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Regio- and stereoselective cycloaddition of stable azomethine imines to (arylmethylidene)malononitriles

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[3+2] Cycloaddition of 1-arylmethylidene-3-oxopyrazolidin-1-ium-2-ides (stable azomethine imines) to (arylmethylidene)malononitriles proceeds regio- and stereoselectively to afford 1,3-diaryl-5-oxotetrahydropyrazolo[1,2-*a*]pyrazole-2-carbonitriles that proved resistant to azomethine imines metathesis.

The 1,3-dipolar cycloaddition is a convenient and general approach to the construction of various five-member heterocyclic compounds[1] that have found medical and crop protection applications.[2–4] Over the past years, the approach has been extensively practiced by our research team to build bicyclic compounds with the pyrazolidine ring fused to pyrazolidine, pyrazoline, triazole, triazoline, thiazolidine, and other rings. In most cases, we used azomethine imines **1** catalytically generated (catalyst $BF_3{\cdot}Et_2O$) by the diaziridine ring opening in available 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **2** (Scheme 1).[5–7] Ionic liquids (ILs) were found to be good media for such reactions although some of them run in organic solvents as well.

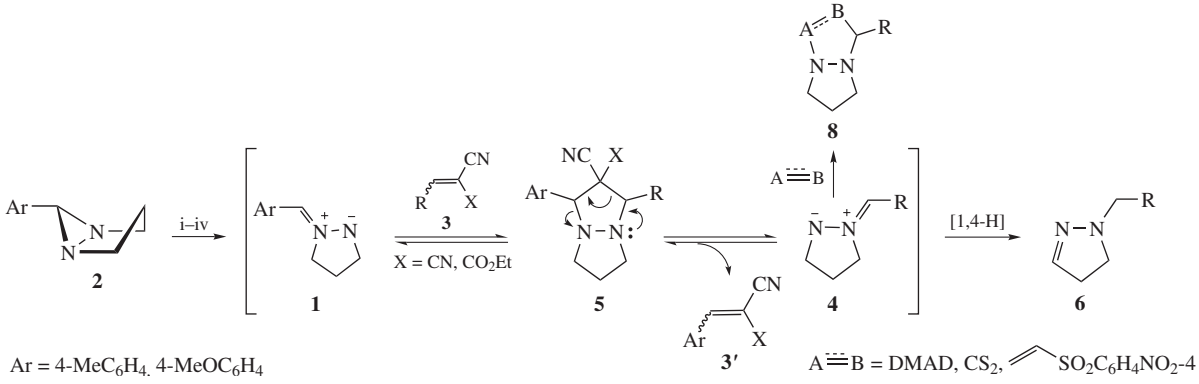
Two new reactions of the azomethine imine metathesis have been discovered recently:[8–10] azomethine imines **1** produced by the catalytic diaziridine ring opening in bicyclic compounds **2** in the course of *in situ* reactions with carbonyl compounds (isatins, 4-nitrobenzaldehyde) or [(het)arylmethylidene]malononitriles **3** transform to new azomethine imines **4** (R = 4-$O_2NC_6H_4$, Het) by domino processes through cyclic intermediates **5** with a simultaneous formation of new (arylmethylidene)malononitriles **3′** (see Scheme 1). Quantum-chemical calculations have shown that the driving force of this process is a formation of the thermodinamically more preferable pair of azomethine imine **4** – (arylmethylidene)malononitrile **3′** in comparison with the initial pair azomethine imine **1** – (arylmethylidene)malononitriles **3**. New azomethine imines **4**, which could not be prepared by conventional methods due to unavailability or insufficient stability of initial bicyclic diaziridines **2**, gave pyrazoline derivatives **6** as a result of the 1,4-H-shift or were fixed *in situ* as [3+2] cycloadducts with different dipolarophiles (DMAD, CS_2, aryl vinyl sulfone) that led to fused heterocyclic structures **8**. The reactions occurred both in ILs at 20 °C and in organic solvents on heating.

With a view to extend this approach we examined herein an interaction of close analogues of azomethine imines **1**, 1-arylmethylidene-3-oxopyrazolidin-1-ium-2-ides **9a**,**b**, with (arylmethylidene)malononitriles **3a–e**. Compounds **9a**,**b** appeared stable under conventional conditions[11] conversely to *in situ* generated azomethine imines **1** since in compounds **9** both positive and negative charges are stabilized by conjugation.

To optimize the reaction conditions, reactants **3a** + **9a** were used as model substrates (Table 1). No reaction occurred at room temperature in IL both with and without the catalyst (entries 2, 3). The reaction in IL was only successful on heating, however, a

Table 1 Optimization of the [3+2] cycloaddition of azomethine imine **9a** to (4-nitrophenylmethylidene)malononitrile **3a**.

Entry	Conditions	Yield of **5a** (%)
1	PhMe, reflux, 2 h	30
2	[bmim]BF_4, 20 °C, 48 h	0
3	[bmim]BF_4, 20 °C ($BF_3{\cdot}Et_2O$, 20 mol%), 48 h	0
4	[bmim]BF_4, 60 °C, 48 h	27
5	[bmim]PF_6, 60 °C, 48 h	33
6	DCE, 60 °C, 6 h	76
7	MeCN, reflux, 8 h	53
8	DCE, [bmim]BF_4 (40 mol%), 60 °C, 6 h	75



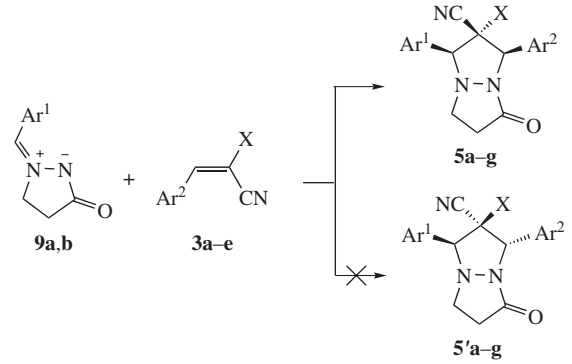
Scheme 1 *Reagents and conditions*: i, $BF_3{\cdot}Et_2O$, [bmim][BF_4]; ii, $BF_3{\cdot}Et_2O$, MeCN, 40 °C; iii, reflux in toluene; iv, reflux in xylene.

Table 2 Synthesis of the bicyclic compounds **5a–g**.

Entry	Ar^1	Compounds **3**		Reaction conditions	Yield of **5** (%)
		Ar^2	X		
1	4-$MeOC_6H_4$ (**9a**)	4-$NO_2C_6H_4$	CN (**3a**)	DCE, 60 °C, 6 h	76 (**5a**)
2	4-$MeOC_6H_4$ (**9a**)	4-$NO_2C_6H_4$	CO_2Et (**3b**)	DCE, 60 °C, 6 h	86 (**5b**)
3	4-$MeOC_6H_4$ (**9a**)	Ph	CN (**3c**)	PhMe, reflux, 4.5 h	21 (**5c**)
4	4-$MeOC_6H_4$ (**9a**)	4-BrC_6H_4	CN (**3d**)	DCE, 60 °C, 6 h	34 (**5d**)
5	4-$MeOC_6H_4$ (**9a**)	4-$CF_3C_6H_4$	CN (**3e**)	DCE, 60 °C, 6 h	31 (**5e**)
6	4-$Me_2NC_6H_4$ (**9b**)	4-$NO_2C_6H_4$	CN (**3a**)	DCE, 60 °C, 6 h	58 (**5f**)
7	4-$Me_2NC_6H_4$ (**9b**)	4-$NO_2C_6H_4$	CO_2Et (**3b**)	DCE, 60 °C, 6 h	73 (**5g**)

new compound (**5a**) was prepared in low yield (entries 4, 5). A similar result was obtained on heating in toluene (entry 1). The best choice was DCE at 60 °C without the catalyst (entry 6). The addition of IL did not affect the reaction output (entry 8). Important, the outcome of this reaction was different from that of the analogous reaction with azomethine imines **1**: it stopped in the [3 + 2] cycloaddition step providing stable 1,5-diazabicyclo-[3.3.0]octane **5a** which did not undergo metathesis to give a new azomethine imine.

The cycloaddition of azomethine imines **9a**,**b** to (aryl-methylidene)malononitriles **3b–e** was performed under the found conditions (Scheme 2, Table 2).† The target bicyclic compounds



Scheme 2

5b–g were prepared in moderate and good yields in all cases. A higher temperature was only needed in the case of **3c** (entry 3). The reaction proceeded completely regio- and stereoselectively according to the classical Michael addition mechanism and gave compounds **5a–g** with *cis*-positioned Ar^1 and Ar^2 groups. Diastereomers **5′a–g** were fixed in neither of the cases.

Structures of the synthesized compounds were established by elemental and spectral analyses (primarily 2D NMR using {^{1}H-^{13}C}HMBC and {^{1}H-^{13}C}HsQC) and mass spectrometry and the structure of **5a** was additionally proven by X-ray diffraction study (Figure 1).‡

Two plausible reaction pathways for the formation of compounds **5a** and **5′a** were modeled by means of DFT calculations. They revealed that the cycloaddition of azomethine imine **9a** to olefin **3a** proceeds in one step (Scheme 3) *via* transition states (TS and TS′). Figure 2 shows the optimized geometry of the transition states TS and TS′ with the bond at N-pole of **9a** being formed slightly earlier. It was found that TS is lower in activation energy than TS′ by 1.84 kcal mol^{-1} and the pathway 1 is also favoured by thermodynamic control since compound **5a** is lower in energy than **5′a** by 1.19 kcal mol^{-1} (see Figure 1S, Online Supplementary Materials).

† *2-(4-Dimethylaminobenzylidene)-5-oxopyrazolidin-2-ium-1-ide* **9b**. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.10 (d, 2H, H_{aryl}, *J* 8.6 Hz), 7.42 (s, 1H, N=CH), 6.78 (d, 2H, H_{aryl}, *J* 8.6 Hz), 4.40 (t, 2H, CH_2C=O, *J* 8.2 Hz), 3.01 (s, 6H, NMe_2), 2.49 (br.s, 2H, NCH_2). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 182.80, 151.64, 133.31, 132.89, 117.12, 111.14, 55.87, 40.74, 29.66. HRMS (ESI), *m*/*z*: 218.1284 (calc. for $C_{12}H_{15}N_3O$ $[M+H]^+$, *m*/*z*: 218.1288).

Compounds **5a**,**b**,**d–g** *(general procedure)*. Azomethine imine **9a** or **9b** (0.10 g, 0.05 mmol) and corresponding ylidene malononitrile (0.5 mmol) **3a**,**b**,**d**,**e** were stirred in DCE (8 ml) at 60 °C for 6 h. The solvent was then evaporated *in vacuo* and the product was isolated chromatographically using ethyl acetate–light petroleum mixtures as eluent.

Compound **5c**. Azomethine imine **9a** (0.10 g, 0.05 mmol) and benzylidene malononitrile (0.08 g, 0.5 mmol) **3c** were refluxed for 6 h in toluene (8 ml). Cycloadduct **5c** was isolated analogously.

(1S,3R*)-1-(4-Methoxyphenyl)-3-(4-nitrophenyl)-5-oxotetrahydropyrazolo[1,2-a]pyrazole-2,2(1H)-dicarbonitrile* **5a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.34, 7.71 (2d, 4H, $H_{nitrophenyl}$, *J* 8.7 Hz), 7.49, 7.01 (2d, 4H, $H_{methoxyphenyl}$, *J* 8.7 Hz), 5.79 (s, 1H, 3-H), 4.24 (s, 1H, 1-H), 3.93–3.72 (m, 4H, OMe, 7a-H), 3.36–3.19 (m, 1H, 7b-H), 2.91–2.74 (m, 2H, 6-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 177.71 (5-C), 160.94 (4-$C_{methoxyphenyl}$), 148.83 (4-$C_{nitrophenyl}$), 141.12 (1-$C_{nitrophenyl}$), 129.57 (2,6-$C_{methoxyphenyl}$), 127.91 (2,6-$C_{nitrophenyl}$), 124.61 (3,5-$C_{nitrophenyl}$), 120.27 (1-$C_{methoxyphenyl}$), 115.07 (3,5-$C_{methoxyphenyl}$), 112.72, 110.15 (2CN), 76.70 (1-C), 65.25 (3-C), 57.42 (2-C), 55.49 (OMe), 44.51 (7-C), 28.90 (6-C). HRMS (ESI), *m*/*z*: 404.1345 $[M+H]^+$ (calc., *m*/*z*: 404.1353). Found (%): C, 62.43; H, 4.32; N, 17.28. Calc. for $C_{21}H_{17}N_5O_4$ (%): C, 62.53; H, 4.25; N, 17.36.

(1S,2S*,3R*)-Ethyl 2-cyano-1-(4-methoxyphenyl)-3-(4-nitrophenyl)-5-oxohexahydropyrazolo[1,2-a]pyrazole-2-carboxylate* **5b**. Since DFT calculations have shown that [3 + 2] cycloaddition of azomethine imines **9** to olefins **3** occurred through pathway 1 (transition state TS) the CO_2Et group in compounds **5b** and **5g** was evidently in *trans*-position to both Ar fragments. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.30 (d, 2H, 3,5-$H_{nitrophenyl}$, *J* 8.7 Hz), 7.64 (d, 2H, 2,6-$H_{nitrophenyl}$, *J* 8.7 Hz), 7.42 (d, 2H, 2,6-$H_{methoxyphenyl}$, *J* 8.8 Hz), 6.95 (d, 2H, 3,5-$H_{methoxyphenyl}$, *J* 8.8 Hz), 5.78 (s, 1H, 3-H), 4.38 (q, 2H, OCH_2, *J* 7.1 Hz), 4.31 (s, 1H, 1-H), 3.83 (s, 3H, OMe), 3.80–3.72 (m, 1H, 7a-H), 3.23–3.15 (m, 1H, 7b-H), 2.92–2.77 (m, 2H, 6-H), 1.33 (t, 3H, Me, *J* 7.1 Hz). ^{13}C NMR (150.90 MHz, $CDCl_3$) δ: 176.10 (5-C), 165.12 (CO_2Et), 160.94 (4-$C_{methoxyphenyl}$), 148.19 (4-$C_{nitrophenyl}$), 142.96 (1-$C_{nitrophenyl}$), 129.76 (2,6-$C_{methoxyphenyl}$), 128.03 (2,6-$C_{nitrophenyl}$), 124.16 (3,5-$C_{nitrophenyl}$), 122.45 (1-$C_{methoxyphenyl}$), 114.37 (3,5-$C_{methoxyphenyl}$), 113.71 (CN), 76.00 (1-C), 65.84 (2-C), 64.51 (OCH_2), 63.91 (3-C), 55.33 (OMe), 44.79 (7-C), 29.51 (6-C), 14.04 (Me). HRMS (ESI), *m*/*z*: 451.1607 $[M+H]^+$ (calc., *m*/*z*: 451.1612). Found (%): C, 61.37; H, 4.86; N, 12.42. Calc. for $C_{23}H_{22}N_4O_6$ (%): C, 61.33; H, 4.92; N, 12.44.

For characteristics of compounds **5c–g**, see Online Supplementary Materials.

‡ *Crystal data for* **5a**. $C_{21}H_{17}N_5O_4$ (*M* = 403.40), triclinic, space group $P\bar{1}$ (no. 2), at 120 K: *a* = 10.2504(6), *b* = 10.7403(6) and *c* = 10.9216(7) Å, α = 86.6460(10)°, β = 67.7200(10)°, γ = 63.2350(10)°, *V* = 984.21(10) Å^3, *Z* = 2, μ(MoKα) = 0.098 mm^{-1}, d_{calc} = 1.361 g cm^{-3}, 13230 reflections measured (4.06 ⩽ 2θ ⩽ 61.02), 6006 unique (R_{int} = 0.0247) which were used in all calculations. The final R_1 was 0.0474 [$I > 2\sigma(I)$] and wR_2 was 0.1180 (all data).

Single crystals of **5a** were slowly grown from propan-2-ol. A suitable crystal was selected, placed on a glass needle and measured on a Bruker APEX-II CCD diffractometer. Using Olex2,[12] the structure was solved with the XS[13] structure solution program using Direct Methods and refined with the XL[13] refinement package using least squares minimisation.

CCDC 1022820 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

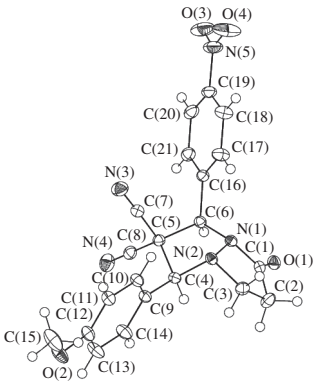
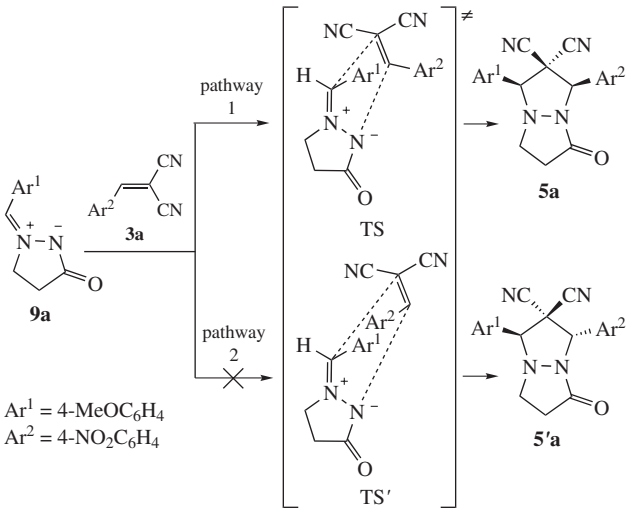


Figure 1 The general view of molecule **5a** in crystal. Atoms are represented by thermal displacement ellipsoids (p = 50%).



Scheme 3

In conclusion, we found that the reaction between stable azomethine imines (1-arylmethylidene-3-oxopyrazolidin-1-ium-2-ides) and arylmethylidene malononitriles stops on [3+2] cycloadducts in contrast to analogous reaction of azomethine imines generated *in situ* by the catalytic diaziridine ring opening in 6-aryl-1,5-diazabicyclo[3.1.0]hexanes, which resulted in the azomethine imines metathesis.

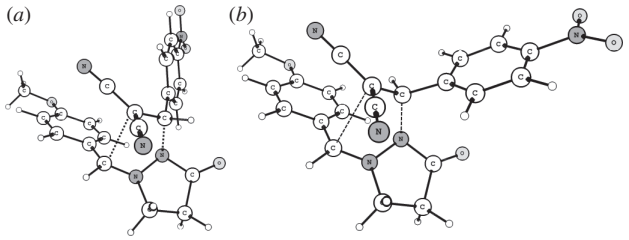


Figure 2 DFT-optimized geometry of the transition states (*a*) TS and (*b*) TS′.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.05.009.

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