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Organocatalytic Regioselective Concomitant Thiocyanation and Acylation of Oxiranes Using Aroyl Isothiocyanates

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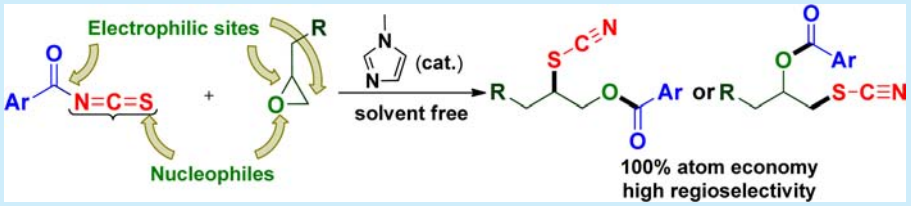
Supporting Information



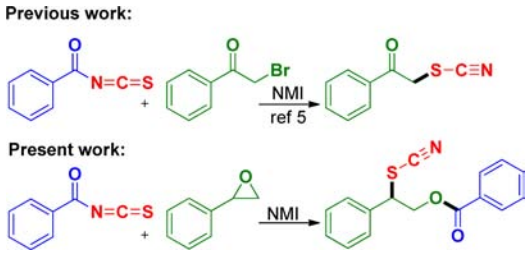
ABSTRACT: A regioselective and concomitant transfer of thiocyanate (−SCN) and aroyl/acyl (−COR) groups from aroyl/acyl isothiocyanates onto oxiranes was achieved, giving thiocyanato benzoates in 100% atom economy. In this biomimetic organocatalytic process, one part (−SCN) of aroyl/acyl isothiocyanates acts as the nucleophile whereas the other half (−COR) serves as an electrophilic partner.

The desire to develop newer methodology for the construction of C−C and C−X (X = heteroatom) bonds has brought about many appealing results in the field of synthetic chemistry.[1] Compared to the traditional electrophiles, epoxides have emerged as attractive coupling partners.[2] The ring strain in epoxides makes them susceptible to ring opening with a range of nucleophiles such as alcohols, amines, thiols, and other strong nucleophilic organometallic reagents like Grignard or organolithium.[3] Recently, there have been many reports on transition-metal-catalyzed coupling of epoxides with aryl halides, arenes, alkenes, alkynes, and boronic acids, resulting in the construction of a variety of alcohols.[4] However, these transition-metal-catalyzed reactions are not universally acceptable due to their high cost and toxicity.

From our previous work on biomimetic thiocyanate group transfer from aroyl isothiocyanate onto α-haloketones, a nucleophilic substitution product was observed in the absence of any real nucleophile. In this process, the α-haloketone serves as an electrophile and the aroyl isothiocyanate as the source of nucleophile (−SCN). Thus, it will be interesting to see if an oxirane can act as the electrophilic partner for this nucleophile-less nucleophilic substitution. Furthermore, if the ring opens up, what will be the fate of the resultant alkoxy ion? Will it form an alcohol (via protonation), or will it undergo further nucleophilic attack onto a suitable electrophile?

To find answers to the above queries, a reaction was carried out with benzoyl isothiocyanate (**1**) (1 equiv) and 2-phenyloxirane (**a**) (1 equiv) in the presence of *N*-methylimidazole (NMI) (1 equiv) in acetonitrile (2 mL) at room temperature, under a reaction condition identical to that reported in our previous work (Scheme 1).[5] Both reactants **1** and **a** were completely consumed (as indicated by TLC), giving a new product. The IR spectra of newly formed product showed a characteristic peak at 2154 cm^{-1}, suggesting the incorporation of a −SCN group. Another peak at

Scheme 1. Benzoyl Isothiocyanate as Thiocynating and Acylating Agent



1705 cm^{-1} may be due to the presence of a carbonyl group in the resultant product. Further, ^{1}H and ^{13}C NMR of the isolated product revealed the presence of an ester functionality. Finally, the structure of the product was confirmed by single-crystal X-ray diffraction study of one of its derivative (2-phenyl-2-thiocyanatoethyl 4-methylbenzoate, **2a**) (Figure S1, Supporting Information, SI), which revealed the presence of a thiocyanate as well as an ester functionality. As anticipated, the thiocyanate acts as a nucleophile and attacks at the Aα position of the epoxide.[6] The resultant alkoxy species obtained by the ring opening of epoxide possibly undergoes benzoylation, giving 2-phenyl-2-thiocyanatoethyl benzoate (**1a**). Here, the reaction gave a single regioisomeric product **1a** in 67% isolated yield. In the absence of NMI, the reaction did not proceed at all, suggesting its definite involvement during this simultaneous electrophilic−nucleophilic process. This unprecedented outcome showing the transfer of both halves (i.e., thiocyanate (−SCN) and the acyl (−COPh) group from **1** onto **a**) results in the formation of a product having new C−S and C−O bonds in 100% atom economy.

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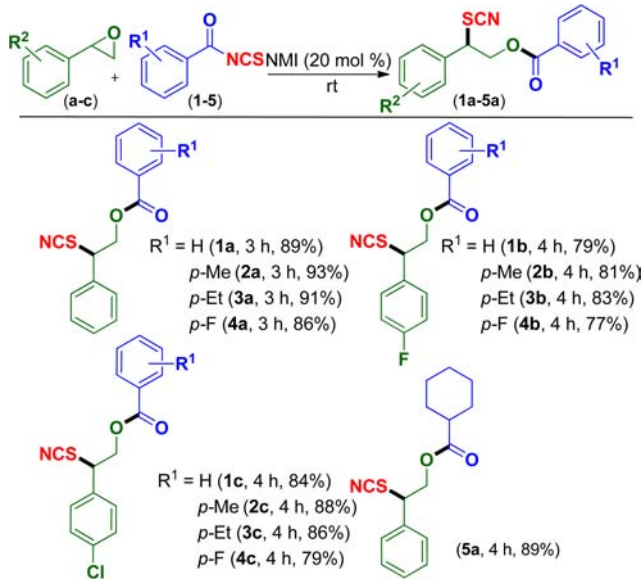
Organic thiocyanates are prevalent subunits in bioactive compounds possessing antimicrobial and antiproliferative activity and are versatile precursors for the synthesis of many sulfur-containing heterocycles.[7] Aryl esters are also a ubiquitous functionality found in pharmaceuticals, agrochemicals, and polymers and are important building blocks for organic synthesis.[8] The presence of both of these important functionalities, viz. thiocyanate and ester, in a single molecule derived from readily available starting material is a boon to synthetic chemists.

Encouraged by this double functional group transfer, we carried out further optimizations to improve the yield of the bisfunctionalized product. Compounds **1** and **a** were chosen for this purpose. With the essential requirement of NMI (a tertiary amine) as the organocatalyst for the reaction to proceed, a set of other tertiary amines were screened. In comparison to NMI (67%), the use of imidazole and DMAP gave inferior yields, 45 and 15% respectively (Table S1, entries 1−3, SI), whereas Et_3N, DBU, and DABCO (Table S1, entries 4−6, SI) resulted in no observable reactions. With NMI as the suitable promoter, increasing its loading from 1 to 1.5 equiv did not improve the yield significantly (69%, Table S1, entry 7, SI). To check whether NMI acts as a promoter or a catalyst, a reaction was performed by decreasing the NMI loading. Interestingly, when the quantity of NMI was reduced to 0.5 and 0.2 equiv, the yield virtually remained unaltered (Table S1, entries 8 and 9, SI). A reduction in the yield (55%) was observed when the NMI loading was decreased further to 0.1 equiv (Table S1, entry 10, SI). This bisfunctionalization route is truly a biomimetic organocatalytic process giving product in 100% atom economy. To see the effect of solvent, if any, a range of other solvents such as DCM (42%), DMF (00%), DMSO (00%), dioxane (00%), toluene (00%), and H_2O (15%) (Table S1, entries 11−16, SI) were screened and all were found to be inferior to that of acetonitrile. Since all the reactants are liquid, we thought of carrying out a neat reaction by mixing **1** (1 equiv), **a** (1 equiv), and NMI (0.2 equiv) at room temperature. Gratifyingly, an improvement in the yield of the isolated product (**1a**, 89%) was observed (Table S1, entry 17, SI). Thus, the nonrequirement of solvent makes the method even more green and sustainable, giving further advantage to the present protocol from a synthetic point of view.[9] To see the effect of temperature, reactions were performed at elevated temperature (50 °C) and below room temperature (10 °C) under otherwise identical conditions, but both the reactions gave reduced yields, 68 and 57%, respectively (Table S1, entries 18 and 19, SI).

With this optimized reaction condition [i.e., the use of benzoyl isothiocyanate (1 equiv), oxirane (1 equiv), and NMI (0.2 equiv) at room temperature], the scope of this methodology was further extended to a range of aroyl/acyl isothiocyanates and oxirane derivatives. At first, the influence of substituents on the phenyl ring of benzoyl isothiocyanates **1**−**4** was explored with **a**. The presence of electron-donating groups such as *p*-Me (**2**) and *p*-Et (**3**) on the phenyl ring of benzoyl isothiocyanate gave corresponding products **2a** and **3a** in 93 and 91% yields, respectively, compared to the unsubstituted analogue (**1a**, 89%). A slight reduction in the yield of **4a** was noticed when a moderately electron-withdrawing group such as *p*-F (**4**) was present on the phenyl ring of benzoyl isothiocyanate. These observations suggest that the presence of either moderately electron-donating or electron-withdrawing groups on benzoyl isothiocyanate had no substantial influence on the product yield (Scheme 2). Next, the influence of substituents such as *p*-F (**b**) and *p*-Cl (**c**) on the phenyl ring of 2-phenyloxirane was evaluated by reacting them separately with various benzoyl isothiocyanates **1**−**4**. A slight reduction in the product yields (**1b**, 79%; **2b**, 81%; **3b**, 83%; **4b**, 77%) suggests the negative influence of electron-withdrawing *p*-F (**b**) substituent on the product outcome. Similar trends in the product yields were observed (**1c**, 84%; **2c**, 88%; **3c**, 86%; **4c**, 79%) when substituent *p*-Cl (**c**) is present on the phenyl ring of 2-phenyloxirane. This double functional group transfer strategy was also equally successful for aliphatic isothiocyanate, that is, cyclohexanecarbonyl isothiocyanate (**5**), giving the bisfunctionalized product **5a** in 89% yield (Scheme 2).

Scheme 2. Synthesis of 2-Phenyl-2-thiocyanatoethyl Benzoates[a,b]



[a]Reaction conditions: benzoyl isothiocyanates **1**−**5** (0.5 mmol), oxiranes **a**−**c** (0.5 mmol), NMI (0.1 mmol) under air at room temperature for 3−4 h. [b]Isolated yield.

All of the oxiranes tested above (Scheme 2) open up via the attack of −SCN at the Aα (benzylic carbon) site, giving single regioisomeric products. If the reaction indeed proceeds via the nucleophilic attack of −SCN onto the epoxide, then the attack should be preferably at the less hindered (Aβ) site, giving the opposite regioisomer. Formation of a single regioisomer in all cases (Scheme 2) is possibly due to the better stability of the incipient carbocation at the benzylic position.

For nonbenzylic oxiranes, it would be interesting to see if a single regioisomer is obtained or a mixture of isomeric products. To check this, a reaction was carried with 2-(phenoxymethyl)-oxirane (**d**) and **1** under an otherwise identical reaction condition. Here again, a single regioisomer (**1d**) was observed, but regioselectivity was opposite that of 2-phenyloxirane derivatives (Scheme 3). The resultant product **1d** (85%) is obtained via the attack of −SCN at the less sterically hindered carbon (Aβ) in oxirane **d**. This observation is in contrast to the 2-phenyloxirane systems (Scheme 2), where the product is obtained via the attack at the more sterically hindered carbon (Aα). The glycidic epoxide **d** was than reacted with various other benzoyl isothiocyanates possessing electron-donating [*p*-Me (**2**), *p*-Et (**3**)] and electron-withdrawing [*p*-F (**4**)] groups, and all gave their single regioisomeric products (**2d**, 89%; **3d**, 87%; **4d**, 78%) (Scheme 3). Another glycidic epoxide, 2-((*o*-tolyloxy)-methyl)oxirane (**e**), on treatment with bezoyl isothiocyanates **1**−

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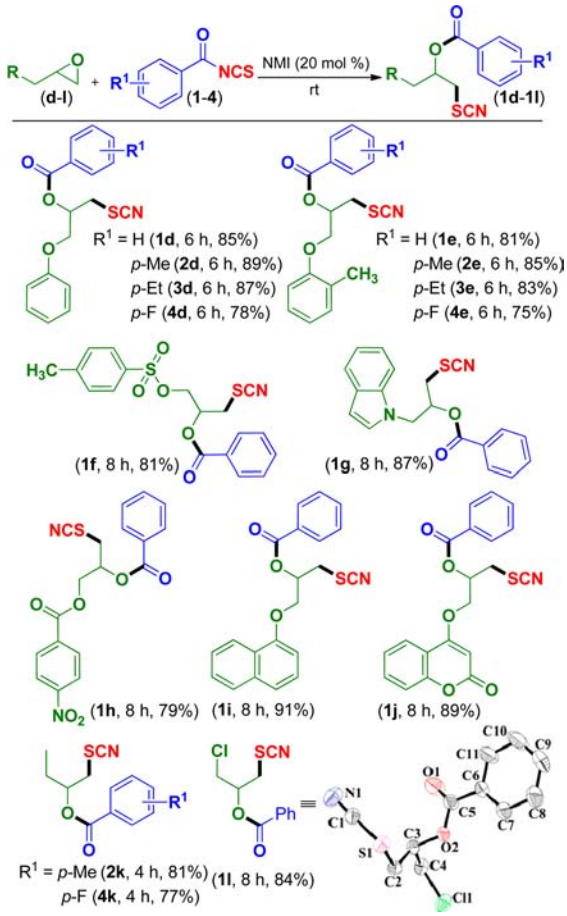
Scheme 3. Synthesis of Various Thiocyanato Benzoates[a,b]



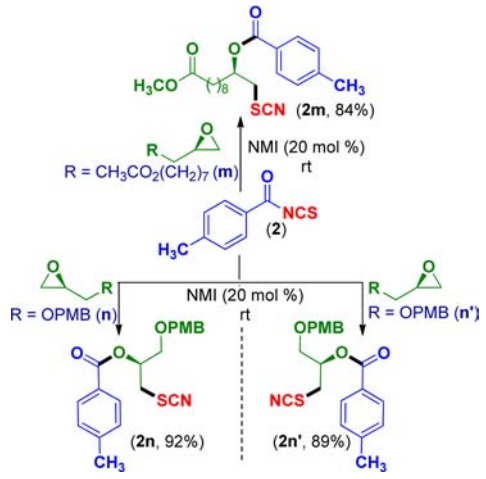
[a]Reaction conditions: benzoyl isothiocyanates **1**–**4** (0.5 mmol), oxiranes **a**–**c** (0.5 mmol), NMI (0.1 mmol) under air at room temperature for 6–8 h. [b]Isolated yield.

4 again gave their sole regioisomeric bis-functionalized products **1e** (81%), **2e** (85%), **3e** (83%), and **4e** (75%) (Scheme 3).

The utility of the present electrophilic–nucleophilic process was successfully demonstrated with a variety of other glycidic epoxides such as oxiran-2-ylmethyl 4-methylbenzenesulfonate (**f**), 1-(oxiran-2-ylmethyl)-1*H*-indole (**g**), oxiran-2-ylmethyl 4-nitrobenzoate (**h**), 2-((naphthalen-1-yloxy)methyl)oxirane (**i**), and 4-(oxiran-2-ylmethoxy)-2*H*-chromen-2-one (**j**) (Scheme 3). All of these oxiranes reacted well with **1** under the optimized reaction condition to afford their regioisomeric products (**1g**–**1l**) in yields ranging from 79 to 91%. Aliphatic oxirane such as 1,2-epoxy ethane (**k**) underwent reaction with **2** and 4-fluorobenzoyl isothiocyanate (**4**) to afford their corresponding products, **2f** (81%) and **4f** (77%), respectively. Similarly, 2-(chloromethyl)oxirane (**l**) underwent smooth bis-functionalization with **1**, giving product **1l** in 84% yield. The structure of this regioisomeric product **1l** has been confirmed by single-crystal X-ray diffraction study (Scheme 3), reconfirming that the attack of −SCN nucleophile is at the less hindered site in glycidic epoxides **d**–**l** (Scheme 3).

To further ascertain the nucleophilic (S_N2) path of oxirane ring opening in glycidic epoxide systems, a chiral epoxide (*R*)-methyl 9-(oxiran-2-yl)nonanoate (**m**) was reacted with **2**. The bifunctionalized product **2m** obtained (84%) was found to be optically active {[α_D] = +23.73, $CHCl_3$}, suggesting a S_N2 path of oxirane ring opening (Scheme 4). Similarly, chiral epoxide (*S*)-2-

Scheme 4. Synthesis of Chiral Thiocyanato Benzoates[a,b]

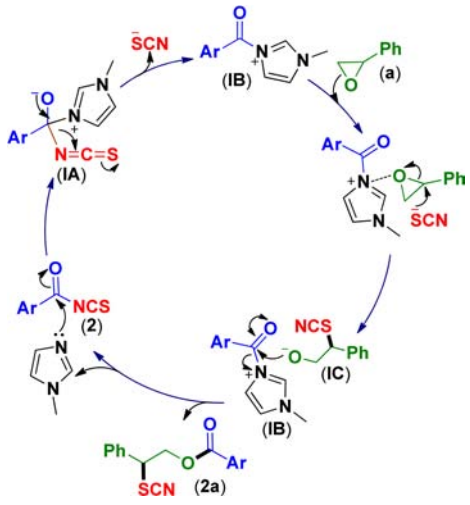


[a]Reaction conditions: **2** (0.5 mmol), oxirane (**m**, **n**, and **n′**) (0.5 mmol), NMI (0.1 mmol) under air at room temperature for 8 h. [b]Isolated yield.

(4-methoxybenzyl)oxirane (**n**) when treated with isothiocyanate **2** gave an optically active bifunctionalized product **2n** (92%) {[α_D] = −55.10, $CHCl_3$}. Interestingly, its enantiomeric chiral epoxide (*R*)-2-(4-methoxybenzyl)oxirane (**n′**) yielded the opposite enantiomeric bifunctionalized product (**2n′**, 89%) {[α_D] = +56.32, $CHCl_3$}. This observation reconfirms that the nucleophilic attack on the epoxide is from the sterically less hindered Aβ carbon site (Scheme 4).

From our previous work and from the literature, a plausible reaction mechanism is proposed, as shown in Scheme 5.[10] The

Scheme 5. Plausible Reaction Mechanism



NMI nitrogen attacks at the carbonyl carbon of **2**, forming a negatively charged tetrahedral intermediate (**IA**). This active intermediate releases the nucleophilic thiocyanate (−SCN), forming a NMI aroylate species (**IB**). Epoxide **a** coordinates with the cationic species **IB**, which is attacked by the nucleophilic −SCN, forming an alkoxy intermediate **IC**. The nucleophilic alkoxy intermediate **IC** then attacks the electrophilic aroyl intermediate **IB**, giving the bis-functionalized product **2a** with concomitant release of NMI for further catalytic cycles. Formation of intermediate **IB** was detected by HRMS analysis

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Org. Lett. 2017, 19, 432–435

of the reaction mixture. When an enantiopure 2-aryloxirane, (*R*)-styrene oxide, was used, the obtained product (*R*)-2-phenyl-2-thiocyanatoethyl-4-methylbenzoate (**2a′**) was found to be optically active {$[\alpha_D]$ = +98.49, $CHCl_3$}, supporting the S_N2 reaction path (Scheme S1, SI). Based on the concept of hard−soft nucleophilic character, an alternative mechanism as proposed previously[5] can also be envisaged for this transformation. NMI attacks at the sp-hybridized carbon of benzoyl isothiocyanate **2**, forming an activated thiolate species (**IIA**) (Scheme S2, SI), which attacks the oxirane ring, giving an alkoxy intermediate (**IIB**). The intramolecular attack of the alkoxy anion at the carbonyl carbon gave product **2a** with the release of NMI (Scheme S2, SI).

In conclusion, we have demonstrated a biomimetic organocatalytic bis-functionalization of oxiranes from aroyl/acyl isothiocyanates in the presence of NMI. In this simultaneous electrophilic−nucleophilic reaction, the thiocyanate (−SCN) of aroyl/acyl serves as the nucleophile, whereas the aroyl part acts as the electrophilic partners, giving products in 100% atom economy. In this metal-free process, C−S and C−O bonds are simultaneously constructed in the presence of NMI under solvent-free conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03430.

Experimental procedures, spectral and analytical data of all products (PDF)
X-ray data for **1l** (CIF)
X-ray data for **2a** (CIF)

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Notes

The authors declare no competing financial interest.

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