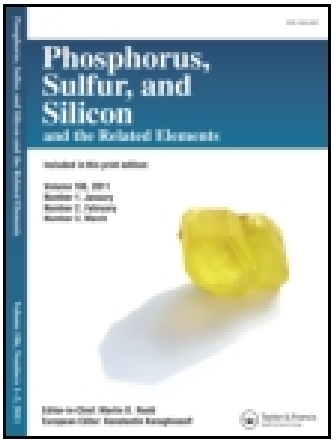

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Ionic Liquid Promoted Efficient Three-Component Synthesis of 2-Thioxo-2H-Thiopyrans

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IONIC LIQUID PROMOTED EFFICIENT THREE-COMPONENT SYNTHESIS OF 2-THIOXO-2*H*-THIOPYRANS

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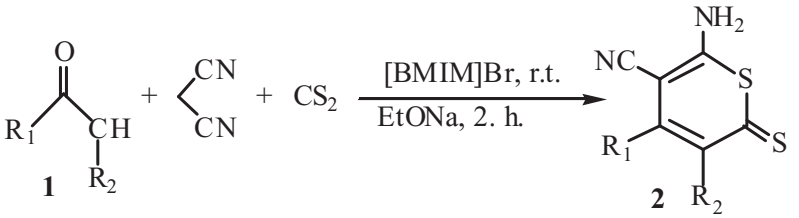
GRAPHICAL ABSTRACT



Abstract *An efficient one-pot three-component method for the synthesis of a variety of 2-thioxo-2H-thiopyrans has been described. Fairly good yields are obtained by cyclization reactions of arylidenemalononitriles, derived in situ from ketones and malononitrile, with carbon disulfide in the presence of a base in the ionic liquid 1-butyl-3-methylimidazolium bromide as reaction medium.*

[Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental resource*: *Selected Data.]*

Keywords Three-component reaction; malononitrile; 1-butyl-3-methylimidazolium bromide; ionic liquids; 2-thioxo-2*H*-thiopyrans

INTRODUCTION

Multicomponent reactions (MCRs) have attracted increasing attention of synthetic chemists as an effective method to generate molecular diversity.[1–3] Devising such types of MCRs, that achieve the formation of multiple bonds in a single operation in which three or more reactants are combined together to generate a desired product without the isolation of any intermediate, is one of the major challenges in modern organic synthesis.[4,5] In contrast to the multistep syntheses, such approaches avoid time-consuming tasks and costly purification processes, as well as protection–deprotection steps. Additionally, they are inherently more environmentally benign and atom-economic,[6] providing a powerful

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approach toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles.[7]

Nowadays, there is a trend toward the least consumption of organic solvents due to environmentally maligned chemical processes. In principle, the application of ionic liquids, as environmentally benign solvents, has the potential to exhibit low human toxities and ecotoxities.[8,9] The most commonly used ionic liquids are based on imidazolium salts including organic cation and appropriate anions. They currently receive a lot of attention as solvent, because they have mp close or near to r.t. and also are immiscible with a range of organic solvents meaning thereby that organic products can be removed and the ionic liquid can be recycled.[10] Due to the solvophobic properties, ionic liquids are capable of generating an internal pressure and promote the association of the reactants in a solvent cavity during the activation process and accelerate the reaction. This property of ionic liquids is very effective concerning MCRs in which the entropy of reaction decreases in the transition state.[11–13]

New approaches have been designed and developed to synthesize diverse arrays of drugs which are increasingly in demand in medicinal chemistry. In this context, thiopyrans have attracted more attention because of their backbone similarity with pyran units as useful biological properties.[14] Particularly, 4-methyl-5-pyrazinyl-1,2-dithiole-3-thione, (Oltipraz), is one of the most promising agents against environmentally induced hepatocellular carcinoma[15] and other cancers.[16] Also, 1,2-dithiole-3-thione itself protects against neoplasia.[17] In the meantime, several 5- and 6-membered sulfur heterocycles have been used as hepatoprotective agent. Among the 6-membered sulfur heterocycles, 6-amino-4-aryl-2-thioxo-2*H*-thiopyran-5-carbonitriles demonstrated activity in all the enzyme parameters at an amount of 6 mg/kg dose (P. O. $\times$ 7 days).[18]

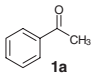
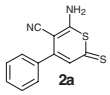
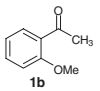
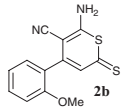
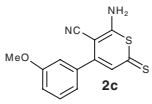
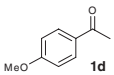
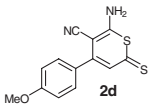
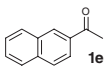
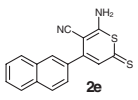
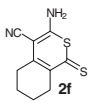
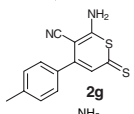
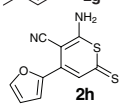
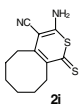
In 1966, Gewald[19] synthesized 6-amino-4-aryl-2-thioxo-2*H*-thiopyran-5-carbon itriles by the cyclization of arylidenemalononitriles with carbon disulfide in the presence of triethylamine in DMF within 24 h. To the best of our knowledge, this is the only method for the synthesis of these compounds that has been described in the literature. However, this method suffers from low product yields, long reaction times (24 h), use of solvent, and limited library of products.

In view of the emerging importance of ionic liquids as novel reaction media and the pharmacological activity of the 2-thioxo-2*H*-thiopyrans, and in line with our research work on the synthesis of heterocycles,[20] herein we wish to report our preliminary results on the preparation of 6-amino-4-aryl-2-thioxo-2*H*-thiopyran-5-carbonitriles by the three-component reaction of aryl methyl ketone (**1**), malononitrile, and carbon disulfide in the presence of a base by using the ionic liquid 1-butyl-3-methylimidazolium bromide as an environmental friendly solvent and promoter (Table 1).

RESULTS AND DISCUSSION

In investigation of the reaction conditions, the reaction of 2-acetyl naphthalene, malononitrile with carbon disulfide at ambient temperature in the presence of a base was selected as a model reaction. As shown in Table 2, the solvent loading exhibits an obvious influence on the reaction yield. The best result (66% yields) was obtained with 1.5 equivalent of sodium ethoxide in 1-butyl-3-methylimidazolium bromide ([BMIM]Br) at r.t. (Table 2, Entry 8). Also, the reaction was carried out in various amounts of ionic liquid at 25 °C (Table 3). The optimum amount of [BMIM] bromide was 1.5 equivalent (Table 3, entry 3), a higher amount of IL did not increase the yield noticeably.

Table 1 Room temperature ionic liquid-promoted synthesis of 6-amino-2-thioxo-2*H*-thiopyrane-5-carbonitrile derivatives (**2a–i**) in the presence of base

Entry	Ketone	Product	Yield[a] (%)
1	 **1a**	 **2a**	79
2	 **1b**	 **2b**	60
3	 **1c**	 **2c**	68
4	 **1d**	 **2d**	65
5	 **1e**	 **2e**	66
6	 **1f**	 **2f**	87
7	 **1g**	 **2g**	65
8	 **1h**	 **2h**	65
9	 **1i**	 **2i**	80

[a]Isolated yield.

Using the optimized reaction conditions, we proceeded to probe the effect of different substrates in the formation of highly substituted 2-thioxo-2*H*-thiopyrans (Table 1). Not only electron-rich aryl ketones, but also electron-deficient aryl ketones in the reactions afforded 2-thioxo-2*H*-thiopyran derivatives in 60–87% yields (Table 1). The 2-thioxo-2*H*-thiopyrans formed can be obtained in pure form by re-crystallizing or passing the crude products through a short plug of silica.

Our protocol exhibits a "green" method for the synthesis of 2-thioxo-2*H*-thiopyran derivatives involving C═S bond using methyl ketones as the starting materials. Our procedure introduces a simple, mild, and useful approach to a variety of 2-thioxo-2*H*-thiopyran derivatives.

Table 2 Reaction of 2-acetylnaphthalene with malononitrile and carbon disulfide at ambient temperature under various conditions

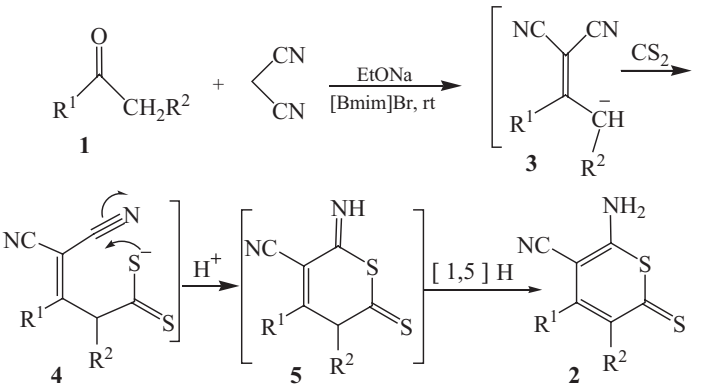
Entry	Solvent	Base (equiv.)	Yield (%)	Time
1	CH_3CN	EtONa (1.5)	30	2 h
2	DMF	EtONa (1.5)	–	2 h
3	DMSO	EtONa (1.5)	–	2 h
4	THF	EtONa (1.5)	15	2 h
5	Toluene	EtONa (1.5)	45	2 h
6	CH_3NO_2	EtONa (1.5)	–	2 h
7	CH_2Cl_2	EtONa (1.5)	10	2 h
8	[BMIM]Br	EtONa (1.5)	66	2 h
9	EtOH	EtONa (1.5)	50	2 h
10	[BMIM] BF_4	EtONa (1.5)	62	2 h
11	[BMIM] PF_6	EtONa (1.5)	10	2 h
12	[BMIM]OH	–	–	2 h
13	[BzMIM]Cl	EtONa (1.5)	5	2 h

The structures of the products **2a–2i** (Table 1) were deduced from the elemental analyses, IR, ^{1}H NMR, and ^{13}C NMR spectra. The IR spectrum of **2a** showed absorption at 2200 cm^{-1} due to the CN triple bond, and two sharp bands at 3300 and 3250 cm^{-1} due to asymmetric and symmetric vibrations of the NH_2 group, and a C=S absorption at 1260 cm^{-1}, respectively. The ^{1}H NMR spectrum of **2a** exhibited a singlet readily recognized as arising from CH-C=S (δ = 6.7 ppm), and a singlet (δ = 7.5 ppm) due to aromatic protons, along with a broad singlet for two amine protons (δ = 9.2 ppm). The ^{13}C NMR spectrum of **2a** showed 10 distinct resonances in agreement with the suggested structure. The ^{1}H NMR and ^{13}C NMR spectra of **2b–j** are similar to those of **2a** except for the R^1 and R^2 groups, which exhibit characteristic signals with appropriate chemical shifts. The thiocarbonyl resonance in the ^{13}C NMR spectra of **2a** appears at 193.2 ppm. So, this observation confirms the structure of the products.

Mechanistically, the reaction can be interpreted as follows. The carbanion **3** generated by the deprotonation of vinylmalononitrile by sodium ethoxide adds to carbon disulfide in a tandem reaction, to furnish the carbodithiate anion **4**. Then, the anion **4** attacks the carbon center of the CN triple bond by an intramolecular nucleophilic addition to produce the imine **5**, which finally isomerizes to give highly substituted 2-thioxo-2*H*-thiopyrans **2** (Scheme 1).

Table 3 Optimization of the amount of ionic liquid for the synthesis of **3e**

Entry	Ionic liquid (mmol)	Base (mol%)	Yield (%)
1	0.5	EtONa (150)	0
2	1	EtONa (150)	52
3	1.5	EtONa (150)	66
4	2	EtONa (150)	66



Scheme 1

CONCLUSIONS

We have developed a simple, convenient, and practical method for the synthesis of 2-thioxo-2*H*-thiopyrans possessing potential biological properties. These products synthesized through a one-pot three-component reaction of ketones, malononitrile, and carbon disulfide in the presence of sodium ethoxide using ionic liquids as an environmentally friendly and novel promoter medium. The use of simple and ready available starting materials and good yields of products are the main advantages of our method.

EXPERIMENTAL

Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Melting points were measured on an Electrothermal 9100 apparatus and were uncorrected. IR spectra (KBr pellets, ν/cm^{-1}) were measured on a Perkin-Elmer 783 infrared spectrophotometer. NMR spectra were measured using a Bruker DRX-250 Avance spectrometer at 300.13 MHz (^{1}H) and 75.47 MHz (^{13}C), respectively. [BMIM]Br, [BMIM]BF_4, [BMIM]PF_6, [BMIM]OH, and [BzMIM]Cl ionic liquids were prepared according to the procedures reported in the literature.[21–23]

Other reagents were obtained from Merck (Germany) and Fluka (Buchs, Switzerland), and all materials were used without further purification.

General Procedure

In a typical experiment, to a round-bottomed flask charged with NaOEt (1.5 mmol) in ionic liquid [BMIM]Br (1.5 mmol), 2-acetylnaphthalene (1.0 mmol), and malononitrile (1 mmol) were added under stirring. The mixture was stirred for 2 h at ambient temperature, and then carbon disulfide (2 mmol) was added drop-wise and the reaction mixture stirred for about 20 min. On completion of the reaction as indicated by TLC, water (10 mL) was added. The reaction mixture was extracted with ethyl acetate (3 × 5 mL), and the combined organic solvent was removed under reduced pressure. In the case of **2a**, **2c**, **2d**, **2e**, and **2i**, cold acetonitrile (5 mL) was added to the residues to produce the pure solid products. For **2b**, **2f**, **2g**, and **2h**, the resulting crude products were purified by column chromatography on silica gel (100–200 mesh) using ethyl acetate/hexane (2:1) to get the pure products.

Selected Data

6-Amino-4-phenyl-2-thioxo-2H-thiopyran-5-carbonitrile (2a). Orange powder (0.19 g, 79%). Mp 268 °C (dec.). IR: 3250–3300 (NH_2), 2200 (CN), 1650 (C=C), 1260 (C=S). ^{1}H NMR (DMSO) δ 6.7 (s, 1H, C*H*-C=S), 7.5 (s, 5H, Ph), 9.2 (s, 2H, NH_2). ^{13}C NMR (DMSO) δ 84.2 (*C*-CN), 115.7 (*C*N), 125.7 (*C*-C=S), 127.8 (C_o of phenyl), 128.6 (C_p of phenyl), 130.0 (C_m of phenyl), 138.0 (C_i of phenyl), 153.0 (*C*-Ar), 171.5 (*C*-NH_2), 193.2 (*C*=S) ppm. Anal. Calcd for $C_{12}H_8N_2S_2$: C, 58.99; H, 3.30; N, 11.47%. Found: C, 57.8; H, 3.2; N, 11.6%.

6-Amino-4-(2-methoxyphenyl)-2-thioxo-2H-thiopyran-5-carbonitrile (2b). Orange powder (0.16 g, 60%). Mp 194 °C (dec.). IR: 3350 (NH) 3250 (NH), 2200 (CN), 1620 (C=C), 1250 (C=S). ^{1}H NMR (DMSO) δ 3.8 (s, 3H, OCH_3), 6.6 (s, 1H, C*H*-*C*=*S*), 7.0 (t, $^3J_{HH}$ = 7.34 Hz, 1H), 7.1 (d, $^2J_{HH}$ = 8.2 Hz, 1H), 7.3 (d, $^2J_{HH}$ = 7.2 Hz, 1H), 7.5 (t, $^3J_{HH}$ = 7.7 Hz, 1H), 9.1 (s, 2H, NH_2). ^{13}C NMR (DMSO) δ 55.5 (O*C*H$_3$), 86.4 (*C*-CN), 111.8 (C_m of phenyl), 115.7 (*C*N), 120.6 (*C*-C=S), 125.9 (C_m of phenyl), 127.2 (C_o of phenyl), 129.0 (C_p of phenyl), 131.2 (C_i of phenyl), 151.4 (*C*-Ar), 155.8 (*C*-OCH_3), 170.2 (*C*-NH_2), 192.8(*C*=S) ppm. Anal. Calcd for $C_{13}H_{10}N_2OS_2$: C, 56.91; H, 3.67; N, 10.21%. Found: C, 57.9; H, 3.7; N, 10.3%.

6-Amino-4-(3-methoxyphenyl)-2-thioxo-2H-thiopyran-5-carbonitrile (2c). Orange powder (0.19 g, 68%). Mp 255 °C (dec.). IR: 3300 (NH), 3225 (NH), 2200 (CN), 1620 (C=C), 1270 (C=S). ^{1}H NMR (DMSO) δ 3.79 (s, 3H, OCH_3), 6.6 (s, 1H, C*H*-*C*=*S*), 7 (3H, CH of phenyl), 7.39 (t, $^3J_{HH}$ = 8 Hz, 1H), 9.1 (s, 2H NH_2).^{13}C NMR (DMSO) δ 55.7 (O*C*H$_3$), 85.6 (*C*-CN), 113.6 (C_p of phenyl), 116.1 (C_o of phenyl), 116.7 (*C*N), 120.4 (C_o of phenyl), 125.0 (*C*-C=S), 130.3 (C_m of phenyl), 140.2 (C_i of phenyl), 153.6 (*C*-Ar), 159.5 (*C*-OCH_3), 171.3 (*C*-NH_2), 192.5(*C*=S) ppm. Anal. Calcd for $C_{13}H_{10}N_2OS_2$: C, 56.91; H, 3.67; N, 10.21%. Found: C, 56.1; H, 3.6; N, 10.3%.

6-Amino-4-(4-methoxyphenyl)-2-thioxo-2H-thiopyran-5-carbonitrile (2d). Orange powder (0.18 g, 65%). Mp 272 °C (dec.). IR: 3300 (NH), 3250 (NH), 2200 (CN), 1600 (C=C), 1250 (C=S). ^{1}H NMR (DMSO) δ 3.8 (s, 3H, OCH_3), 6.7 (s, 1H, C*H*), 7.0 (m, 2H), 7.5 (m, 2H), 9.1 (s, 2H, NH_2). ^{13}C NMR (DMSO) δ 55.8 (O*C*H$_3$), 84.9 (*C*-CN), 114.5 (C_m of phenyl), 116.7 (*C*N), 125.7 (*C*-C=S), 130.1 (C_o of phenyl), 130.6 (C_i of phenyl), 153.4 (*C*-Ar), 161.2 (*C*-NH_2), 171.8 (*C*-OCH_3), 192.4 (*C*=S) ppm. Anal. Calcd for $C_{13}H_{10}N_2OS_2$: C, 56.91; H, 3.67; N, 10.21%. Found: C, 55.9; H, 3.6; N, 10.3%.

Supplementary Data

Selected data for products **2e–2i** are available. Supplementary data associated with this article can be found in the online version.

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