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Metathesis of azomethine imines in reaction of 6-aryl-1,5-diazabicyclo[3.1.0]hexanes with (het)arylidenemalononitriles

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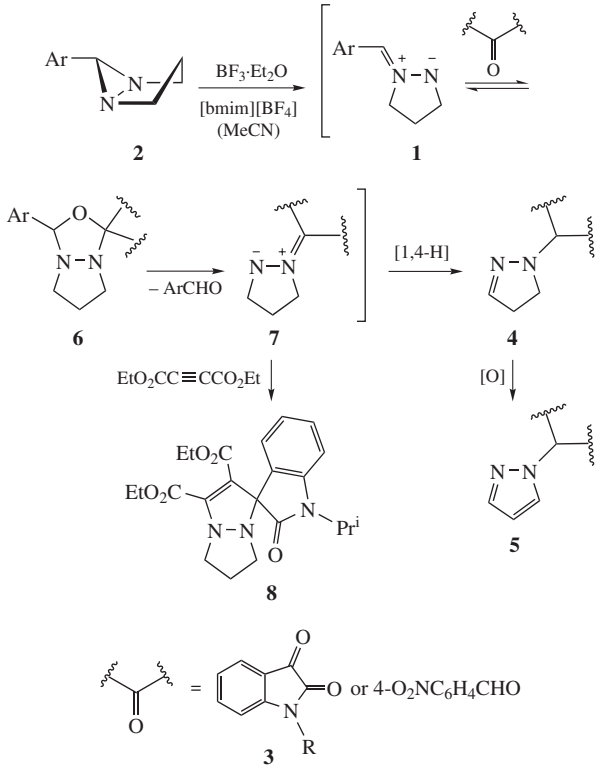
Ring opening in 6-aryl-1,5-diazabicyclo[3.1.0]hexanes gives cyclic azomethine imines which are prone to exchange of arylidene moiety with (het)arylidenemalononitriles to form the metathesis products being new azomethine imines. These species were fixed as pyrazolines due to the 1,4-H shift or trapped by dimethyl acetylenedicarboxylate or CS_2.

One of our scientific interests is the investigation of diaziridine ring expansion under the action of electrophilic agents.[1,2] In particular, some untrivial heterocyclic systems were accessed by [3+2]-cycloaddition of diverse dipolarophiles to cyclic azomethine imines **1** generated by the diaziridine ring opening in bicyclic diaziridines **2** in ionic liquids (ILs).[3–8] The synthesized structures relate to the classes of compounds important for practical applications, among which γ-lactam antibiotics and other antibacterial agents,[9,10] TNF-α-inhibitors,[11] herbicides, fungicides,[12,13] and high-conductivity organic crystals were revealed.[14] Note that the developed procedures are based on simple two-step protocol – a synthesis of diaziridine derivatives[15] and their interaction with commercial reagents.



Scheme 1

Recently,[16] during the studying of reaction between bicyclic diaziridines **2** and isatins **3** we have discovered new method for the azomethine imine generation (Scheme 1). In these reactions, mixtures of isatin pyrazolines **4** and pyrazoles **5** were obtained instead of expected fused heterocyclic systems **6**, with aromatic aldehydes used for the preparation of initial bicyclic diaziridines **2** having been isolated in high yields. We supposed that expected compounds **6** could be produced at the first reaction step. However, in the presence of $BF_3{\cdot}Et_2O$, the formed 1,3,4-oxadiazolidine ring can be opened with an aromatic aldehyde release and generation of new azomethine imines **7**. The latter would transform to pyrazolines **4** due to the 1,4-H shift. The transformation of azomethine imines **1** to azomethine imines **7** may be regarded as azomethine imine metathesis. In one case species **7** was trapped as [3+2] adduct **8** with DEAD. Our attempts to extend this reaction on other aromatic and heteroaromatic aldehydes failed, except for 4-nitrobenzaldehyde.

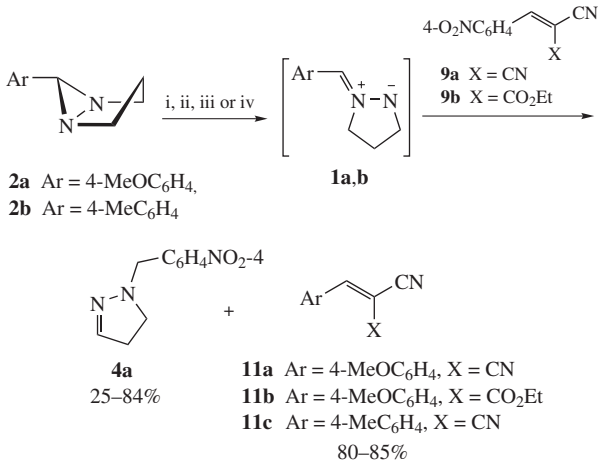
In this work we continued researching reagents for the azomethine imine metathesis using (het)arylidenemalononitriles **9** as dipolarophiles. The investigations began from a reaction of 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **2a**,**b** with donor MeO and Me substituents in the aromatic ring and available[17] arylidenemalononitriles **9a**,**b** with an electron-withdrawing NO_2 substituent in the aromatic ring (Scheme 2). To find the optimal conditions, we tested different methods[2,16,18] (i–iv) for azomethine imine generation.[†] However, instead of anticipated bicyclic structures

[†] *General procedure for the synthesis of 4,5-dihydro-1*H*-pyrazoles* **4**.

Methods i, ii. A catalytic amount (20 mol%) of $BF_3{\cdot}Et_2O$ was added to a mixture of 6-aryl-1,5-diazabicyclo[3.1.0]hexane **2a**,**b** (0.5 mmol) and (het)arylidenemalononitrile **9a**–**g** (0.5 mmol) in IL [bmim][BF_4] (1.5 ml, method i) or anhydrous MeCN (3 ml, method ii). The reaction mixture was stirred at 40 °C until the disappearance of the starting material (TLC control). The reaction products were either extracted from IL (CH_2Cl_2–Et_2O, 1:5, 4×3 ml) or isolated by the removal of MeCN under reduced pressure. The residue was separated by column chromatography on SiO_2 (eluent, AcOEt–light petroleum). Reaction time is indicated in Table 1.

Methods iii, iv: A mixture of compound **2a** or **2b** (0.5 mmol) and compound **9** (0.5 mmol) was refluxed in 5 ml of toluene (0.5–2 h, method iii) or xylene (10 min, method iv). The reaction mixture was allowed to cool to room temperature. The solvent was then removed under reduced pressure and the residue was separated by column chromatography on SiO_2 (eluent, AcOEt–light petroleum). Reaction time is specified in Table 1.

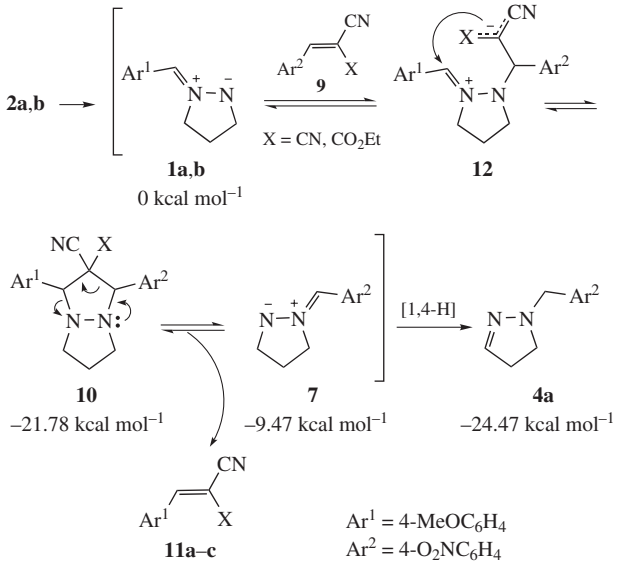
For characteristics of products **4d–f**, see Online Supplementary Materials.



Scheme 2 *Reagents and conditions*: i, $BF_3{\cdot}Et_2O$, [bmim][BF_4], 40 °C;[2] ii, $BF_3{\cdot}Et_2O$, MeCN, 40 °C;[16] iii, reflux in toluene;[18(a),(b)] iv, reflux in xylene.[18(a),(b)]

10 (see Scheme 3) pyrazoline **4a** was obtained regardless of a method employed to prepare azometine imines. The best yield of **4a** was achieved in IL (method i). Along with compound **4a** other arylidenemalononitriles **11a–c** containing aromatic fragments of the starting bicyclic diaziridines **2a**,**b** were isolated in high yields (see Scheme 2).

The mechanism of this process is outlined in Scheme 3 and is evidently similar to that of the pyrazolines **4** formation in the reaction of **2** with carbonyl compounds (see Scheme 1). At first, arylidenemalononitriles **9a**,**b** are linked to the negative pole of azomethine imines **1** in accordance with Michael-type interaction yielding expected bicyclic products **10** through intermediate **12**. However, compounds **10** apparently generate new azomethine imines **13** with a release of new arylidenemalononitriles **11a–c**. Probably, azomethine imines **13** are precursors of compound **4a** due to the 1,4-H shift. Thus, the found reaction is also the azomethine imine metathesis between primary azomethine imines **1** and new azomethine imines **7**. Compounds **1**, **7**, **10–12** in the reaction mass are evidently at equilibrium, while the driving force of the whole process is the pyrazoline **4a** formation. The reaction runs through a transfer of cyanomethylidene fragment from arylidenemalononitriles **9** to the ArCH fragment of initial azomethine imines **1** with a release of new arylidenemalononitriles **11a–c**. A similar transfer of the dicyanomethylene group between arylidenemalononitriles and aldehydes has been reported.[19]



Scheme 3

Table 1 Reaction of 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **2a**,**b** with compounds **9a–g**.

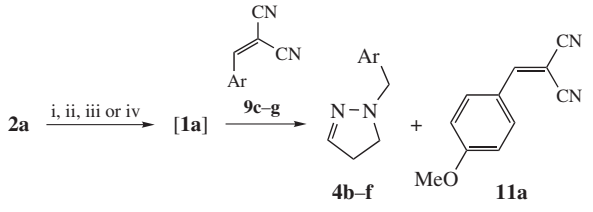
Entry	Ar in **9**	Conditions (*t*/h)	Yield of **4** (%)
1	4-$O_2NC_6H_4$ (**9a**)	i (1)	**4a** (84)
2	4-$O_2NC_6H_4$ (**9a**)	ii (2)	**4a** (60)
3	4-$O_2NC_6H_4$ (**9a**)	iii (0.5)	**4a** (25)
4	4-$O_2NC_6H_4$ (**9b**)	ii (0.5)	**4a** (60)
5	Ph (**9c**)	iii (1)	**4b** (30)
6	3-$O_2NC_6H_4$ (**9d**)	i (6)	**4c** (30)
7	3-$O_2NC_6H_4$ (**9d**)	iii (2)	**4c** (20)
8	2-$O_2NC_6H_4$ (**9e**)	ii (2)	**4d** (60)
9	2-$O_2NC_6H_4$ (**9e**)	iii (2)	**4d** (60)
10	4-BrC_6H_4 (**9f**)	iii (0.2)	**4e** (60)
11	5-O_2N-2-furyl (**9g**)	iv (0.2)	**4f** (32)

In addition, quantum chemical calculations [B3LYP 6-31G(d)] have shown that species **7** was energetically more favourable than species **1** (see Scheme 3).

Since pyrazolines occur in a number of biologically active molecules,[20(a)–(e)] we continued studying reactions between 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **2** and other (het)arylidenemalononitriles **9** with a view to afford new pyrazolines **4**, which we had failed to synthesize in the similar reaction from carbonyl compounds. As the pyrazoline **4a** and arylidenemalononitriles **11a–c** yields did not depend on the structure of initial bicyclic diaziridine **2a**,**b**, 6-(4-methoxyphenyl)-1,5-diazabicyclo[3.1.0]-hexane **2a** was only used in further investigations.

The aforesaid methods i–iv were used to prepare azomethine imine **1a** (see Table 1). It was found that interaction of bicyclic diaziridine **2a** with arylidenemalononitriles **9c–g** (Scheme 4, Table 1) also resulted in pyrazolines **4b–f** in moderate to good yields (see Table 1, entries 5–11, only optimal conditions for each reaction have been tabulated). Meanwhile, the corresponding pyrazolines were not accessed under any conditions in reactions of hetarylidenemalononitriles with furan, thiophene and isatin substituents, whereas arylidenemalononitrile **11a** was isolated in all cases in high yields (80–85%) (Scheme 4).

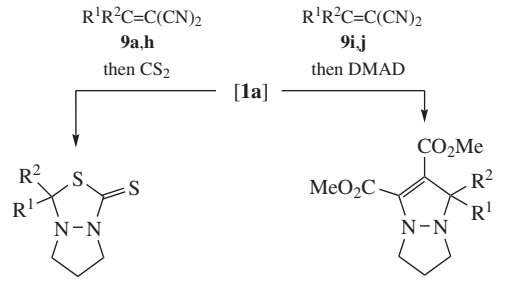
High yields of arylidenemalononitriles **11a–c** and zero or low yields of pyrazolines **4** in some cases testify to low thermal stability of newly formed azomethine imines **7**, especially with 2-furyl, 2-thienyl and isatin-3-yl substituents at hetarylidenemalononitriles **9h–j**, under the reaction conditions. To confirm the formation of azomethine imine **7** in these cases, we used dipolarophiles (DMAD, CS_2) for their trapping.‡ In fact, azomethine imines **7a**,**h–j** were



Scheme 4

‡ *Trapping of azomethine imines* **7** *with DMAD and* CS_2. A mixture of compound **2a** (0.5 mmol) and **9** (0.5 mmol) with a catalytic amount of $BF_3{\cdot}Et_2O$ in 2 ml of dry MeCN (conditions ii) for DMAD or in IL [bmim][BF_4] (1.5 ml) (conditions i) for CS_2 was stirred for 10–60 min at 20–40 °C. Then DMAD (0.5 mmol) or CS_2 (5 mmol) was added dropwise, and the reaction mixture was stirred at this temperature for 1.5 h. MeCN was evaporated, the residue was dissolved in CH_2Cl_2 (the reaction mixture in IL was dissolved in CH_2Cl_2), washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and separated by column chromatography on SiO_2 (eluent, AcOEt–light petroleum).

For characteristics of products **13a**,**b** and **14a**,**b**, see Online Supplementary Materials.



14a R^1 = 4-$O_2NC_6H_4$, R^2 = H, conditions i, 40%
14b R^1 = 2-furyl, R^2 = H, conditions i, 30%
13a R^1 = 2-thienyl, R^2 = H, conditions ii, 30%
13b $R^1 + R^2$ = isatin-3-ylidene, conditions i, 65%

9a R^1 = 4-$O_2NC_6H_4$, R^2 = H
9h R^1 = 2-furyl, R^2 = H
9i R^1 = 2-thienyl, R^2 = H
9j $R^1 + R^2$ = isatin-3-ylidene

Scheme 5

fixed as bicyclic compounds **13a**,**b** and **14a**,**b** in rather high yields (Scheme 5). In all cases arylidenemalononitrile **11a** was also isolated in high yield.

Compounds synthesized were separated by preparative column chromatography on SiO_2 and characterized by elemental and spectral analysis data, primarily NMR using procedures such as {^{1}H-^{13}C}HMBC, {^{1}H-^{13}C}HSQC, and mass spectrometry. The structure of compound **14a** was also confirmed by the X-ray diffraction study (Figure 1).§

To conclude, the found approach for the azomethine imine generation is a new contribution to the understanding of 1,3-dipolar cycloreversion reactions and can be employed for synthesizing other fused heterocyclic systems.

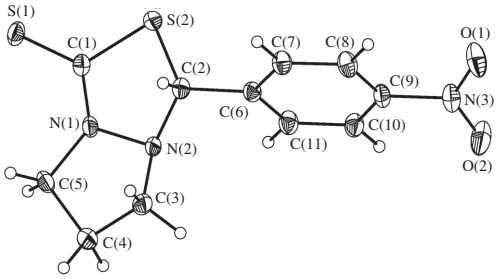


Figure 1 Molecular structure of compound **14a**.

§ *Crystallographic data*. Crystals of **14a** ($C_{11}H_{11}N_3O_2S_2$, M = 281.35) are monoclinic, space group $P2_1/c$, at 100 K: a = 14.9197(7), b = 7.4169(4) and c = 12.1107(6) Å, β = 113.8100(8)°, V = 1226.08(11) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.524 g cm^{-3}, μ(MoKα) = 4.31 cm^{-1}, F(000) = 584. Intensities of 14 132 reflections were measured with a Bruker SMART APEX2 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 58°$], and 3256 independent reflections (R_{int} = 0.0315) were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The hydrogen atoms were refined in the isotropic approximation in riding model. The refinement converged to wR_2 = 0.0833 and GOF = = 1.003 for all independent reflections [R_1 = 0.0320 was calculated against F for 2763 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.[21]

CCDC 887393 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2013.

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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.2013.01.012.

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