

A *N*-heterocyclic carbene derived highly regioselective ambident C–C–S and C–C–N 1,3-dipolar system†

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N-Heterocyclic carbene derived 2-phenylthiocarbamoyl benzimidazolium and imidazolinium inner salts are a unique ambident C–C–S and C–C–N 1,3-dipolar system able to undergo highly efficient and regioselective cycloaddition with dimethyl acetylenedicarboxylate and ethyl propiolate to furnish, respectively, spiro[imidazole-2,3'-thiophene] and spiro[imidazole-2,3'-pyrrole] derivatives in good to excellent yields.

Since Huisgen's milestone work in the 1960s,¹ 1,3-dipolar cycloaddition reactions have been developed into powerful protocols for the construction of various five-membered ring heterocycles.² They have also found wide application in the synthesis of natural products and organic compounds of biological importance.² Most of the 1,3-dipolar systems reported to date are either of propyl-allenyl type (Fig. 1, A), including diazoalkanes, nitrile ylides, nitrile imines, nitrile oxides and azides, or allyl type (Fig. 1, B), such as azomethine ylides, azomethine imines and nitrones. Both types contain a central heteroatom, such as nitrogen or oxygen (Y = O or N), because their lone pair electrons can participate in the stabilization of zwitterionic resonance structures. Although carbon-centered 1,3-dipoles (Y = C) were proposed decades ago,^{3–6} their chemistry has scarcely been explored. Only 2-arylthiocarbamoyl imidazolinium salts, for example, were claimed as the C–C–N 1,3-dipolar component to undergo cycloaddition with electron deficient alkenes or alkynes to give spiro[4*H*-imidazole-2,3'-pyrrole] derivatives (Scheme 1).^{3,4}

As a part of our ongoing research project on the chemistry of heteroatom-substituted carbenes,⁷ we investigated the three-component reaction of *N*-heterocyclic carbenes with phenyl isothiocyanate and electron deficient alkynes. We found for the

first time that 1,3-dialkyl-2-phenylthiocarbamoyl-benzimidazolium and -imidazolinium inner salts, readily formed from the interaction of benzimidazole carbenes and imidazoline carbenes with phenyl isothiocyanate, actually behave as the novel ambident C–C–S or C–C–N (Fig. 1, C) 1,3-dipolar components. They undergo highly efficient 1,3-dipolar cycloaddition reactions with dimethyl acetylenedicarboxylate (DMAD) to furnish spiro[benzimidazoline-2,3'-thiophenes] or spiro[imidazolidine-2,3'-thiophenes] as the predominant products, while with ethyl propiolate, spiro[benzimidazoline-2,3'-pyrroles] or spiro[imidazolidine-2,3'-pyrroles] are obtained in good to excellent yields. Here, we report our observations.

In practice, benzimidazole carbenes or imidazoline carbenes were generated *in situ* by deprotonation of the corresponding benzimidazolium or imidazolinium salt using sodium hydride. The carbenes formed reacted with phenyl isothiocyanate at room temperature to form crystalline 2-phenylthiocarbamoyl benzimidazolium inner salts **1** or imidazolinium inner salts **2** in the yields of 63–89%. When treated with one equivalent of DMAD in 1,2-dichloroethane at ambient temperature, the zwitterionic intermediates **1** were very rapidly transformed into spiro[benzimidazoline-2,3'-dihydrothiophenes] **3** in 90–95% yield. In addition to the red-purple thiophene product **3**, only a tiny amount of dark green colored spiro[benzimidazoline-2,3'-dihydropyrrole] **4** was observed (Scheme 2). As demonstrated in Table 1, all of the zwitterionic adducts **1** or **2**, derived from both benzimidazole and imidazoline carbenes, act as predominantly C–C–S rather than C–C–N 1,3-dipolar systems to afford dihydrothiophene products **3** or **5** in excellent yields. It should be noted that these reactions are in sharp contrast to those documented in the literature.³

When zwitterions **1** and **2** were allowed to react with ethyl propiolate under identical conditions to those for DMAD, the reaction proceeded very slowly. Only at an elevated temperature (60–80 °C) using either a large excess of ethyl propiolate or a prolonged reaction period (5–28 h) did the reaction go to completion (see supporting information†). Most surprisingly, however, in all cases, the reaction led to the formation of C–C–N 1,3-dipolar cycloaddition adducts spiro[benzimidazoline-2,

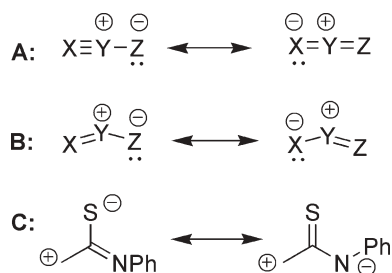
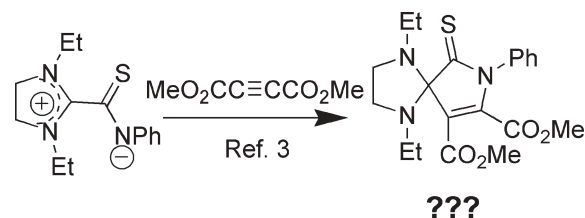


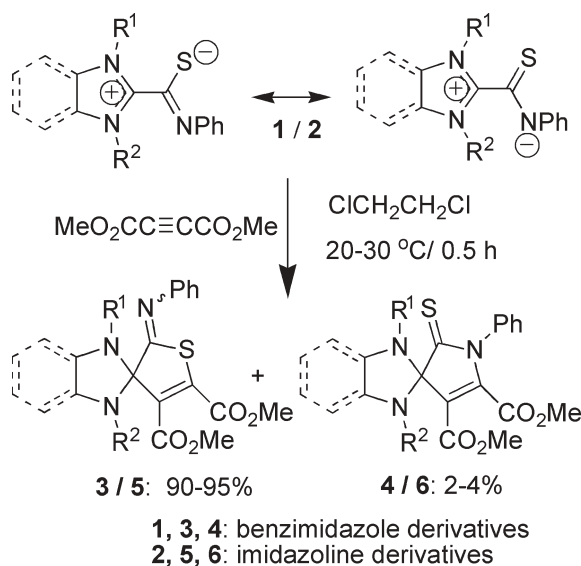
Fig. 1

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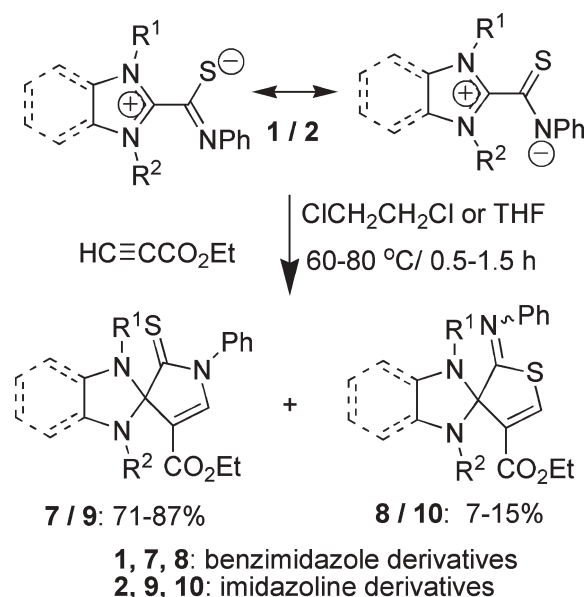
† Electronic supplementary information (ESI) available: Experimental procedures and full characterization for all new compounds. See DOI: 10.1039/b517700f



Scheme 1



Scheme 2



Scheme 3

Table 1 Cycloaddition reactions between salts 1 or 2 and DMAD

Starting material	R ¹ and R ²	1 or 2 : DMAD	Solvent	Product	Yield (%)
1a	Et	1 : 1	DCE ^a	3a	93
	Et			4a	— ^b
1b	ⁿ Bu	1 : 1	DCE	3b	90
	ⁿ Bu			4b	4
1c	Bz	1 : 1	DCE	3c	95
	Bz			4c	—
1d	Et	1 : 1	DCE	3d	92
	ⁿ Bu			4d	—
1e	ⁱ Pr	1 : 1	DCE	3e	90
	ⁿ Bu			4e	—
1f	Et	1 : 1	DCE	3f	91
	Bz			4f	—
1g	ⁿ Bu	1 : 1	DCE	3g	94
	Bz			4g	4
2a	Et	1 : 1	DCE	5a	95
	Et			6a	—
2b	ⁿ Bu	1 : 1	DCE	5b	93
	ⁿ Bu			6b	—
2c	ⁱ Bu	1 : 1	DCE	5c	94
	ⁱ Bu			6c	—
2d	Bz	1 : 1	DCE	5d	92
	Bz			6d	3
2e	MeOBz	1 : 1	DCE	5e	93
	MeOBz			6e	2

^a DCE = 1,2-dichloroethane. ^b A tiny amount of the minor product was observed.

3'-dihydropyrroles] 7 or spiro[imidazolidine-2,3'-dihydropyrroles] 9 as the major products (71–87%). Dihydrothiophene products 8 and 10 were isolated only as by-products in 7–15% yield (see Scheme 3 and Table 2).

The structures of all products were fully characterized from their spectroscopic data and by microanalysis. It is worth noting that the dihydrothiophene products 3, 5, 8 and 10 gave their ¹³C-NMR diagnostic C=N signal at 165–170 ppm while dihydropyrrole compounds 4, 6, 7 and 9 showed their C=S carbon signal in a downfield range between 200 and 210 ppm. To identify the isomers beyond doubt, the structures of 3c, 4b, 5c and 7c were also

Table 2 Cycloaddition reactions between salts 1 or 2 and ethyl propiolate

Starting material	R ¹ and R ²	1 or 2 : ethyl propiolate	Solvent	Product	Yield (%)
1a	Et	1 : 5	DCE ^a	7a	84
	Et			8a	— ^b
1b	ⁿ Bu	1 : 5	DCE	7b	80
	ⁿ Bu			8b	—
1c	Bz	1 : 5	DCE	7c	82
	Bz			8c	8
1d	Et	1 : 5	DCE	7d	87
	ⁿ Bu			8d	—
1e	ⁱ Pr	1 : 5	DCE	7e	86
	ⁿ Bu			8e	—
1f	Et	1 : 5	DCE	7f	85
	Bz			8f	7
1g	ⁿ Bu	1 : 5	DCE	7g	82
	Bz			8g	—
2d	Bz	1 : 5	THF	9d	73
	Bz			10d	15
2e	MeOBz	1 : 5	THF	9e	71
	MeOBz			10e	15

^a DCE = 1,2-dichloroethane. ^b A tiny amount of the minor product was observed.

determined unambiguously by single crystal X-ray diffraction analysis (Fig. 2).‡

The high and ambident 1,3-dipolar cycloaddition reactivity of 2-phenylthiocarbamoyl-benzimidazolium and -imidazolium inner salts and, in particular, their clear cut cycloaddition reaction pathways between C–C–S and C–C–N 1,3-dipolar systems when treated with DMAD and ethyl propiolate, respectively, is remarkable and intriguing. For example, the use of various organic solvents, including THF, acetone, 1,2-dichloroethane and acetonitrile, at different temperatures did not affect the reaction pathway. As indicated in Table 1, the substituents on the nitrogen atoms of the imidazoline ring also have negligible effect on the outcome of the reaction. In order to shed light on the different

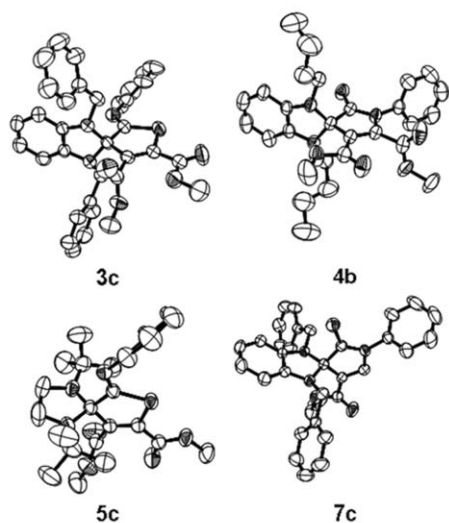


Fig. 2 ORTEP drawings of the single-crystal structures of compounds **3c**, **4b**, **5c** and **7c**.§

selectivity of zwitterionic species in the reaction with DMAD and ethyl propiolate, the relative energies of two pairs of isomers, **3c** and **4c**, and **7c** and **8c**, were calculated on the basis of their B3LYP/6-31G* optimized structures. The calculation showed that spiro[2*H*-benzimidazole-2,3'-2*H*-thiophene] derivatives **3c** (9.639 kcal mol⁻¹) and **8c** (10.798 kcal mol⁻¹) have much higher relative energies than spiro[2*H*-benzimidazole-2,3'-2*H*-pyrrole] isomers **4c** (0.000 kcal mol⁻¹) and **7c** (0.000 kcal mol⁻¹). The formation of pyrrole derivatives, *i.e.* the cycloaddition proceeding through a C–C–N 1,3-dipolar component, is apparently thermodynamically controlled. As such, the reaction requires heating, a lengthy reaction time or an excess amount of the 1,3-dipolarophile. The cycloaddition of the C–C–S 1,3-dipolar moiety of **1** or **2** onto DMAD, on the other hand, proceeds through a kinetically favored route to afford thiophene adducts rapidly and irreversibly because DMAD is a stronger 1,3-dipolarophile. The unique ambident 1,3-dipolar cycloaddition reactivity of zwitterions **1** and **2** lies in their structure, in which the positive charge on the terminal carbon is stabilized by its adjacent nitrogen atoms while the negative charge is delocalized onto the sulfur and nitrogen of thiocarbamoyl group (Fig. 1, C).

In summary, we have discovered for the first time that the *N*-heterocyclic carbenes derived from 2-phenylthiocarbamoyl-benzimidazolium and -imidazolium inner salts are a unique type of stable ambident C–C–S and C–C–N 1,3-dipolar system. They are able to undergo highly efficient and regioselective 1,3-dipolar cycloaddition reactions with DMAD and ethyl propiolate to furnish, respectively, spiro[imidazole-2,3'-thiophene] and

spiro[imidazole-2,3'-pyrrole] derivatives as the predominant products in good to excellent yields. This work has probably revealed a new type of ambident 1,3-dipolar compound whose regioselectivity in reactions might be regulated by the reactivities of its reaction partners. A systematic study on the application of ambident 1,3-dipolar systems in cycloaddition reactions with other dipolarophiles along with a mechanistic study are under way in our laboratory.

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Notes and references

† Crystal data for **3c**: C₃₄H₂₉N₃O₄S, *M* = 575.66, *T* = 293 K, triclinic, space group *P*-1, *a* = 11.114(3), *b* = 14.156(3), *c* = 19.352(5) Å, α = 80.220(4), β = 85.469(4), γ = 89.231(4)°, *V* = 2991.0(12) Å³, *Z* = 4, ρ_{calcd} = 1.278 g cm⁻³, absorption coefficient 0.151 mm⁻¹, reflections collected/unique 16183/10405 [*R*_{int} = 0.0362], final *R* indices [*I* > 2σ(*I*)] *R*₁ = 0.0547, *wR*₂ = 0.1239. **4b**: C₂₈H₃₃N₃O₄S, *M* = 507.63, *T* = 294 K, monoclinic, space group *P*2(1)/*n*, *a* = 10.175(18), *b* = 20.817(4), *c* = 13.993(3) Å, α = 90.00, β = 108.821(3), γ = 90.00°, *V* = 2805.4(9) Å³, *Z* = 4, ρ_{calcd} = 1.202 g cm⁻³, absorption coefficient 0.152 mm⁻¹, reflections collected/unique 15800/5760 [*R*_{int} = 0.0454], final *R* indices [*I* > 2σ(*I*)] *R*₁ = 0.0529, *wR*₂ = 0.1351. **5c**: C₂₄H₃₃N₃O₄S, *M* = 459.60, *T* = 293 K, triclinic, space group *P*-1, *a* = 10.097(2), *b* = 10.422(2), *c* = 13.951(3) Å, α = 73.04, β = 69.52(3), γ = 66.32°, *V* = 1239.9(4) Å³, *Z* = 2, ρ_{calcd} = 1.231 g cm⁻³, absorption coefficient 0.164 mm⁻¹, reflections collected/unique 5630/5630 [*R*_{int} = 0.000], final *R* indices [*I* > 2σ(*I*)] *R*₁ = 0.0654, *wR*₂ = 0.1742. **7c**: C₃₃H₂₉N₃O₂S, *M* = 531.65, *T* = 294 K, triclinic, space group *P*-1, *a* = 9.7945(18), *b* = 10.295(2), *c* = 14.282(2) Å, α = 70.912, β = 88.222(3), γ = 89.992°, *V* = 1360.2(5) Å³, *Z* = 2, ρ_{calcd} = 1.298 g cm⁻³, absorption coefficient 0.155 mm⁻¹, reflections collected/unique 7402/4731 [*R*_{int} = 0.0263], final *R* indices [*I* > 2σ(*I*)] *R*₁ = 0.0468, *wR*₂ = 0.1023. CCDC 286158 (**3c**), 286159 (**4b**), 286160 (**5c**) and 286161 (**7c**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b517700f

§ 50% probability was chosen for the ellipsoids. There are two independent molecules of **3c** in the asymmetric unit, only one of which is shown in Fig. 2.

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