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An efficient conjugate hydrothiocyanation of chalcones with a task-specific ionic liquid

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Abstract—A new and efficient method of conjugate hydrothiocyanation of chalcones along with the preparation of a probe for demonstrating the utility of the resulting β-thiocyanato ketones in heterocyclic synthesis is reported. Chalcones undergo an efficient conjugate hydrothiocyanation with the task-specific ionic liquid (TSIL), 1-*n*-butyl-3-methylimidazolium thiocyanate ([bmim]SCN) followed by reaction with $AcONH_4$ or an amine to afford chemically and pharmaceutically interesting 2-amino-1,3-thiazines at room temperature in a one-pot procedure. After isolation of the product, the ionic liquid [bmim]OH could be used for the synthesis of [bmim]SCN, thus allowing recycling of the TSIL for further use.

Organic thiocyanates are of considerable importance from both the chemical and biological viewpoints. They are versatile intermediates for the synthesis of various heterocycles;[1,2] some of which exhibit herbicidal and other important biological activities.[3,4] The thiocyanate functionality is useful as a masked mercapto group. Furthermore, the thiocyanato group occurs as an important functionality in several anticancer natural products formed by deglycosylation of glucosilonates derived from cruciferous vegetables.[5]

Thiocyanation is generally carried out via nucleophilic substitution using thiocyanate anions. The low nucleophilicity of the SCN anion requires rather harsh reaction conditions. Metal thiocyanates and organic halides or sulfonates are generally used to introduce the thiocyanate functionality into an organic molecule.[6] However, thiocyanates are not very stable when heated or under acidic conditions. Chromatography on silica gel or prolonged heating over 50 °C can cause intramolecular rearrangement of the thermodynamically favoured isothiocyanate isomers.[7] Thiocyanates have been obtained from alcohols,[8] silyl ethers[9] or amines[10] using $Ph_3P(SCN)_2$. However, many drawbacks have been observed in these thiocyanation methodologies,[11] particularly for β-thiocyanation of carbonyl compounds as the ease of nucleophilic substitution at the β-carbon is far less than that at the α-carbon. Thus, an efficient method for the introduction of a thiocyanate functionality at the β-position of carbonyl compounds under mild conditions appeared interesting.

Ionic liquids (ILs) have attracted increasing interest in the context of green chemistry owing to their great potential as environmentally benign reaction media.[12–15] ILs also play significant roles as catalysts[15–17] and reagents[18,19] and are easy to recycle.[18,19] A recent review[20] presents studies on applications of ILs to asymmetric syntheses showing their ever-increasing importance.

The literature records only one report describing a single example of conjugate hydrothiocyanation of a chalcone using ammonium thiocyanate and sulfuric acid to afford the β-thiocyanato ketone in 63% yield.[21] The present Letter reports a new and efficient method of conjugate hydrothiocyanation of chalcones using a task-specific ionic liquid to afford β-thiocyanato ketones in 85–93% yields without requiring any other catalyst or solvent. The present work is part of our continuing drive to devise new one-pot cyclization processes under environmentally benign conditions.[22–26] The strategy reported herein was successfully realized by stirring a mixture of a task-specific ionic liquid (TSIL)[18] [bmim]SCN **1** and a chalcone **2** at room temperature for 2–3 h to afford β-thiocyanato ketones **3** in 85–93% yields (Scheme 1).[27]

Keywords: Hydrothiocyanation; Conjugate addition; Chalcones; Ionic liquids; Thiocyanates; 1,3-Thiazines.
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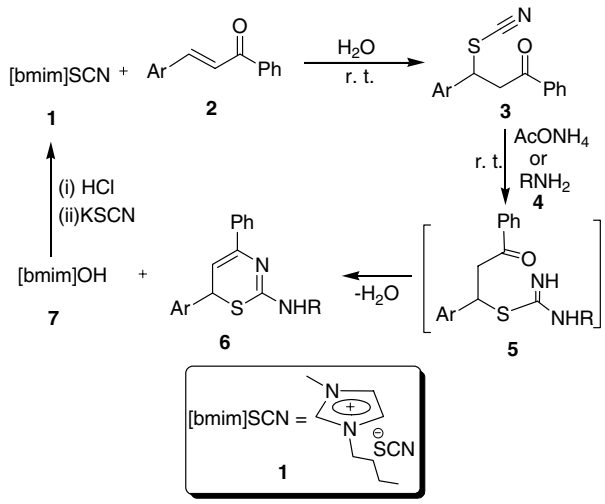

Product	Ar	R	Yield (%)*
3a	Ph	-	91
3b	4-$MeOC_6H_4$	-	85
3c	4-ClC_6H_4	-	88
6a	Ph	H	87
6b	Ph	Ph	86
6c	Ph	4-$MeOC_6H_4$	89
6d	Ph	4-FC_6H_4	82
6e	4-$MeOC_6H_4$	H	86
6f	4-$MeOC_6H_4$	Ph	85
6g	4-$MeOC_6H_4$	4-$MeOC_6H_4$	87
6h	4-$MeOC_6H_4$	4-FC_6H_4	81
6i	4-ClC_6H_4	H	91
6j	4-ClC_6H_4	Ph	92
6k	4-ClC_6H_4	4-$MeOC_6H_4$	92
6l	4-ClC_6H_4	4-FC_6H_4	83

* Yields of isolated and purified products.

Scheme 1. Postulated intermediates leading to the formation of thiazines **6**.

The pure products **3** were extracted with ether from the ionic liquid. No column chromatography or recrystallization was required thus avoiding the possibility of rearrangement of thiocyanates **3** to the thermodynamically favoured isothiocyanates.

As a probe for demonstrating the application of β-thiocyanato ketones **3** in heterocyclic synthesis, we have synthesized 2-amino-1,3-thiazines **6** which are chemically and pharmaceutically interesting entities.[28–31] These were synthesized from chalcones **2**, task-specific ionic liquid **1** and $AcONH_4$ or an amine **4** in a one-pot procedure at room temperature in 81–92% yields.[32] Postulated intermediates leading to the formation of thiazines **6** are depicted in Scheme 1. The pathway is supported by the observation that an isolated and purified β-thiocyanato ketone **3** reacts with $AcONH_4$ or an amine **4** to afford a thiazine **6**. A comparison with **1** was carried out by reacting chalcone **2**, (Ar = Ph) in [bmim]BF_4 with 1.5 equiv of KSCN at rt. In this case, the hydrothiocyanation resulting in the corresponding β-thiocyanato ketones **3** took place with only 35% conversion even after 4 h of reaction time. This indicates that the nucleophilicity of the SCN anion is much higher in [bmim]SCN compared to that from KSCN in [bmim]BF_4. After isolation of products **3** or **6**, the ionic liquid [bmim]OH **7** could be recycled to [bmim]SCN **1** for use in subsequent runs. This was accomplished by treating **7** with conc. HCl in acetone followed by stirring with KSCN at room temperature for 48 h.

2-Amino-1,3-thiazines have also been prepared from chalcones and thiourea in a one-pot procedure.[21,33–35] The reaction of thiourea, as an ambident nucleophile, with enones in the presence of a strong base in refluxing ethanol is a point of argument among synthetic organic chemists. For example, Madkour et al.,[21] Takamizawa et al.[33] and Ingarsal et al.[34] have found that the reaction provides a synthetic route to thiazines, whereas El-Hashash et al.[35] isolated pyrimidine-2-thione derivatives. However, the method reported herein (Scheme 1) has several advantages, such as exclusive formation of 2-amino-1,3-thiazines **6**, high yields (81–92%), a one-pot reaction at room temperature, use of an easily recyclable hydrothiocyanating agent **1** and does not require any other catalyst or solvent.

In summary, we have developed an efficient protocol for the synthesis of β-thiocyanato ketones via the conjugate hydrothiocyanation of chalcones with the task-specific ionic liquid [bmim]SCN. The application of this protocol in heterocyclic chemistry is demonstrated by a one-pot synthesis of chemically and pharmaceutically interesting 2-amino-1,3-thiazines.

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27. *General procedure for the hydrothiocyanation of chalcones* **2**: A mixture of [bmim]SCN **1** (6.0 mmol), chalcone **2** (5.0 mmol) and a few drops of distilled water was taken in a 50 mL round-bottomed flask and stirred at rt for 2–3 h. After completion of the reaction as indicated by TLC, the product was extracted with ether (3×20 mL). The combined ether extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure to give a pure β-thiocyanato ketone **3** as yellowish solid. The remaining ionic liquid, [bmim]OH **7** was dissolved in acetone (10 mL) and treated with conc. HCl (1.2 equiv) followed by reaction with KSCN (2 equiv) at rt for 48 h to afford TSIL [bmim]SCN **1** which was used in subsequent runs. Physical data of representative compounds: **3a:** yellowish solid, yield 91%, mp 61–62 °C. IR (KBr) ν_{max} 3021, 2069, 1691, 1603, 1579, 1456 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6/TMS) δ: 3.01 (dd, 1H, $J = 13.7$ Hz, $J = 8.4$ Hz, 2-Ha), 3.32 (dd, 1H, $J = 13.7$ Hz, $J = 3.1$ Hz, 2-Hb), 4.88 (dd, 1H, $J = 8.4$ Hz, $J = 3.1$ Hz, 3-H), 7.05–7.81 (m, $10H_{arom}$). ^{13}C NMR (100 MHz; DMSO-d_6/TMS) δ: 41.3 (*CH*Ph), 50.3 (CH_2CO), 112.4 (CN), 126.9, 128.2, 129.4, 131.5, 132.7, 133.5, 134.3, 135.9 ($2 \times$ Ph), 192.8 (CO). EIMS (*m*/*z*): 267 (M^+). Anal. Calcd for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24. Found: C, 71.52; H, 4.99; N, 5.46%. **3c**: yellowish solid, yield 88%, mp 120–121 °C. IR (KBr) ν_{max} 3023, 2070, 1692, 1601, 1585, 1452 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6/TMS) δ: 3.03 (dd, 1H, $J = 13.7$ Hz, $J = 8.4$ Hz, 2-Ha), 3.35 (dd, 1H, $J = 13.7$ Hz, $J = 3.1$ Hz, 2-Hb), 4.92 (dd, 1H, $J = 8.4$ Hz, $J = 3.1$ Hz, 3-H), 7.09–7.85 (m, $9H_{arom}$). ^{13}C NMR (100 MHz; DMSO-d_6/TMS) δ: 41.1 (*CH*Ph), 50.5 (CH_2CO), 112.7 (CN), 127.4, 128.3, 129.1, 131.3, 132.7, 133.6, 134.2, 135.7 (Ph, 4-ClC_6H_4), 192.5 (CO). EIMS (*m*/*z*): 301 (M^+). Anal. Calcd for $C_{16}H_{12}ClNOS$: C, 63.68; H, 4.01; N, 4.64. Found: C, 63.97; H, 4.33; N, 4.28.
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32. *General procedure for the synthesis of 2-amino-1,3-thiazines* **6**: A mixture of [bmim]SCN **1** (6.0 mmol), chalcone **2** (5.0 mmol) and a few drops of distilled water was taken in a 50 mL round-bottomed flask and stirred at rt for 2–3 h. Then, $AcONH_4$ or an amine **4** (5.0 mmol) was added and the reaction mixture was stirred at rt for a further 3–4 h. After completion of the reaction as indicated by TLC, the product was extracted with ether (3×25 mL). The combined ether extracts were evaporated under reduced pressure to leave the crude product, which was recrystallized from EtOH to afford an analytically pure sample of **6** as yellowish crystals. The remaining ionic liquid [bmim]OH **7** was converted into [bmim]SCN **1** for use in subsequent runs as described above.[27] Physical data of representative compounds: **6a: y**ellowish crystals, yield 87%, mp 110–112 °C. IR (KBr) ν_{max} 3341, 3027, 1643, 1599, 1582, 1451 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6/TMS) δ: 3.81 (s, 2H, NH_2 exchangeable with D_2O), 3.96 (d, 1H, $J = 7.6$ Hz, 6-H), 6.12 (d, 1H, $J = 7.6$ Hz, 5-H), 7.06–7.30 (m, $10H_{arom}$). ^{13}C NMR (100 MHz; DMSO-d_6/TMS) δ: 35.3 (4-C), 110.9 (5-C), 126.5, 127.9, 128.7, 131.2, 131.9, 132.7, 133.4, 134.6 ($2 \times$ Ph), 142.7 (6-C), 161.2 (SC=N). EIMS (*m*/*z*): 266 (M^+). Anal. Calcd for $C_{16}H_{14}N_2S$: C, 72.15; H, 5.30; N, 10.52. Found: C, 71.91; H, 5.21; N, 10.72. **6j**: yellowish crystals, yield 92%, mp 183–185 °C. IR (KBr) ν_{max} 3343, 3025, 1645, 1602, 1585, 1449 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6/TMS) δ: 5.23 (s, 1H, NHPh exchangeable with D_2O), 3.98 (d, 1H, $J = 7.6$ Hz, 6-H), 6.15 (d, 1H, $J = 7.6$ Hz, 5-H), 7.11–7.78 (m, $14H_{arom}$). ^{13}C NMR (100 MHz; DMSO-d_6/TMS) δ: 35.5 (4-C), 111.7 (5-C), 126.2, 127.1, 127.8, 128.4, 129.6, 130.5, 131.2, 131.9, 132.7, 133.5, 134.2, 134.9 (4-ClC_6H_4, $2 \times$ Ph), 143.1 (6-C), 161.5 (SC=N). EIMS (*m*/*z*): 376 (M^+). Anal. Calcd for $C_{22}H_{17}ClN_2S$: C, 70.11; H, 4.55; N, 7.43. Found: C, 70.37; H, 4.39; N, 7.51.
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