Specifically, the yield of **4a** of 95% after the first cycle was only lowered



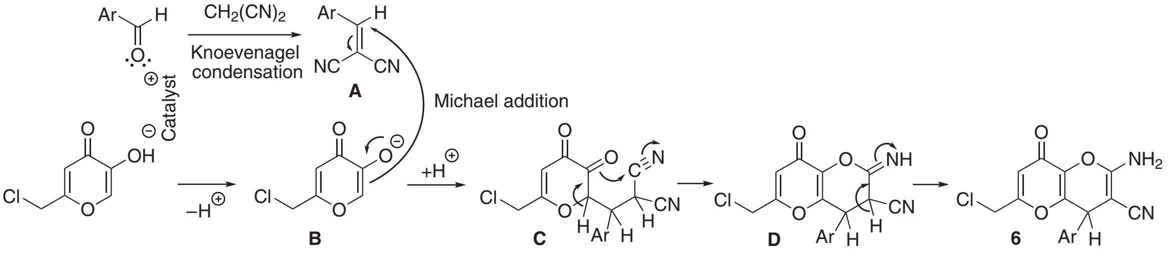
4a: Ar = *p*-tolyl (95%, 10 min); mp 204–206 [37]
4b: Ar = phenyl (91%, 10 min); mp 220–222 [25]
4c: Ar = 4-fluorophenyl (93%, 10 min); mp 248–250 [25]
4d: Ar = 2-chloropheny (87%, 15 min); mp 201–203 [37]
4e: Ar = 4-chlorophenyl (95%, 10 min); mp 198–200 [37]
4f: Ar = 3-bromophenyl (89%, 10 min); mp 242–244 [25]
4g: Ar = 4-bromophenyl (90%, 10 min); mp 224–226 [37]
4h: Ar = 4-methoxyphenyl (81%, 15 min); mp 220–223 [37]
4i: Ar = 3-nitrophenyl (96%, 10 min); mp 215–217 [37]
4j: Ar = pyridin-4-yl (85%, 15 min); mp 233–235 [25]
4k: Ar = thiophen-2-yl (83%, 15 min); mp 235–237 [25]
4l: Ar = furan-2-yl (82%, 15 min); mp 223–225 [25]

Scheme 2 Fe_3O_4@SiO_2-IL-Fc catalyzed three-component synthesis of pyrano[3,2-*b*]pyran derivatives in EtOH/H_2O (70:30) at room temperature under ultrasonic irradiation.



6a: Ar = 4-isopropylphenyl (90%, 10 min)
6b: Ar =*p*-tolyl (90%, 10 min)
6c: Ar = 4-nitrophenyl (95%, 5 min)
6d: Ar = 3-nitrophenyl (92%, 5 min)
6e: Ar = 4-chlorophenyl (95%, 8 min)
6f: Ar = thiophen-2-yl (88%, 10 min)

Scheme 3 Synthesis of pyrano[3,2-*b*]pyran derivatives **6a–f**.



Scheme 4 Proposed mechanism for the Fe_3O_4@SiO_2-IL-Fc catalyzed three-component reaction.

to 90% after the sixth cycle and the initial reaction time of 10 min had to be increased to 12 min to complete the reaction.

Conclusion

A simple, rapid and efficient method for the three-component synthesis of pyrano[3,2-*b*]pyran derivatives using a novel Fe_3O_4 supported ionic liquid phase catalyst with a ferrocenyl group under ultrasonic irradiation was developed. The protocol provides a practical benefit of facile removal of the catalyst that can subsequently be reused.

Experimental

Melting points were measured with a MEL-TEMP model 1202D. Fourier transform infrared (FT-R) spectra were recorded on a Bruker Tensor 27 spectrometer using KBr disks. The ^1H NMR spectra (400 MHz) were determined with a Bruker Spectrospin Avance 400 spectrometer with DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. Elemental analyses were performed on a Vario EL III analyzer. Sonication was performed using a Hielscher (UP400s) ultrasonic probe system at a frequency of 24 KHz. XRD patterns of samples were taken on a Siemens D500 X-ray powder diffraction diffractometer (CuK radiation, $\lambda = 1.5406$ Å). FE-SEM images of the products were visualized with a TESCAN MIRA3 FE-SEM.

Synthesis of 1-(4-ferrocenylbutyl)-1*H*-imidazole

To a suspension of NaH (60%, 0.80 g, 20 mmol) in dry THF (100 mL), imidazole (1.36 g, 20 mmol) was added and the mixture was stirred at 0°C for 1 h. Then, 4-chlorobutylferrocene (1.38 g, 5 mmol) was added and the mixture was heated under reflux for 12 h. After cooling, the excess amount of NaH was quenched by the addition of water. After extraction with dichloromethane, the extract was concentrated and the residue was subjected to silica column chromatography eluting with *n*-hexane/ethyl acetate, 9:1, to give 1-(4-ferrocenylbutyl)-1*H*-imidazole as brown viscous oil; IR: 3394, 2859, 1506, 1453, 1105, 1228, 1000, 650, 486 cm^{-1}; ^1H NMR: δ 1.42–1.49 (m, 2H, $-CH_2-$), 1.75–1.78 (m, 2H, $-CH_2-$), 2.34 (t, $J = 7.5$ Hz, 2H, $-CH_2-$), 3.90 (t, $J = 6.6$ Hz, 2H, $-CH_2-$), 4.00–4.03 (m, 4H, Cp-H), 4.06 (s, 5H, Cp-H), 6.98–7.26 (m, 2H, imid-H), 7. 49 (s, 1H, imid-H); ^{13}C NMR: δ 27.0, 28.0, 29.7, 45.9, 66.1, 66.9, 67.3, 87.0, 118.2, 128.7, 136.6 ppm.

Synthesis of Fe_3O_4@SiO_2-IL-Fc

Fe_3O_4@SiO_2-propyl chloride nanoparticales were prepared as previously reported [38, 39]. Then, a mixture of Fe_3O_4@SiO_2-$(CH_2)_3Cl$ (1.0 g) and 1-(4-ferrocenylbutyl)-1*H*-imidazole (0.92 g, 3 mmol) in 10 mL of toluene was heated at 80°C in an oil bath. After 72 h, the residue was filtered, washed with toluene (3×20 mL), MeOH (3×20 mL), CH_2Cl_2 (3×20 mL) and dried under reduced pressure at 50°C for 48 h to afford Fe_3O_4@SiO_2-IL-Fc.

General procedure for the synthesis of pyrano[3,2-*b*] pyrans 4a–l and 6a–f

A 50-mL flask was charged with aldehyde (1 mmol), malononitrile (1.2 mmol), kojic acid or chlorokojic acid (1 mmol) and Fe_3O_4@SiO_2-IL-Fc nanocatalyst (6 mg) in 3 mL EtOH/H_2O (70:30). The mixture was sonicated at 25°C. When the reaction was completed [monitored by thin layer chromatography (TLC), using *n*-hexane/ethyl acetate (3:1) as eluent], the catalyst was separated using an external magnet and the reaction mixture was cooled and the precipitate was filtered, washed and dried. The crude product was crystallized from ethanol. The structures of new compounds **6a–f** were characterized by IR, ^1H NMR, ^{13}C NMR and CHN analysis. The spectra for **4a–l** were virtually identical with those reported (Scheme 2).

2-Amino-6-(chloromethyl)-4-(4-isopropylphenyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (6a) White powder; mp 207–209°C; IR: 3379, 3290, 3027, 2960, 2199, 1647, 1598 cm^{-1}; ^1H NMR: δ 1.18 (d, 6H, $J = 6.47$ Hz, $2CH_3$), 2.84–2.90 (m, 1H, CH), 4.52–4.60 (m, 2H, CH_2), 4.78 (s, 1H, methin-H), 6.59 (s, 1H, Ar-H), 7.18–7.27 (m, 6H, NH_2, Ar-H); ^{13}C NMR: δ 23.8, 33.1, 40.8, 41.2, 55.7, 114.9, 119.4, 126.9, 127.6, 136.5, 138.3, 148.0, 150.0, 159.2, 161.9, 169.6. Anal. Calcd for $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.80; N, 7.85. Found: C, 63.71; H, 4.84; N, 7.89.

2-Amino-6-(chloromethyl)-8-oxo-4-(*p*-tolyl)-4,8-dihydropyrano [3,2-*b*]pyran-3-carbonitrile (6b) White powder; mp 236–238°C; IR: 3376, 3322, 3017, 2953, 2200, 1647, 1599 cm^{-1}; ^1H NMR: δ 2.28 (s, 3H, CH_3), 4.51–4.59 (m, 2H, CH_2), 4.78 (s, 1H, methin-H), 6.59 (s, 1H, Ar-H), 7.16 -7.21 (m, 4H, Ar-H), 7.25 (s, 2H, NH_2); ^{13}C NMR: δ 20.6, 39.6, 40.8, 55.7, 114.9, 119.2, 127.6, 129.5, 136.5, 137.1, 137.6, 149.9, 159.1, 161.8,169.4. Anal. Calcd for $C_{17}H_{13}ClN_2O_3$: C, 62.11; H, 3.99; N, 8.52. Found: C, 61.88; H, 4.03; N, 8.57.

2-Amino-6-(chloromethyl)-4-(4-nitrophenyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (6c) White powder; mp 193–195°C ; IR: 3400, 3300, 3084, 2924, 2197, 1642, 1591 cm^{-1}; ^1H NMR: δ 4.51–4.59 (m, 2H, CH_2), 5.14 (s, 1H, methin-H), 6.62 (s, 1H, Ar-H), 7.42 (s, 2H, NH_2), 7.64 (d, 2H, $J = 8.23$ Hz, Ar-H), 8.26 (d, 2H, $J = 8.23$ Hz, Ar-H); ^{13}C NMR: δ 39.6, 40.8, 55.2, 114.9, 119.0, 128.9, 129.8, 132.6, 136.6, 139.5, 149.2, 159.1, 161.8, 169.4. Anal. Calcd for $C_{16}H_{10}ClN_3O_5$: C, 53.42; H, 2.80; N, 11.68. Found: C, 53.18; H, 2.83; N, 11.72.

2-Amino-6-(chloromethyl)-4-(3-nitrophenyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (6d) White powder; mp 208–210°C ; IR: 3395, 3325, 3080, 2957, 2191, 1638, 1597 cm^{-1}; ^1H NMR: δ 4.51–4.60 (m, 2H, CH_2), 5.19 (s, 1H, methin-H), 6.62 (s, 1H, Ar-H), 7.43 (s, 2H, NH_2), 7.71 (t, 1H, $J = 5.5$ Hz, Ar-H), 7.83 (d, 1H, $J = 7.67$ Hz, Ar-H), 8.21 (m, 2H, Ar-H); ^{13}C NMR: δ 39.6, 40.8, 54.5, 115.0, 119.0, 122.7, 123.1, 130.7, 134.8, 136.8, 142.6, 148.0, 148.5, 159.4, 161.9, 169.5. Anal. Calcd for $C_{16}H_{10}ClN_3O_5$: C, 53.42; H, 2.80; N, 11.68. Found: C, 53.15; H, 2.84; N, 11.73.

2-Amino-6-(chloromethyl)-4-(4-chlorophenyl)-8-oxo-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (6e) White powder; mp 217–219°C; IR: 3374, 3312, 3028, 2958, 2198, 1641, 1594 cm^{-1}; ^1H NMR: δ

4.52–4.59 (m, 2H, CH_2), 4.91 (s, 1H, methin-H), 6.60 (s, 1H, Ar-H), 7.32–7.36 (m, 4H, Ar-H and NH_2), 7.46 (d, 2H, $J = 8.34$ Hz, Ar-H); ^{13}C NMR: δ 39.6, 40.7, 55.2, 114.9, 119.0, 128.9, 129.8, 132.6, 136.6, 139.5, 149.2, 159.1, 161.8, 169.4. Anal. Calcd for $C_{16}H_{10}Cl_2N_2O_3$: C, 55.04; H, 2.89; N, 8.02. Found: C, 54.85; H, 2.92; N, 8.10.

2-Amino-6-(chloromethyl)-8-oxo-4-(thiophen-2-yl)-4,8-dihydropyrano[3,2-*b*]pyran-3-carbonitrile (6f) White powder; mp 190–192°C ; IR: 3381, 3312, 3028, 2925, 2200, 1640, 1598 cm^{-1}; ^1H NMR: δ 4.58–4.65 (m, 2H, CH_2), 5.21 (s, 1H, methin-H), 6.62 (s, 1H, Ar-H), 7.02 (t, $J = 4.39$ Hz, 1H, Ar-H), 7.09 (s, 1H, Ar-H), 7.37 (s, 2H, NH_2), 7.52 (d, $J = 4.75$ Hz, 1H, Ar-H); ^{13}C NMR: δ 35.5, 40.8, 55.6, 115.0, 119.0, 126.1, 126.4, 127.3, 135.9, 144.6, 149.1, 159.3, 161.9, 169.4. Anal. Calcd for $C_{14}H_9ClN_2O_3S$: C, 52.43; H, 2.83; N, 8.73. Found: C, 52.19; H, 2.87; N, 8.80.

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