The unprecedented ring transformation from thiazoline-spiro-thiophene to thieno[2,3-*b*]pyrazine involved in the reaction of 2-thiocarbamoyl thiazolium salts with dimethyl acetylenedicarboxylate†

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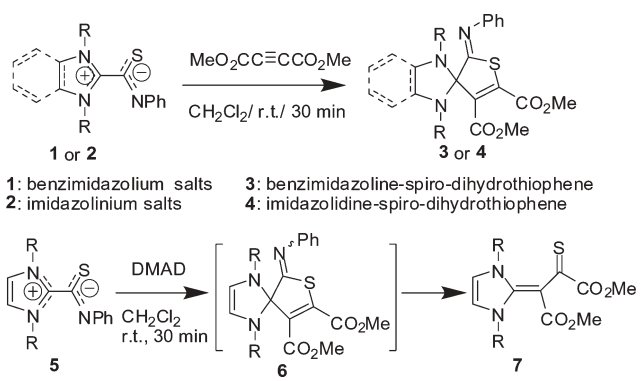
Reaction of 2-thiocarbamoyl thiazolium salts with dimethyl acetylenedicarboxylate proceeded *via* a tandem [3 + 2] cycloaddition and a unprecedented ring transformation to produce functionalized thieno[2,3-*b*]pyrazine derivatives in good to excellent yields.

Ring transformation reactions constitute a research area of particular interest both synthetically and theoretically. For decades, ring transformations have become important and fascinating strategies for the construction of cyclic and, especially, heterocyclic compounds which are not easily accessible by other methods.[1] Some ring transformations, for example, have been successfully used in the total synthesis of natural products and bioactive compounds.[2] In addition to their synthetic values, ring transformations usually, if not always, proceed through intriguing reaction mechanisms, which largely enrich the theory of organic reactions. Most of the ring transformation reactions were induced by some reagents such as acids,[3a,b] bases,[3c] nucleophiles[3d] or oxidants[3e] that proceed intermolecularly or intramolecularly, whereas a few transformations took place simply through thermal ring rearrangements.[4] The transformation of a spirocyclic compound to a fused one generally proceeds *via* a sigmatropic shift of the chemical bond from the spiro atom to its adjacent atom.[5] Ring expansion transformation of a spiro heterocycle involving an exocyclic atom is very rare.[6]

Nucleophilic N-heterocyclic carbenes including benzimidazole, imidazoline, imidazole, triazole and thiazole carbenes are known to react with isothiocyanates to form stable zwitterions, 2-thiocarbamoyl benzimidazolium,[7a] -imidazolinium,[7b,c] -imidazolium,[7d] -triazolium[5a] and -thiazolium inner salts,[7e,f] respectively. Very recently, we found that the inner salts derived from imidazole-type carbenes are unique ambident bis-dipolar compounds.[8] Depending on the nature of the dipolarophiles, these ambident zwitterions can act as either C^+–C–S^- or C^+–C–N^-dipolar species toward electron-deficient alkynes, alkenes and ketenes to produce [3 + 2] cycloadducts, spiro-thiophene or spiro-pyrrole derivatives.[8a–c] We have also shown that the structure of N-heterocyclic carbenes also played an intriguing part in regulating the outcomes of the reactions. For example, 2-arylthiocarbamoyl benzimidazolium **1** or imidazolinium salts **2** reacted with dimethyl acetylenedicarboxylate (DMAD) to produce respectively, cycloadduct benzimidazoline-spiro-thiophenes **3** or imidazolidine-spiro-thiophenes **4**,[8a,b] whereas the same reaction between 2-arylthiocarbamoyl imidazolium salts **5** and DMAD afforded imidazoline substituted olefins **7** *via* cycloaddition followed by fragmentation of the thiophene ring (Scheme 1).[8d] In order to gain a full understanding of the chemistry of 2-thiocarbamoyl iminium inner salts and to further explore their synthetic applications, we undertook the current study of the reaction of 2-thiocarbamoyl thiazolium inner salts with DMAD. Interestingly, the reaction proceeded through a tandem [3 + 2] cycloaddition and an unprecedented ring transformation reaction to produce novel thieno[2,3-*b*]pyrazine derivatives in good to excellent yields.

In this work, 2-arylthiocarbamoyl thiazolium inner salts **8** were prepared in 64–95% yield from the reaction of aryl isothiocyanates with thiazole carbenes, which were generated *in situ* from the thiazolium salts with sodium hydride. We started our investigation by examining the reaction between *N*-ethyl-2-(*p*-nitrophenyl)thiocarbamoyl thiazolium salt **8a** and DMAD. When treated with one equivalent of DMAD in dichloromethane at ambient temperature, the zwitterion **8a** was transformed into thieno[2,3-*b*]pyrazine **9a** in 48% yield (based on **8a**). Having realized the formation of adduct **9a** from reactants in a 1 : 2 ratio, the reaction was optimized under various conditions employing 2.5 equivalents of DMAD (Table 1). As summarized in Table 1, the reaction proceeded very rapidly and efficiently. In most cases, for example, the conversion of **8a** into **9a**, which was monitored by TLC, was completed within 30 min. The highest chemical yield (97%) was obtained when the reaction was performed in dichloromethane at 0 °C (entry 2). High reaction



Scheme 1 Reaction of 2-thiocarbamoyl benzimidazolium, -imidazolinium, -imidazolium salts with DMAD.

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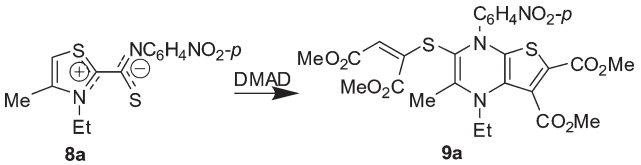
† Electronic supplementary information (ESI) available: Experimental procedures for the preparation of dipoles **8** and products **9**, full characterization for **8** and **9**, and NMR spectra of all products **9**. See DOI: 10.1039/b712098b

Table 1 The reaction of *N*-ethyl-2-(*p*-nitrophenyl)thiocarbamoyl thiazolium salt **8a** with DMAD under different conditions



8a **9a**

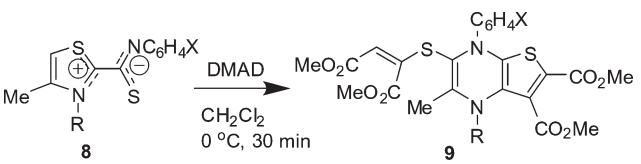
Entry	Reaction conditions[a]	Yield of **9a**[b] (%)
1	CH_2Cl_2, −25 °C, 2.5 h	87
2	CH_2Cl_2, 0 °C, 30 min	97
3	CH_2Cl_2, rt, 30 min	89
4	CH_2Cl_2, reflux, 10 min	84
5	$ClCH_2CH_2Cl$, 0 °C, 30 min	95
6	THF, 0 °C, 30 min	94
7	C_6H_6, 0 °C, 40 min	72
8	CH_3COCH_3, 0 °C, 30 min	84
9	CH_3CN, 0 °C, 30 min	87

[a] The ratio between reactants **8a** and DMAD was 1 : 2.5. [b] Isolated yield.

temperature led to a slight decrease of chemical yield, while at lower temperature the conversion became slightly slow. Other solvents such as 1,2-dichloroethane, THF, benzene, acetone and acetonitrile were proved to be good media for the reaction giving product **9a** in yields of 72–95% (entries 5–8).

The scope of the reaction was then studied under optimal conditions by using dipoles **8** that bear different substituents. As evidenced by the results summarized in Table 2, the reaction showed tolerance for the substituent on the zwitterion reactants **8**. All reactions underwent completion in 30 min to afford products **9** in good to excellent yields. The *N*-ethyl (R = Et) and *N*-butyl (R = *n*-Bu) substituted reactants **8a** and **8b** gave an almost quantitative yield of **9a** and **9b**, respectively (entries 1 and 2, Table 2). When the *N*-substituent on the thiazolium was replaced by a benzyl (CH_2Ph) or a substituted benzyl group, chemical yields in the range of

Table 2 The reaction of 2-arylthiocarbamoyl thiazolium inner salts **8** with 2.5 equivalents of DMAD in CH_2Cl_2 at 0 °C



8 **9**

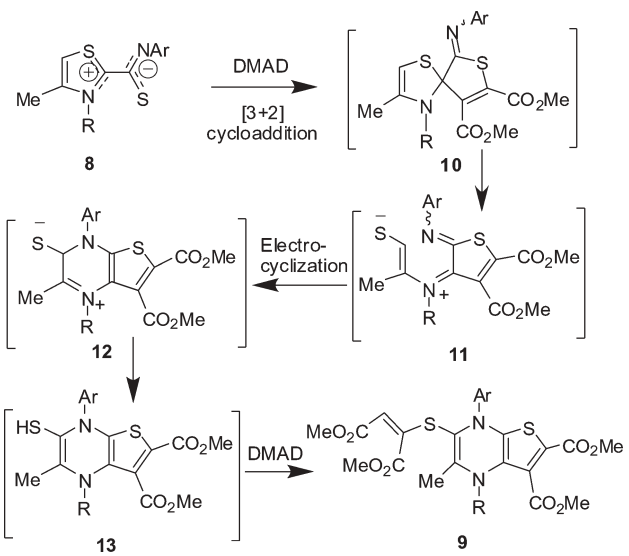
Entry	**8**	R	X	**9**	Yield (%)
1	**8a**	Et	*p*-NO_2	**9a**	97
2	**8b**	*n*-Bu	*p*-NO_2	**9b**	95
3	**8c**	Bn	*p*-NO_2	**9c**	82
4	**8d**	*p*-MeBn	*p*-NO_2	**9d**	85
5	**8e**	*p*-BrBn	*p*-NO_2	**9e**	80
6	**8f**	Bn	H	**9f**	75
7	**8g**	Bn	*p*-Me	**9g**	72
8	**8h**	Bn	*p*-F	**9h**	77
9	**8i**	Bn	*m*-NO_2	**9i**	77
10	**8j**	Bn	*p*-CF_3	**9j**	82
11	**8k**	*p*-MeBn	*p*-F	**9k**	72
12	**8l**	*p*-MeBn	*p*-CF_3	**9l**	81
13	**8m**	*p*-BrBn	*p*-Me	**9m**	76
14	**8n**	*p*-BrBn	*p*-F	**9n**	82
15	**8o**	*p*-BrBn	*m*-NO_2	**9o**	82
16	**8p**	*p*-BrBn	*p*-CF_3	**9p**	82

80–85% were obtained (entries 3–5). The nature of the aryl group on the thiocarbamoyl function exhibited only marginal effect on the reaction, as all reactions produced the products **9f–9p** in 72–82% yields (entries 6–16).

The structures of all products were elucidated on the basis of spectroscopic data and microanalysis. The NMR spectra, mass spectral data and elemental analysis indicated that the product **9** was the adduct of one dipole **8** and two DMAD molecules. Since spectroscopic data did not allow full verification of the structure, X-ray diffraction analysis indicated unambiguously that the compound **9b** was (*E*)-1-butyl-2-methyl-3-(1,2-dimethoxycarbonylvinylthio)-4-(*p*-nitrophenyl)-1,4-dihydrothieno[2,3-*b*]pyrazine-6,7-dicarboxylate (see Fig. 1 in ESI†).[9]

The formation of fused thieno[2,3-*b*]pyrazine ring product from the 2-thiocarbamoyl thiazolium salt with DMAD is very intriguing. Although the di(methoxycarbonyl)-substituted thiophene substructure was conceivable based on the [3 + 2] cycloaddition between the C^+–C–S^- dipolar specie of **8** and DMAD followed by aromatization, the construction of fully substituted 1,4-dihydro-1,4-pyrazine was not expected. A plausible mechanism is proposed in Scheme 2. Acting as a C^+–C–S^- dipolar component, zwitterion **8** undergoes 1,3-dipolar cycloaddition reaction with DMAD to form thiazole-spiro-thiophene intermediate **10**. Selective S–C bond cleavage of **10** probably gives a zwitterion **11** that undergoes an aromatizative electrocyclization reaction to form the fused ring intermediate **12**. Isomerization of **12** followed by S-nucleophilic addition to DMAD affords product **9** (Scheme 2). The rearrangement of thiazole-spiro-thiophene to thieno[2,3-*b*]pyrazine proceeded *via* a unique ring transformation process, in which the thiazole ring was expended to the *exo*-cyclic nitrogen atom with its sulfur atom being contracted out of the ring system.

The different reaction outcomes of thiazolium **8** from benzimidazolium **1** and imidazolinium **2** and from imidazolium inner salts **5** (Scheme 1) deserve comment. All ambident dipoles derived from the reaction between N-heterocyclic carbenes such as benzimidazole, imidazoline, imidazole and thiazole carbene and



8 **10** **12** **11** **13** **9**

Scheme 2 The proposed mechanism for the formation of thieno[2,3-*b*]pyrazine **9**.

aryl isothiocyanates act as the highly reactive C^+–C–S^- dipolar species toward DMAD to produce [3 + 2] spiro-thiophene cycloadducts. The stability and reactivity of the resulting spiro-thiophene cycloadducts, however, are strongly dependent on the structures of the heterocyclic N-carbenes. Apparently, the benzimidazoline-spiro-thiophenes and imidazolidine-spiro-thiophenes are stable at the ambident temperature. The imidazoline-spiro-thiophene and thiazoline-spiro-thiophene analogues, on the contrary, are not isolable products under the reaction conditions. Interestingly, imidazoline-spiro-thiophene and thiazoline-spiro-thiophene intermediates follow dramatically different ring transformation pathways. For example, imidazoline-spiro-thiophenes undergo selectively thiophene ring fragmentation reaction *via* a cheletropic elimination to give imidazoline-substituted olefins (Scheme 1).[8a,b,d] In sharp contrast, however, thiazoline-spiro-thiophenes selectively expand the thiazole ring to yield thieno[2,3-*b*]pyrazines *via* the electrocyclization reaction. It seems that the cleavage of C–S bond rather than that of a C–N bond occurs.

The thieno[2,3-*b*]pyrazine ring system has been found in natural products such as urothion and its derivatives,[10] and in some synthetic compounds with biological activities.[11] For example, thieno[2,3-*b*]pyrazine-2,3-diones are useful in treating central nervous system ailments,[11c] and benzothieno[2,3-*b*]pyrazine is active against both Gram positive and negative bacteria and fungi.[11a] The known methods for the construction of the thieno[2,3-*b*]pyrazine skeleton are all based on the annulation of a functionalized pyrazine[10d,12] or a thiophene derivative.[13] No ring transformation methodology has been reported so far in the construction of a thieno[2,3-*b*]pyrazine ring system. To the best of our knowledge, this is the first report of the preparation of thieno[2,3-*b*]pyrazine derivatives using a ring transformation method starting from neither a pyrazine nor a thiophene compound.

In conclusion, we have shown that the interaction of 2-thiocarbamoyl thiazolium inner salts with DMAD proceeded *via* a tandem [3 + 2] cycloaddition/ring-expansion process to produce thieno[2,3-*b*]pyrazine derivatives in good to excellent yields. A unique ring transformation reaction from thiazoline-spiro-thiophene to thieno[2,3-*b*]pyrazine was unveiled. The easy availability of 2-thiocarbamoyl thiazolium salts and their high efficiency in the reaction with DMAD render this reaction a powerful and unique ring-transformation methodology for the construction of polyfunctional thieno[2,3-*b*]pyrazine derivatives that are not readily accessible by other methods. This work revealed that the N-heterocyclic carbene-derived ambident 1,3-dipoles are remarkable intermediates not only in synthesis of spiro heterocycles but also fused heterocyclic compounds.

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9 *Crystal data* for **9b**: $C_{27}H_{29}N_3O_{10}S_2$, M = 619.65, T = 113 K, monoclinic, space group $P2_1/n$, a = 15.1455(12), b = 12.530(1), c = 15.4095(12) Å, β = 92.180(5)°, V = 2922(4) Å^3, Z = 4, D_c = 1.408 g cm^{-3}, absorption coefficient 0.243 mm^{-1}, reflections collected/unique 36155/6953 (R_{int} = 0.0527), final R indices [$I > 2\sigma(I)$]: R_1 = 0.0496, wR_2 = 0.1100. CCDC 656512. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b712098b.

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