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# Metathesis of azomethine imines in the reaction of 6-aryl-1,5-diazabicyclo[3.1.0]hexanes with carbonyl compounds

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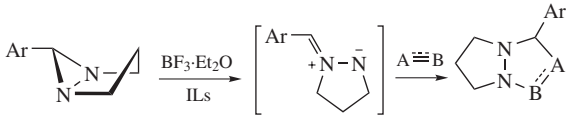
An interaction of carbonyl compounds (isatins, 4-nitrobenzaldehyde) with azomethine imines generated by the diaziridine ring opening in 6-aryl-1,5-diazabicyclo[3.1.0]hexanes in the presence of $BF_3·Et_2O$ as a catalyst induced the metathesis to other azomethine imines with the elimination of aldehydes ArCHO. New azomethine imines were trapped with diethyl acetylenedicarboxylate, otherwise they transformed to the corresponding pyrazolines due to a 1,4-H shift.

Over a few past years our laboratory has been engaged in investigating of 1,3-dipolar cycloaddition reactions of diverse dipolarophiles (carbon disulfide,[1,2] activated olefins,[3] activated nitriles,[2,4] ketenes[5]) to azomethine imines **1** generated by the catalytic diaziridine ring opening in 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **2** in ionic liquids (ILs) in the presence of $BF_3·Et_2O$ (Scheme 1).[6] In all instances, products were bicyclic fused systems **3** where the pyrazolidine cycle was annelated by various heterocycles. Analogues of the synthesized structures have been reported or patented for medical, agricultural and technology applications.[7–11]

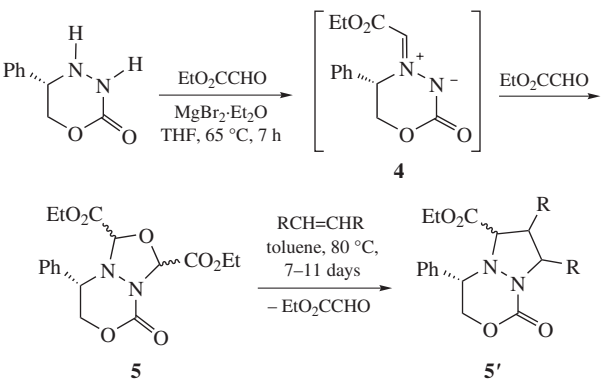



**2** **1** **3**

A≡B = EWG–CN, $Ar^1$–CH=$CHNO_2$, $CS_2$, PhCH=CHCOPh

**Scheme 1**

In this work the research was focused on a possibility to prepare fused systems where the pyrazolidine cycle was annelated by the 1,3,4-oxadiazolidine heterocycle on a basis of the reaction between azomethine imines **1** and carbonyl compounds. According to reported data[12,13] analogues of azomethine imines **1** having the C=O group in the heterocyclic moiety (*e.g.*, azomethines **4**) are capable of reacting with carbonyl compounds to give bicyclic products **5**. Note that compounds **5** can thermally eliminate ethyl glyoxylate and generate initial azomethine imine **4**. The latter in the presence of various dipolarphiles yields 1,3-dipolar cycloaddition products **5′**, however, for that it has to be heated at 80 °C within 7–11 days (Scheme 2).




**4**

**5** **5′**

**Scheme 2**

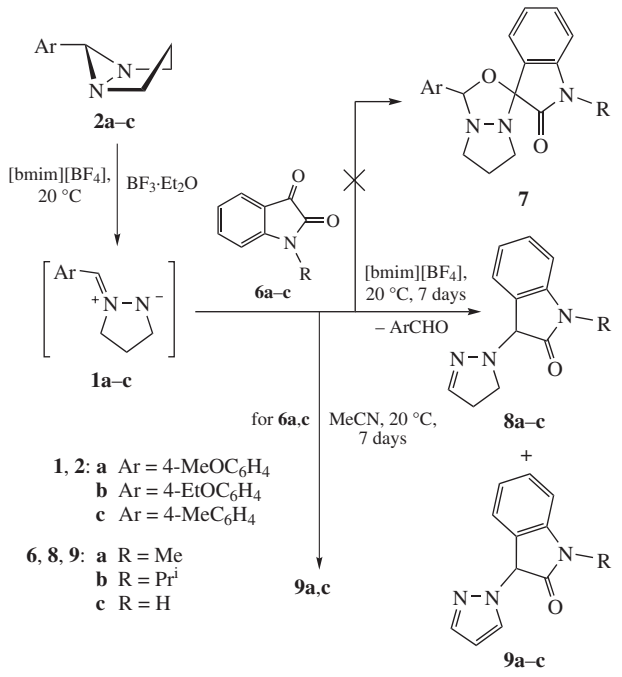
Isatin derivatives **6a–c** substituted in different ways at the nitrogen atom were selected as carbonyl compounds (isatins are known to display a variety of pharmacological activity[14] and serve as a source of dyes, pesticides, insecticides, *etc.*[15,16]). We anticipated that the interaction of **6a–c** with azomethine imines **1a–c** would proceed at the 3-C=O (*cf.* ref. 17).

Azomethine imines **1** were prepared[1–6] from 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **2a–c** in ILs catalyzed by $BF_3·Et_2O$ at 20 °C. We expected that the reaction products would be bicyclic structures **7** containing spiroconjugated indolin-2-one moieties (Scheme 3).

The research started with compound **2a** and isatin **6a**. To generate azomethine imine **1a** the reaction was performed in the IL 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][$BF_4$]) at 20 °C with $BF_3·Et_2O$ (0.2 mmol per 1 mmol of **2a**). Under these conditions, the reaction was complete only in 7 days (TLC control), however, instead of expected **7a**, a mixture of two compounds was attained in low yields. The C(3) atom of isatin in the compounds appeared to be bound to nitrogen atoms of pyrazoline (**8a**) and pyrazole (**9a**) cycles. A mixture of the same compounds **8a** and **9a**, also in low yields, was obtained in the reaction between isatin **6a** and two other 6-aryl-1,5-diazabicyclo-[3.1.0]hexanes **2b**,**c** under similar conditions (Scheme 3, Table 1).[†] By analogy running the reaction of compound **2a** with isatins

[†] *General procedure for the interaction of 6-aryl-1,5-diazabicyclo[3.1.0]-hexanes* **2a–c** *with 1*H*-indole-2,3-diones* **6a–c** *and 4-nitrobenzaldehyde.* A catalytic amount (0.20 mmol) of $BF_3·Et_2O$ and 1 mmol of corresponding isatin **6a–c** or 4-nitrobenzaldehyde was added to a mixture of 1 mmol of 6-aryl-1,5-diazabicyclo[3.1.0]hexane **2a–c** and 1.5 ml of ([bmim][$BF_4$]) or MeCN. The reaction mass was stirred at 18–20 °C until the initial isatin disappeared (TLC control) for ~7 days (for 4-nitrobenzaldehyde, the reaction runs at 40–50 °C for 3 days). The reaction mass was diluted with the equal water amount and extracted with 3×5 ml $CH_2Cl_2$. The combined extract was dried over $MgSO_4$. The organic solvent was evaporated and the products were separated using column chromatography (eluent: ethyl acetate–light petroleum, 1.5:1). In all the cases, aromatic aldehydes ArCHO (Ar = 4-$MeOC_6H_4$, 4-$EtOC_6H_4$, 4-$MeC_6H_4$) were eluted first and were identified by comparison with the authentic samples. To regenerate the IL, the water phase was evaporated on a rotary evaporator at 90 °C to reach the constant mass.

For characteristics of compounds **8a–c** and **9a–c**, see Online Supplementary Materials.




**Scheme 3**

**Table 1** Yields of pyrazolines **8** and pyrazoles **9**.

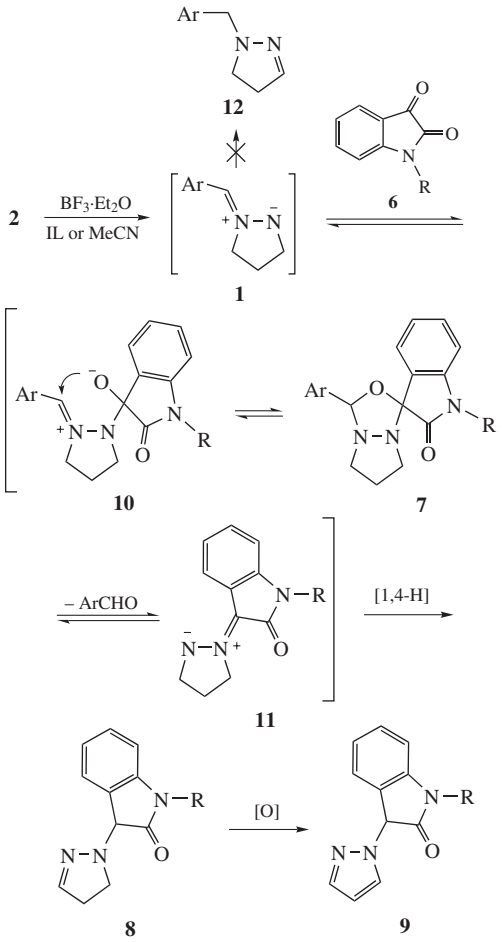
| Starting **2** | Starting isatin, reaction medium, yields of products **8** and **9** (%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **6a** | | | **6b** | | | **6c** | | |
| | [bmim][$BF_4$] | | MeCN | [bmim][$BF_4$] | | MeCN | [bmim][$BF_4$] | | MeCN |
| | **8a** | **9a** | **9a** | **8b** | **9b** | **9b** | **8c** | **9c** | **9c** |
| **2a** | 15 | 12 | 46 | 49 | 25 | — | 15 | 42 | 42 |
| **2b** | 14 | 10 | 31 | 57 | — | — | 24 | 32 | 41 |
| **2c** | 18 | 37 | 23 | | | | | | |

**6b**,**c** afforded a mixture of pyrazolines **8b**,**c** and pyrazoles **9b**,**c** but in higher yields. The interaction of compound **2b** with isatin **6b** resulted only in pyrazoline derivative **8b** whereas both types of compounds **8c** and **9c** were obtained from reactants **2b** and **6c** (Table 1). Furthermore, processing 6-aryl-1,5-diazabicyclo-[3.1.0]hexanes **2** and isatins **6** in MeCN gave only pyrazole derivatives **9a**,**c**. No interaction of azomethine imines **1a**,**b** with isatin **6b** occurred in MeCN (Scheme 3).

In all cases, compounds **8** and **9** were separated by column chromatography on $SiO_2$ and characterized by elemental and spectral analysis data, primarily NMR using procedures such as COSY, {$^1$H–$^1$H}gNOESY, {$^1$H–$^{13}$C}HMBC, {$^1$H–$^{13}$C}HSQC, and {$^1$H–$^{15}$N}HMBC. Aromatic aldehydes used in the synthesis of initial bicycles **2a–c** and some amount of isatins were detected in all cases. Also, noticeable resinification was observed, especially in the case of isatin **6a**. Raising the reaction temperature both in IL and in MeCN enhanced resinification and dropped the yields of products **8** and **9**.

A plausible mechanism of the reaction pathway is given in Scheme 4. At first, the 3-C=O isatin group adds to the negative pole of azomethine imine **1** to generate a new dipolar intermediate **10** that would cyclize to expected 1,3,4-oxadiazolidines **7**. However, despite the low reaction temperature (20 °C), oxadiazolidines **7** appeared insufficiently stable. Their decay was probably caused by $BF_3·Et_2O$, which promoted the oxadiazolidine cycle opening and splitting-off the aromatic aldehydes followed by the generation of other azomethine imines **11**. 1,3,4-Oxadiazolidines are known[18] to be acid-sensitive.

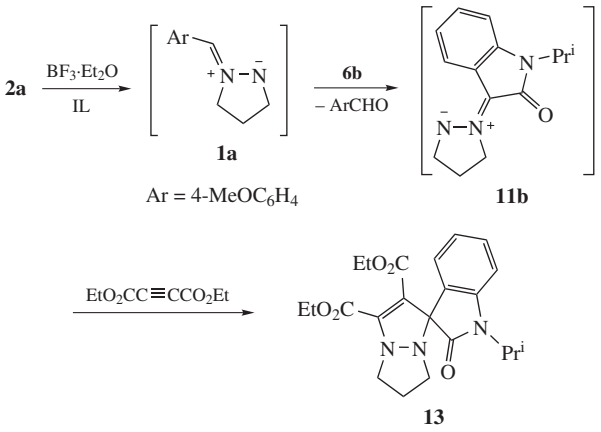
Most likely, compounds **1**, **10**, **7** and **11** are in balance with each other in the ongoing reaction and the driving force of the



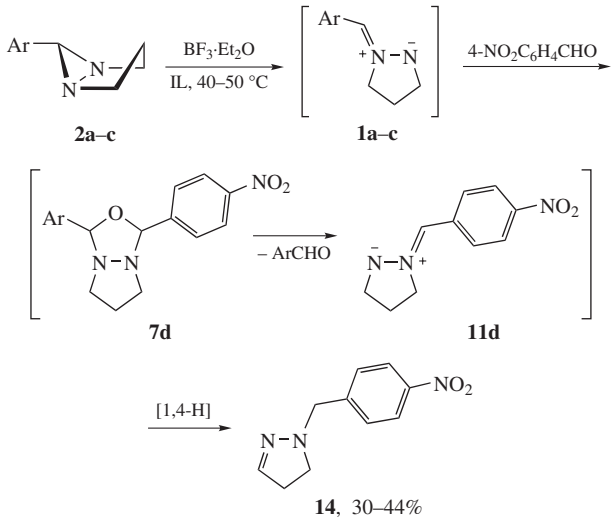

**Scheme 4**

overall process is the formation of pyrazolines **8** induced by a formal 1,4-H shift in azomethine imine **11**. It is obvious that azomethine imines **11** are capable of transforming to pyrazolines **8** at room temperature whereas azomethine imines **1** give analogous pyrazolines **12** only at heating.[19] Pyrazoles **9** are most likely to emerge in oxidation of pyrazolines **8** by air oxygen.[20] The obtaining of sole pyrazole derivatives **9** from the reaction in MeCN is apparently related to an easier oxidation reaction course in organic solvents than in strongly polar ILs.

With a view to support the proposed mechanism, the reaction mixture of **2a** and **6b**, after its maintaining for 2 days at 20 °C, was treated with diethyl acetylenedicarboxylate as a 'trap'. In fact, its 1,3-dipolar cycloaddition with azomethine imine **11b** resulted in a polycyclic product **13** (Scheme 5), whose structure was rigorously proved by elemental analysis and spectroscopic data.‡




**Scheme 5**




**Scheme 6**

The discovered metathesis of azomethine imines proved to be of rather general nature. The interaction of **2a–c** with 4-nitrobenzaldehyde in [bmim][$BF_4$] with a catalytic amount of $BF_3{\cdot}Et_2O$ at gentle heating (40–50 °C) withing 3 days afforded pyrazoline **14** in 30–44% yield. Maximum yield of **14** was achieved in the reaction with azomethine imine **1a**. In MeCN, compounds **2a–c** and 4-nitrobenzaldehyde did not react. The generation of pyrazoline **14** evidently proceeds analogously to that of pyrazolines **8** *via* oxadiazolidine **7d** and azomethine imine **11d** (Scheme 6).‡

Summing up, the metathesis of azomethine imines (the generation of new azomethine imines **11** instead of original azomethine imines **1**) was revealed in the interaction of 6-aryl-1,5-diazabicyclo[3.1.0]hexanes with isatins and 4-nitrobenzaldehyde in ILs (with isatins in MeCN as well) catalyzed by $BF_3{\cdot}Et_2O$ under mild conditions. The transformation may be of use in the preparation of other representatives of similar promising structures.

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‡ For the synthesis of compound **13** and characteristics of compounds **13** and **14**, see Online Supplementary Materials.

*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.01.012.

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