Domino Reaction

Domino Staudinger/*aza*-Wittig/Mannich Reaction: An Approach to Diversity of Di- and Tetrahydropyrrole Scaffolds

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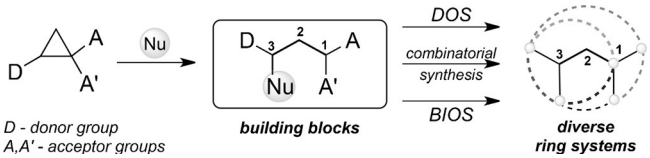
Abstract: A highly efficient and selective domino reaction producing valuable di- and tetrahydropyrrole-based skeletons from azidoethyl-substituted CH-acids and (thio)carbonyl compounds has been developed. By involving the additional functional groups in starting compounds into the domino reaction or postmodification of the primary reaction products, the simple construction of the pharmaceutically relevant three- and polycyclic azaheterocyclic scaffolds was demonstrated.

Rationally designed multifunctional compounds are in high demand as valuable templates for combinatorial diversity-(DOS)[1] or biology-oriented syntheses (BIOS),[2] which aim to access chemical libraries with broad structural and functional variability. These compounds, possessing multiple reactive sites with a high potential for further orthogonal functionalization, inspire the development of time-efficient and highly selective domino processes[3] that make it possible to achieve molecular complexity in an expedient manner.

The nucleophilic ring opening of donor–acceptor (D–A) cyclopropanes,[4] resulting in various compounds with 1,3-arrangement of functional groups,[5,6] is an example of a rapid and efficient approach to such polyfunctional templates (Scheme 1). Recently, we developed the S_N2-like ring opening of D–A cyclopropanes with the azide ion as an efficient route to γ-azidocarbonyl compounds **1**.[7] The densely functionalized azides **1** were shown to act as versatile building blocks in the synthesis of γ-aminobutyric acid derivatives as well as various ring systems, including natural compounds and medical drugs.[8] Among the principal advantages of azides **1** as reagents for DOS are the following: a) Ease, selectivity, and scalability of the synthesis of **1** in both racemic and enantiopure form from commercially available compounds; b) presence of multiple functional groups with excellent compatibility in **1**; c) ability of **1** to undergo manifold transformations depending on the used reaction partners and reaction conditions.



Scheme 1. Building blocks from D–A cyclopropanes in cyclic system assembly.

In this work, we propose a concept of the rapid conversion of azides **1** to pyrrole-based structures **2–4** by means of a new domino reaction that includes the formation of iminophosphorane (Staudinger reaction) and its reaction with a (thio)carbonyl component (*aza*-Wittig reaction), followed by an intramolecular Mannich reaction (Scheme 2 a). A variety of carbonyl and thiocarbonyl compounds, such as aldehydes **5**, iso(thio)cyanates **6** and **7**, or carbon disulfide **8**, were involved in this domino reaction, a common feature of which is the final 1,5-cyclization. As a result, polyfunctional pyrrolidines **2**, 2-amino-Δ^1-pyrrolines **3**, and thioxopyrrolidines **4** can be constructed in a straightforward manner by a phosphine-mediated assembly based on a γ-azidocarbonyl platform.

Moreover, the presence of reactive functionalities in **2–4** ensures the possibilities for: a) elongation of the title domino reaction through involvement of additional functionalities in parent compounds; b) postmodifications of **2–4** to convert them into more complex *aza*-heterocyclic structures, for example benzo[*d*]pyrrolo[1,2-*a*]imidazoles, pyrrolo[3,2-*c*]quinolines, and pyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indoles (Scheme 2 b).

The persistent interest in efficient approaches to the pyrrolidine ring stems from its ubiquitous occurrence as the core fragment in natural and synthetic products exhibiting a broad

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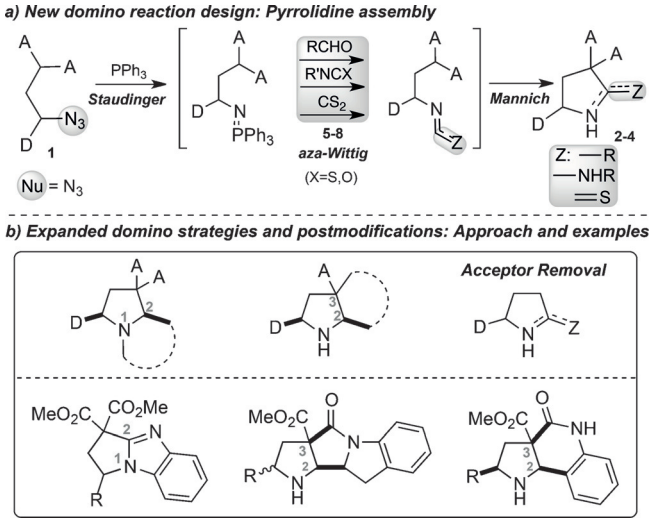


Scheme 2. Azides **1** in the pyrrolidine assembly.

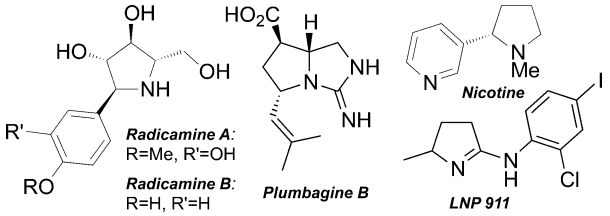
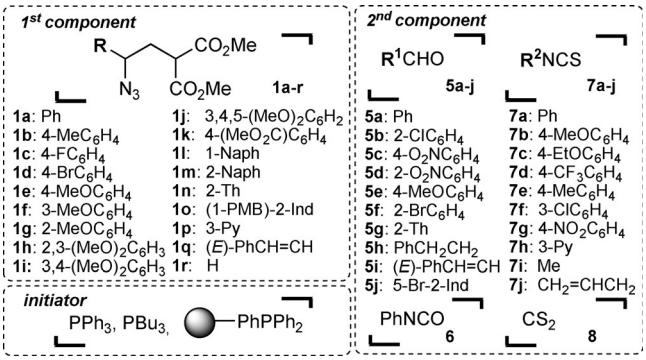


Figure 1. Selected examples of pyrrolidine-based bioactive compounds.

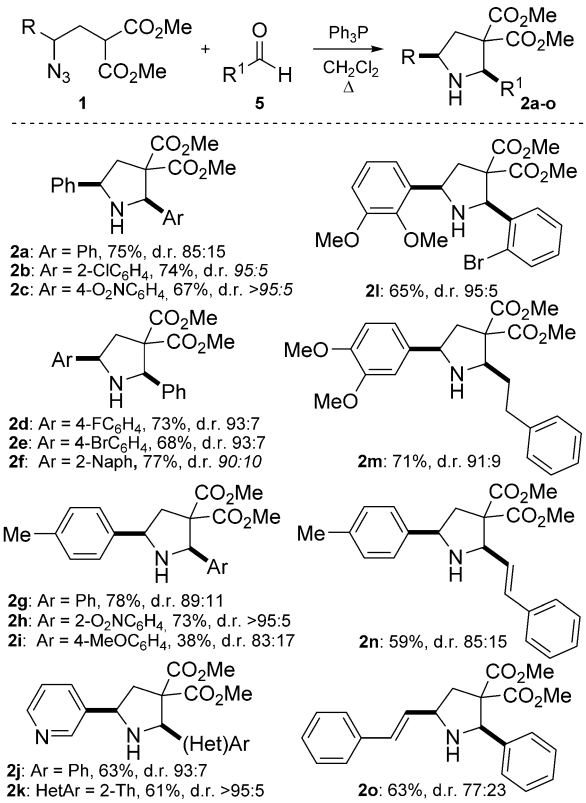
range of bioactivity, for example, high affinity to nicotinic acetylcholine and dopamine receptors, anticancer, anticoagulant, and antiviral activities (Figure 1).[9]

From a design perspective, we envisioned that aldehydes, iso(thio)cyanates, and carbon disulfide can participate in the proposed phosphine-mediated coupling with 2-azidoethyl-substituted malonates **1** (Scheme 3). We started our research by exploring the conditions for the model reaction between azidoester **1a** and benzaldehyde (**5a**). A series of experiments was carried out by varying the ratio and concentration of reagents, reaction temperature, and duration, as well as initiating additives.[10] We found that the target product **2a** was obtained in the highest yield under prolonged microwave heating (40 °C, 22 h) of 1 M dichloromethane solution of azide **1a** with an excess of aldehyde **5a** and a stoichiometric amount of Ph_3P.



Scheme 3. Variation of reaction partners.

With the optimized conditions in hand, we examined the scope of this new domino reaction using a variety of azides **1** and a series of aldehydes **5** (Scheme 4). The electroneutral (Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 2-Naph), electron-enriched (2,3-$(MeO)_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$), and electron-deficient (3-Py)



Scheme 4. Scope of the reaction of **1** with aldehydes **5** (isolated yields). Reaction conditions: Azide **1** (0.69 mmol), aldehyde **5** (0.76–3.45 mmol), PPh_3 (0.72 mmol), CH_2Cl_2 (0.7 mL), microwave heating at 40 °C for 22 h.

aromatic groups can be readily installed at the C(5) position of pyrrolidines **2a–n** through the reaction of the corresponding azides **1** with diverse aldehydes **5**. Variation of substituents in azides **1** has no significant effect on the efficiency of the studied process. This transformation was found to successfully proceed for both (hetero)aromatic (**5a–g**) and aliphatic (**5h**) aldehydes. It is noteworthy that alkenyl substituents in both azides **1** and aldehydes **5** are tolerant towards the reaction conditions. Pyrrolidines **2n** and **2o**, containing a styryl group at either the C(2) or C(5) atom, were obtained in good yield. The pyrrolidine formation proceeds with good to excellent diastereoselectivity. Pyrrolidines **2a–o** were predominantly or exclusively formed as *cis* isomers, regardless of the substituents in the parent azides **1** and aldehydes **5**.[10,11]

A proposed mechanism for the formation of pyrrolidines **2** is presented in Scheme 5. The transformation begins with the

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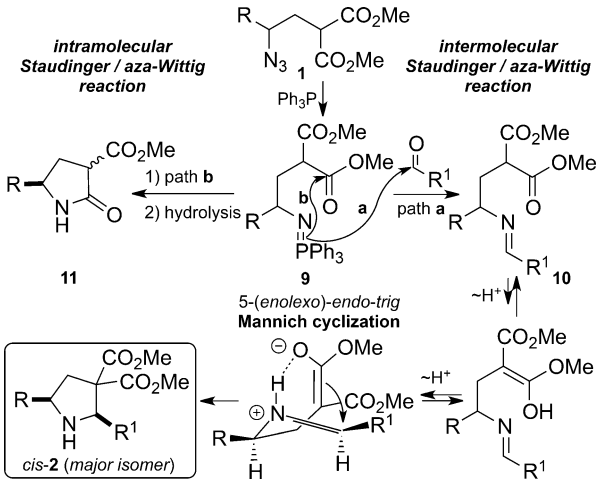
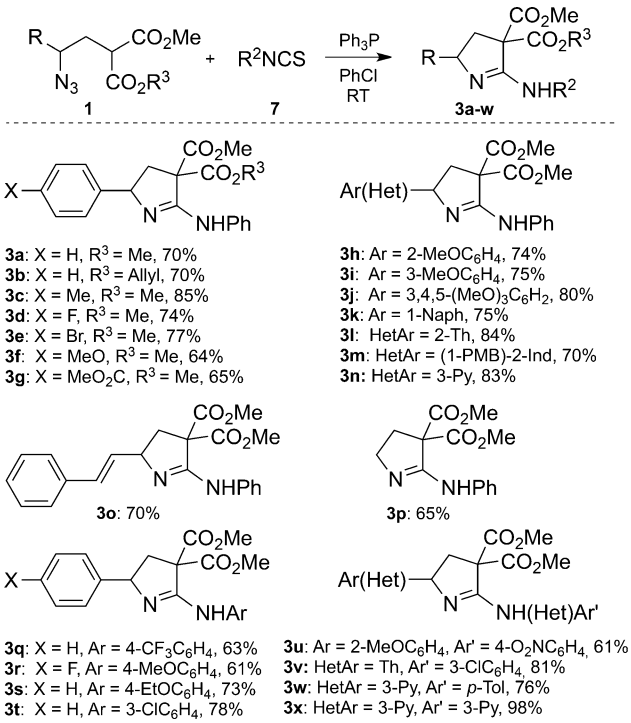


Scheme 5. Proposed mechanism for the formation of pyrrolidines **2**.

formation of iminophosphorane **9**. Its intermolecular reaction with aldehyde **5** affords imine **10** (path **a**), the intermediacy of which was detected by monitoring the reaction progress by NMR. The competitive intramolecular reaction yielding (after hydrolysis) pyrrolidone **11** (path **b**) occurred when higher reaction temperature or more reactive Bu_3P were used.[10] The final cyclization of imine **10** to pyrrolidine **2** proceeds, presumably, by proton transfer followed by nucleophilic attack of the malonate anion on the iminium cation moiety. High *cis*-diastereoselectivity apparently arises from the five-membered transition state of the Mannich ring closure, where bulky groups R and R^1 are placed in pseudoequatorial positions.[10]

Next, we focused on the domino reaction of azides **1** with other partners in the *aza*-Wittig step, for example isocyanate, isothiocyanate, or carbon disulfide, aiming to obtain a diversity of polyfunctional pyrrolidine-based structures. Isocyanate **6** was found to produce a complex mixture of products from which aminopyrroline **3a** was isolated in low yield. The high reactivity of isocyanates against nucleophiles, such as the malonate moiety in **1** or the amino group in **3**, is presumably responsible for the low efficiency of this reaction. To our delight, the PPh_3-mediated reaction of azides **1** with the less reactive isothiocyanates **7** proceeded with excellent chemoselectivity, producing 2-amino-Δ^1-pyrrolines **3** in good yields under mild reaction conditions (Scheme 6).

As in the case of the reaction with aldehydes, a broad variety of azides **1**, bearing aromatic groups with alkyl, alkoxy, halogen, or ester substituent(s) at various positions, or heteroaromatic (thienyl, indolyl, pyridyl) as well as alkenyl substituents, were successfully used in the title domino reaction with isothiocyanates. 5-Unsubstituted 2-aminopyrroline **3p** was also obtained in reasonable yield. The reaction is highly chemoselective except for the case of methyl and allyl isothiocyanates that resulted in a complex mixture of products. The slightly lower observed yields of **3a**–**w** were due to some loss of product during a separation from triphenylphosphine oxide.[12] We demonstrated that the use of polymer-supported phosphine enables the production of pure 2-aminopyrroline **3x** in quantitative yield without any additional treatment.

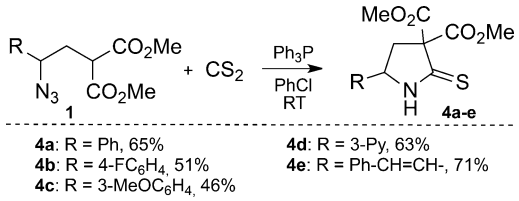


Scheme 6. Scope of the reaction of **1** with isothiocyanates **7** (isolated yields). Reaction conditions: 1 M solution of azide **1** in chlorobenzene, PPh_3 (1 equiv), isothiocyanate **7** (1.1–1.5 equiv), RT, 3 h; more **7** (0.4 equiv), RT, 15 h.

It is noteworthy that products **3** were obtained as 2-aminopyrroline but not 2-iminopyrrolidine tautomers.[11] This result can be explained by the higher stability of 2-aminopyrrolines, which is supported by our DFT calculations.[10,13]

The introduction of carbon disulfide into the Ph_3P-initiated reaction with azidoesters **1** containing diverse substituents (aryl-, hetaryl, alkenyl-) provides rapid access to thioxopyrrolidines **4a**–**e**. These reactions occurred smoothly at ambient temperature, affording thioamides in reasonable yields (Scheme 7).[11]

It is remarkable that isothiocyanates **7** and carbon disulfide **8** react with azides **1** at room temperature, whereas aldehydes, being more reactive carbonyl compounds, require heating. This indicates that the rate-limiting step for the total process is not the *aza*-Wittig reaction but rather the Mannich cyclization. For intermediate **10**, this is a disfavored 5-*endo-trig* process, whereas for the corresponding intermediates in the PPh_3-initiated reaction of **1** with isothiocyanates **7** or carbon disulfide **8**,



Scheme 7. Scope of the reaction of **1** with carbon disulfide **8** (isolated yields). Reaction conditions: 1 M solution of azide **1** in chlorobenzene, PPh_3 (1 equiv), **8** (2 equiv), RT, 24–72 h.

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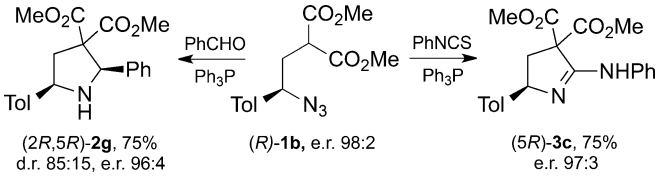
the rate-limiting step is a favored 5-*exo-trig* cyclization.[14] As a result, the reaction of **1** with aldehydes **5** has a higher energy barrier than the corresponding reactions with **7** or **8**. Nevertheless, it is known that the significant polarization of a double bond raises the possibility of a 5-*endo-trig* cyclization.[15] In the discussed reaction, the intramolecular proton transfer (see Scheme 5) ensures the aforementioned polarization as well as increasing the nucleophilicity of the malonate moiety.

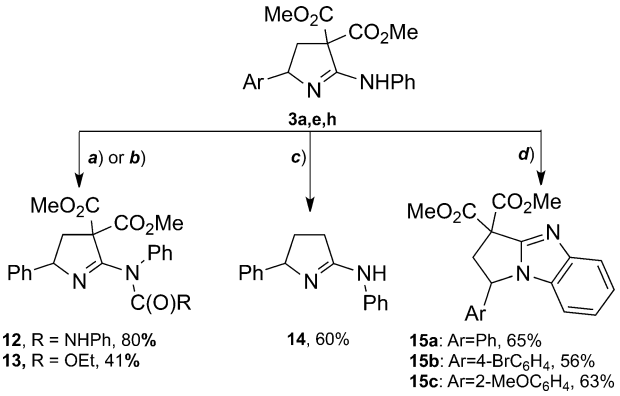
Development of synthetic approaches to enantiopure pyrrolidines is essential in the context of their further application in the synthesis of biologically active compounds. Our method provides a straightforward route to the optically active pyrrolidines and pyrrolines **2** and **3** starting from the chiral azides **1**, which can be obtained by the enantiospecific ring opening of the readily available chiral D–A cyclopropanes with the azide ion.[7] For example, the domino Staudinger/*aza*-Wittig/Mannich reaction of azide (*R*)-**1 b** with **5 a** or **7 a** affords the chiral products (2*R*,5*R*)-**2 g** and (5*R*)-**3 c**, respectively (Scheme 8).



Scheme 8. Synthesis of (2*R*,5*R*)-**2 g** and (5*R*)-**3 c**.

Enantiomeric purity of (2*R*,5*R*)-**2 g** and (5*R*)-**3 c** was determined by ^{1}H NMR after derivatization with (*S*)-α-methylbenzyl isocyanate.[16] We studied the reactions of **3** with different acylating agents and found that both phenyl isocyanate and ethyl chloroformate produce exclusively the products of exocyclic amino group acylation **12** and **13** (Scheme 9 a, b).[10]

Additionally, we have demonstrated that both ester groups in compounds **3** can be removed under unusually mild conditions. In the case of **3 a**, heating to reflux in aqueous methanol

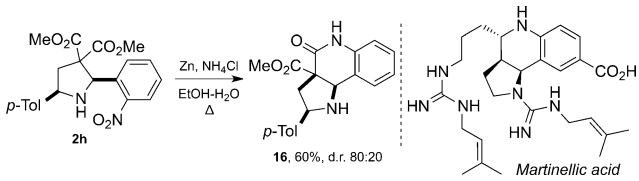


Scheme 9. Post-modifications of 2-aminopyrrolines **3**. Reaction conditions: a) 1 M solution of **3 a** in acetonitrile, PhNCO (2 equiv), RT, 3 h; b) 1 M solution of **3 a** in CH_2Cl_2, $ClCO_2Et$ (1.5 equiv), Et_3N (1.5 equiv), RT, 24 h; c) 0.05 M solution of **3 a** in H_2O/MeOH (1:1), reflux, 9 h; d) 0.1 M solution of **3** in acetonitrile, $PhI(OAc)_2$, RT, 30 h.

for 9 h results in full conversion, affording 5-phenyl-2-phenylamino-Δ^1-pyrroline **14** in 60% yield (Scheme 9 c). Consequently, in the transformation of **1** to **14** ester moieties serve as auxiliary groups that are initially essential for the construction of the five-membered nitrogen ring but can be removed afterwards.

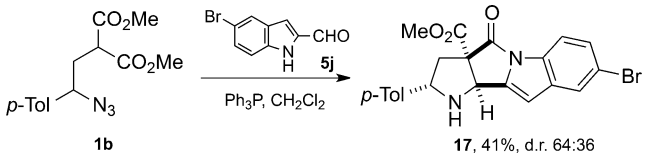
Moreover, the synthetic utility of the obtained pyrrolidines **2**–**4** can be significantly extended through diverse post-modifications of their multiple functionalities, thus affording more complex molecules, including bioactive ones. In particular, we converted amidines **3 a**, **e**, and **h** into not easily accessible 1,2-dihydro-3*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazoles **15 a**–**c** through $PhI(OAc)_2$-promoted oxidative cyclization (Scheme 9 d).[17]

Furthermore, we designed an approach to a tricyclic framework of pyrrolo[3,2-*c*]quinoline, a structural fragment of the alkaloid martinellic acid and many other bioactive compounds. The pyrrolidine **2 h**, obtained by reaction of azide **1 b** with 2-nitrobenzaldehyde, was easily transformed to pyrrolo[3,2-*c*]quinolone **16** through nitro group reduction followed by a spontaneous amidative ring closure (Scheme 10).



Scheme 10. Reductive cyclization of **2 h** to pyrrolo[3,2-*c*]quinolone **16**.

Additional functional groups in the starting compounds can also be included in the domino reaction. Thus, the PPh_3-induced reaction of 2-indolecarbaldehyde **5 j** with azide **1 b** proceeds as a domino process wherein the Staudinger/*aza*-Wittig/Mannich sequence is followed by amidative cyclization. This four-step process results in compound **17** with the quaint pyrrolo[2′,3′:3,4]pyrrolo[1,2-a]indole tetracyclic system (Scheme 11).[18] Compounds of this type can be considered as structural analogues of some anticancer, antibacterial, and anti-inflammatory agents.[19]



Scheme 11. Pyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole **17** assembly.

It is noteworthy that diastereomerically pure pyrrolidine **2 h** produced **16** as a mixture of two diastereomers. Moreover, tetracyclic compound **17** has *trans*-arrangement of *p*-tolyl and indolyl moieties, whereas *cis*-selectivity was found for the formation of 2,5-diarylpyrrolidines **2**. This is presumably explained by *cis*–*trans* isomerization of 2,5-diarylpyrrolidines before cyclization.[20]

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In conclusion, we have developed a convenient and efficient method for the synthesis of a broad variety of densely substituted di- and tetrahydropyrroles, including optically active ones, as well as three- and polycyclic pyrrolidine-based structures, through a new domino Staudinger/*aza*-Wittig/Mannich reaction. This synthetic methodology offers powerful opportunities to assemble diverse products of synthetic and pharmaceutical relevance.

Acknowledgements

We thank the Russian Science Foundation (Project 14-13-01178) for support of this work.

Keywords: azides · domino reactions · donor–acceptor cyclopropanes · nitrogen heterocycles · synthesis design

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[10] For details, see the Supporting Information.

[11] CCDC 1000244 (**2c**), 1029552 (**2h**), 1044525 (**2l**), 1047977 (**3c**), 1483968 (**3l**), 1411421 (**3n**), 1483970 (**4e**), and 1493404 (**14**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre; X-Ray analysis was performed on a STOE STADI VARI PILATUS-100 K diffractometer purchased through the MSU Development Program.

[12] This loss is low to moderate in reactions of aryl isothiocyanates, however significant for allyl and benzyl isothiocyanates.

[13] According to B3LYP/6–311G** calculations, **3a** is 12.4 kJ mol^{-1} more stable than the 2-(phenylimino)pyrrolidine tautomer **3a**′.

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Received: August 25, 2016
Published online on October 31, 2016

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