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Synthesis of Densely Functionalized 3a,4-Dihydro-1*H*-Pyrrolo[1,2-*b*]Pyrazoles via Base Mediated Domino Reaction of Vinyl Malononitriles with 1,2-Diaza-1,3-dienes

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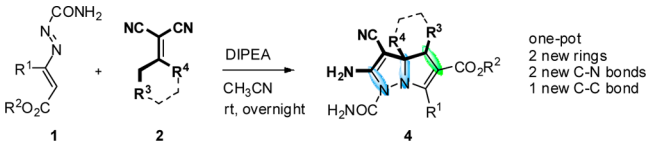
ABSTRACT



A domino reaction of vinyl malononitriles (VMs) with 1,2-diaza-1,3-dienes (DDs) produce unprecedented 3a,4-dihydro-1*H*-pyrrolo[1,2-*b*]pyrazole systems in a chemo-, regio-, and stereoselective fashion. This base promoted (DIPEA) one-pot transformation involving multiple steps constructs one new C−C bond, two C−N bonds, and two new fused heterocyclic rings with total atom economy.

In pharmaceutical and biomedical research, densely functionalized and diversified heterocyclic molecules can be extremely useful for obtaining biological leads and exploring molecular recognition events. Therefore, the availability of efficient and practical synthetic procedures to generate heterocycle modules for the preparation of natural and biomimetic compounds remains a great challenge. One of the ways to fulfill this goal is the development of domino reactions[1] which allow the sequential transformations of two or more reactions in the same reaction vessel, thereby minimizing the number of laboratory operations, the generation of waste chemicals, time, and cost.

Heteroaromatic molecules containing *N*-fused bicyclic fragments (and their partially or completely reduced analogues) are important components in a large number of pharmaceutical, agrochemical, and natural products.[2,3] Antibacterial and antifungal activities have been ascribed to many of these *N*-fused heterocycles. Additionally, some of them have been identified as potential anxiolytic, antineoplastic, antiplasmodial, and anticancer agents.[4]

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(1) For recent reviews, see: (a) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442–524. (b) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278–1293. (c) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581. (d) Nicolau, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (e) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (f) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.

(2) For review, see: Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 675–696.

(3) For a review, see: (a) Liu, T.; Fu, H. *Synthesis* **2012**, *44*, 2805–2824. For select examples, see: (b) Zhang, H.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. *Eur. J. Org. Chem.* **2012**, 6798–6803 and references cited therein. (c) Li, M.; Shao, P.; Wang, S.-W.; Kong, W.; Wen, L.-R. *J. Org. Chem.* **2012**, *77*, 8956–8967. (d) Tyagi, V.; Khan, S.; Bajpai, V.; Gauniyal, H. M.; Kumar, B.; Chauhan, P. M. S. *J. Org. Chem.* **2012**, *77*, 1414–1421. (e) Chernyak, D.; Gevorgyan, V. *Org. Lett.* **2010**, *12*, 5558–5560. (f) Chen, W.; Hu, M.; Wu, J.; Zou, H.; Yu, Y. *Org. Lett.* **2010**, *12*, 3863–3865. (g) Tomilov, Y. V.; Novikov, R. A.; Nefedov, O. M. *Tetrahedron* **2010**, *66*, 9151–9158. (h) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 3433–3436.

(4) (a) Katritzky, A. R.; Tymoshenko, D. O.; Monteux, D.; Vvedensky, V.; Nikonov, G.; Cooper, C. B.; Deshpande, M. *J. Org. Chem.* **2000**, *65*, 8059–8062. (b) Maryanoff, B. E.; McComsey, D. F.; Ho, W.; Shank, R. P.; Dubinsky, B. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 333–338. (c) Reitz, A. B.; Gauthier, D. A.; Ho, W.; Maryanoff, B. E. *Tetrahedron* **2000**, *56*, 8809–8812. (d) Rida, S. M.; Soliman, F. S. G.; Badawey, E.; Kappe, T. *J. Heterocycl. Chem.* **1988**, *25*, 1725–1728. (e) Rida, S. M.; Soliman, F. S. G.; Badawey, E.; El-Ghazzawi, E.; Kader, O.; Kappe, T. *J. Heterocycl. Chem.* **1988**, *25*, 1087–1093. (f) Badawey, E.; Kappe, T. *Eur. J. Med. Chem.* **1995**, *30*, 327–332. (g) El-Hawash, S. A. M.; Badawey, E.; Kappe, T. *Pharmazie* **1999**, *54*, 341–346.

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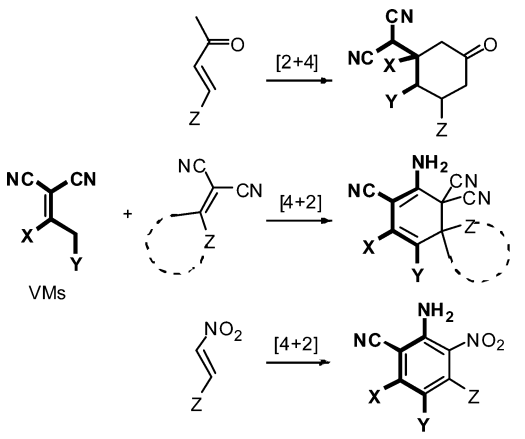
However, to the best of our knowledge fused 3a,4-dihydro-1*H*-pyrrolo[1,2-*b*]pyrazole (with one nitrogen atom shared by two rings) has not been reported in the literature. Accordingly, development of new methodologies to rapidly assembly strucurally diverse *N*-fused bicyclic molecules, such as *N*-fused pyrrolo-pyrazole scaffolds, are of high demand.

The vinylogous version of the Michael addition reaction has emerged as immensely useful, strategic maneuvers in the art of contemporary organic synthesis.[5] Altough vinylogous addition of vinyl malononitriles (VMs) to suitable conjugated acceptors including activated α,*β*-unsaturated aldehydes[6] and ketones,[7] alkylidene/isatylidene malononitriles,[8,9] nitroalkenes,[10] and azodicarboxylates[11] was explored, the reported examples in this area are confined to synthetize carbocycles (Scheme 1). Recently, Perumal et al. reported a novel method for the synthesis of functionalized spirocyclic oxindoles by a one-pot tandem reaction of VMs with isatylidene malononitriles.[8b] Vinylogous Michael addition of VMs with nitroolefins was also realized in the one-pot synthesis of polysubstituted benzene derivatives.[9b]

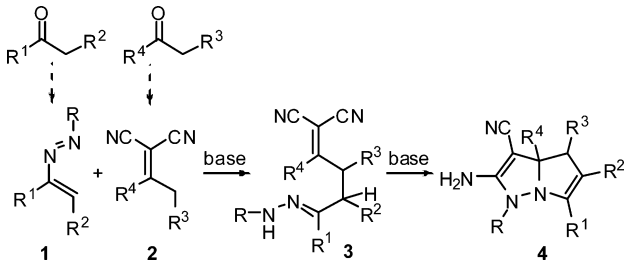
Our ongoing studies on 1,2-diaza-1,3-dienes (DDs)[11] **1** indicated these as potentially attractive substrates for the vinylogous Michael reaction.

We found, in fact, that VMs **2** (obtained from ketones via a Knovenagel reaction) can react with DDs **1** (obtained from ketones via a dehydrohalogenation reaction of α-halogenated hydrazones) in the presence of a base. So highly functionalized pyrrolo-pyrazole systems **4** can be obtained by means of a one-pot domino transformation via hydrazonic adduct intermediate **3** (Scheme 2). Thus, a novel method for the synthesis of densely funcionalized

Scheme 1. Various Pathways for Base-Mediated Annulations of VMs with Different Michael Acceptors: Construction of Carbocycles



Scheme 2. Strategy for Synthesis of Pyrrolo-Pyrazole Compounds from Ketones



fused pyrrolo-pyrazole compounds using ketones as the starting materials is described for the first time.

We began our investigation by studying the vinylogous Michael addition reaction between the VM **1a** and DD **2a** in the presence of a catalytic amount of DIPEA (20 mol %) in CH_3CN at rt (Table 1). After 5 min, the disappearance of the red color of the starting azoene was observed. The TLC of the crude mixtures revealed the presence of a single product spot easily identified as the vinylogous hydrazonic Michael adduct **3a** (89%). Subsequently, we found that the vinylogous hydrazonic Michael adduct (**3a**) could undergo sequential cyclization reactions to give new 3a,4-dihydro-1*H*-pyrrolo[1,2-*b*]pyrazole **4a** (Table 1).

Then, we investigated the best conditions for the heterocyclization processes of vinylogous hydrazonic Michael adduct **3a** selected as a model reaction. Various solvents and DIPEA loading have been tried (Table 1, entries 1–9), and the best result (67% yield) was obtained with 100 mol % DIPEA in CH_3CN (Table 1, entry 9). No reaction occurred without the addition of DIPEA in refluxing CH_3OH overnight (Table 1, entry 5).

With these results in hand, we moved toward the principal aim of our investigations, the development of a one-pot domino sequence, leading to bicyclic products

(5) For reviews, see: (a) Zanardi, F.; Rassu, G.; Battistini, L.; Curti, C.; Sartori, A.; Casiraghi, G. In *Targets in Heterocyclic Systems—Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Società Chimica Italiana: Rome, 2012; Vol. 16, p 56. (b) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076–3154.

(6) (a) Lu, J.; Liu, F.; Zhou, W.-J.; Loh, T.-P. *Tetrahedron Lett.* **2008**, 5389–5392. (b) Bell, M.; Frisch, K.; Jørgensen, A. *J. Org. Chem.* **2006**, *71*, 5407–5410. (c) Xie, J.-W.; Yue, L.; Xue, D.; Ma, X.-L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Chem. Commun.* **2006**, 1563–1565.

(7) (a) Kang, T.-R.; Xie, J.-W.; Du, W.; Feng, X.; Chen, Y.-C. *Org. Biomol. Chem.* **2008**, *6*, 2673–2675. (b) Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 389–392.

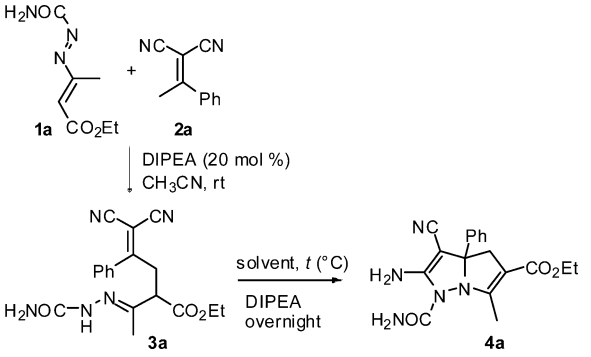
(8) (a) Wang, X.-S.; Wu, J.-R.; Zhou, J.; Tu, S.-J. *J. Comb. Chem.* **2009**, *11*, 1011–1022. (b) Babu, T. H.; Joseph, A. A; Muralidharan, D.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 994–996.

(9) (a) Guo, Z.-W.; Li, X.-S.; Zhu, W.-D.; Xie, J.-W. *Eur. J. Org. Chem.* **2012**, 6924–6932. (b) Xue, D.; Li, J.; Zhang, Z.-T.; Deng, J.-G. *J. Org. Chem.* **2007**, *72*, 5433–5445. (c) Poulsen, T. B.; Bell, M.; Jørgensen, A. *Org. Biomol. Chem.* **2006**, *4*, 63–70. (d) Xue, D.; Chen, Y.-C.; Wang, Q.-W.; Cun, L.-F.; Zhu, J.; Deng, J.-G. *Org. Lett.* **2005**, *7*, 5293–5296.

(10) Poulsen, T. B.; Alemparte, C.; Jørgensen, A. *J. Am. Chem. Soc.* **2005**, *127*, 11614–11615.

(11) For a review on the chemistry of DDs, see: (a) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Perrulli, F. R.; Santeusanio, S. *Eur. J. Org. Chem.* **2009**, 3109–3127. For some recent examples, see: (b) Chen, J.-R.; Dong, W.-R.; Candy, M.; Pan, F.-F.; Jörres, M.; Bolm, C. *J. Am. Chem. Soc.* **2012**, *134*, 6924–6927. (c) Attanasi, O. A.; Bartoccini, S.; Favi, G.; Giorgi, G.; Perrulli, F.; Santeusanio, S. *J. Org. Chem.* **2012**, *77*, 1161–1167. (d) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Mantellini, F.; Nicolini, S. *J. Org. Chem.* **2011**, *76*, 8320–8328. (e) Attanasi, O. A.; Favi, G.; Mantellini, F.; Moscatelli, G.; Santeusanio, S. *J. Org. Chem.* **2011**, *76*, 2860–2866. (f) Hatcher, J. M.; Coltart, D. M. *J. Am. Chem. Soc.* **2010**, *132*, 4546–4547.

Table 1. Reaction of DD **1a** with VM **2a**: Optimization of the Reaction Conditions for the Heterocyclization Process (**3a**→**4a**)[a]



entry	DIPEA (mol %)	solvent	t (°C)	**4a** yield (%)[b]
1	20	CH_2Cl_2	rt	trace
2	100	CH_2Cl_2	rt	8
3	20	THF	rt	trace
4	100	THF	rt	10
5	–	CH_3OH	reflux	–
6	20	CH_3OH	rt	51
7	100	CH_3OH	rt	56
8	20	CH_3CN	rt	trace
9	100	CH_3CN	rt	67

[a] All reactions were performed at a 0.5 mmol scale of **3a**. [b] Yields of isolated product **4a**.

from easily accessible starting materials. Gratifyinly, a one-pot cascade via DIPEA-assisted double aza-annulations in CH_3CN at rt was found to take place easily, with a good yield (64%) of the bicyclic product **4a** (Table 2, entry 1).

Having established the optimal conditions, the scope of the one-pot reaction was probed using a range of doubly EWG activated DDs (**1a**–**h**)[12] reacting with 2-(1-phenylethylidene)malononitrile **2a**[13] (Table 2, entries 1–8).

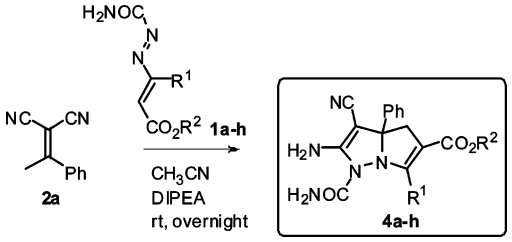
The increase of the alkyl chain length (R^1 = Me, Et, *n*-Pr, *n*-Bu) as well as the nature of the ester group (CO_2R^2; R^2 = Me, Et, *t*-Bu, Bn, Allyl) revealed minimal influence on the reaction yield. In all cases, the reaction proceeded at rt under very mild reaction conditions, and the desired functionalized pyrrolo-pyrazole compounds (**4a**–**h**) were consistently obtained in moderate to good yields.

The generality of this one-pot reaction shown in Table 2 prompted us to investigate the reaction for a series of alkylidene malononitriles (**2b**–**g**) with DDs (**1a**–**h**). The results are reported in Table 3. The reaction's scope proved to be quite broad with respect to acyclic or cyclic and alkyl and aryl-substituted VMs **2b**–**f**.[13] The presence of either electron-withdrawing or -donating groups on the aromatic ring of **2** (**2b** and **2c**) afforded comparable results (Table 3, entries 1–5). Both (1-methyl-2-phenylethylidene)-malononitrile **2d** and (1-phenylpropylidene)malononitrile

(12) DDs **1a**–**h** were synthesized from the corresponding chlorohydrazones by treatment with a base (see Supporting Information).

(13) VMs **2a**–**f** were synthesized via a Knoevenagel reaction from ketones and malononitriles (see Supporting Information).

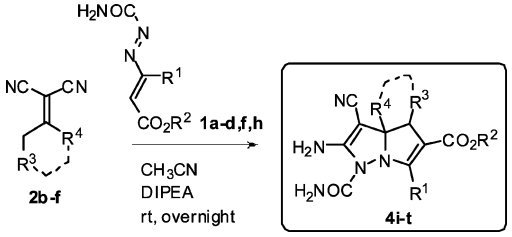
Table 2. One-Pot Synthesis of Pyrrolo-Pyrazole Systems **4a**–**h**: Reaction Scope of VM **2a** with Respect to DDs **1a**–**h**[a]



	DDs **1**	products **4**	
entry	**1** (R^1, R^2)	**4**	yield (%)[b]
1	**1a** (Me, Et)	**4a**	64
2	**1b** (Me, Me)	**4b**	63
3	**1c** (Me, *t*-Bu)	**4c**	67
4	**1d** (Me, Bn)	**4d**	55
5	**1e** (Me, Allyl)	**4e**	46
6	**1f** (Et, Me)	**4f**	71
7	**1g** (*n*-Pr, Et)	**4g**	65
8	**1h** (*n*-Bu, Me)	**4h**	69

[a] Reagents and conditions: **1a**–**h** (0.5 mmol), **2a** (0.6 mmol), DIPEA (0.6 mmol), CH_3CN (3 mL), rt, overnight. [b] Yield of pure isolated products.

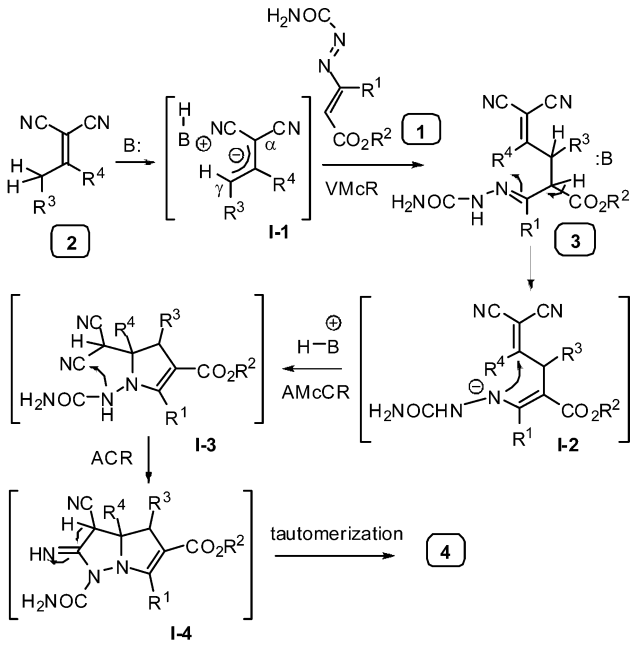
Table 3. One-Pot Synthesis of Pyrrolo-Pyrazole Systems **4i**–**t**: Reaction Scope with Respect to VMs **2b**–**f**[a]



	DDs **1**	VMs **2**	products **4**	
entry	**1** (R^1, R^2)	**2** (R^3, R^4)	**4**	yield[b] (%)
1	**1b** (Me, Me)	**2b** (H, *p*-OMe-C_6H_4)	**4i**	50
2	**1c** (Me, *t*-Bu)	**2b** (H, *p*-OMe-C_6H_4)	**4j**	42
3	**1a** (Me, Et)	**2b** (H, *p*-OMe-C_6H_4)	**4k**	39
4	**1d** (Me, Bn)	**2c** (H, *p*-Br-C_6H_4)	**4l**	49
5	**1a** (Me, Et)	**2c** (H, *p*-Br-C_6H_4)	**4m**	63
6	**1a** (Me, Et)	**2d** (H, Bn)	**4n**	51
7	**1c** (Me, *t*-Bu)	**2d** (H, Bn)	**4o**	50
8	**1c** (Me, *t*-Bu)	**2e** (Me, Ph)	**4p**	71
9	**1h** (*n*-Bu, Me)	**2e** (Me, Ph)	**4q**	49
10	**1a** (Me, Et)	**2e** (Me, Ph)	**4r**	52
11	**1f** (Et, Me)	**2f** (-$(CH_2)_4$-)	**4s**	52[c]
12	**1a** (Me, Et)	**2f** (-$(CH_2)_4$-)	**4t**	46[c]

[a] Reagents and conditions: **1a**–**d,f,h** (0.5 mmol), **2b**–**f** (0.6 mmol), DIPEA (0.6 mmol), CH_3CN (3 mL), rt, overnight. [b] Yield of pure isolated products. [c] CH_2Cl_2 was used as the solvent.

Scheme 3. Plausible Mechanism



2e also exhibited good reactivity and the relative pyrrolo-pyrazole derivatives **4n**–**r** were obtained in total regio- and stereoselective fashion (Table 3, entries 6–10). Interestingly, cyclohexanone malononitrile **2f** was successfully employed in the one-pot sequence, thus generating intriguing new N-bridged tricyclic heterocycles **4s** and **4t** (Table 3, entries 11 and 12).

All of the products **4a**–**t** are new compounds, with the structures deduced from their IR, mass, ^{1}H NMR, and ^{13}C NMR spectral data.[14]

A plausible mechanism for the formation of these novel pyrrolo-pyrazoles **4** is pictured in Scheme 3. The first step involves a facile deprotonation of vinyl malononitrile **2** to furnish vinylogous carbanion **I-1** which attacks DD **1** (regioselective γ Michael addition or VMcR) through the effect of a base. In the second step, the acidic proton adjacent to the ester group of hydrazonic Michael adduct **3** is abstracted by DIPEA to produce the azaallylic anion intermediate **I-2**. Similar intermediates have been described by De Kimpe et al. in their excellent review.[15] Then, **I-2** undergoes intramolecular (5-*exo*-trig) aza-Michael cyclization (AMcCR) to give the bicyclic intermediate **I-3**. Next, a subsequent (5-*exo*-dig) cyclization by the carbamic N-atom on a nitrile function (ACR) leads to the bicyclic imine intermediate **I-4**. Finally, the resulting **I-4** immediately tautomerizes to form the more stable amino pyrrolo-pyrazole **4**.

In conclusion, we have developed a novel, metal-free, and atom-economical method for the synthesis of fully decorated pyrrolo-pyrazole systems by the one-pot, domino transformation of DDs with VMs under mild conditions for the first time. The overall transformation may involve the following steps: vinylogous Michael addition (VMcR)/aza-Michael cyclization (AMcCR)/aza-cyclization (ACR)/imine-enamine tautomerization.[16]

Notably, the reactions are very highly chemo-, regio-, and stereoselective, simultaneously producing molecular complexity (two C–N bonds, one C–C bond, and two rings) from readily available substrates.

Moreover, the presence of different functional groups around the pyrrole-pyrazole core could furnish interesting points of postfunctionalization to give a wide range of useful intermediates that are difficult to obtain via other procedures.

Further investigations are underway in our laboratory to determine the applicability and usefulness of this reaction. We hope this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry.

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Supporting Information Available. Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) The structure of the obtained products **4** was assigned on the basis of the spectroscopic data of **4a**. In particular, the ^{1}H and ^{13}C NMR spectra of **4a** in either $CDCl_3$ or DMSO-d_6 exhibit some peculiarities: (i) one singlet at 5.87 ppm and two broad singlets at 5.03 and 6.06 ppm (all exchangeable with D_2O) attributed to the protons of the diagnostic primary amino (NH_2) and ureido ($CONH_2$) groups, respectively; (ii) two double doublets at 2.96 and 3.41 ppm ascribable to a CH_2 pattern in a strained pyrrole system where both geminal (^2J = 16.2 Hz) and homoallylic coupling (^5J = 1.4 and 2.4 Hz) were observed; (iii) the presence of two distinctive C-sp^3 signals at 41.2 ppm and 63.3 ppm attributed to methylene (CH_2) and quaternary (C) carbons, respectively; (iv) the presence of four C-sp^2 signals (155.8, 153.9, 107.5, and 76.2 ppm) assignable to the CC double bond of the bicyclic structure. In addition the mass spectrum of **4a** displayed a molecular ion peak at m/z = 353 [M$^+$].

(15) For a review on 1-azaallylic anions in heterocyclic chemistry, see: Mangelinckx, S.; Giubellina, N.; De Kimpe, N. *Chem. Rev.* **2004**, *104*, 2353–2399.

(16) Although the final yields of these reactions are apparently not very high, they can be considered good or excellent taking into account the multiple steps of the whole process.

The authors declare no competing financial interest.