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Lewis Acid-Catalyzed Synthesis of Functionalized Pyrroles

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Abstract: The synthesis of highly functionalized pyrroles is described. The sequence involves the preliminary preparation of α-aminohydrazones by Michael addition of primary amines to 1,2-diaza-1,3-butadienes. The treatment of these compounds with dialkyl acetylenedicarboxylates produces α-(*N*-enamino)-hydrazones that were converted into the corresponding pyrroles by Lewis acid-catalyzed ring closure. A screening of several Lewis/Brønsted acid catalysts was also performed.

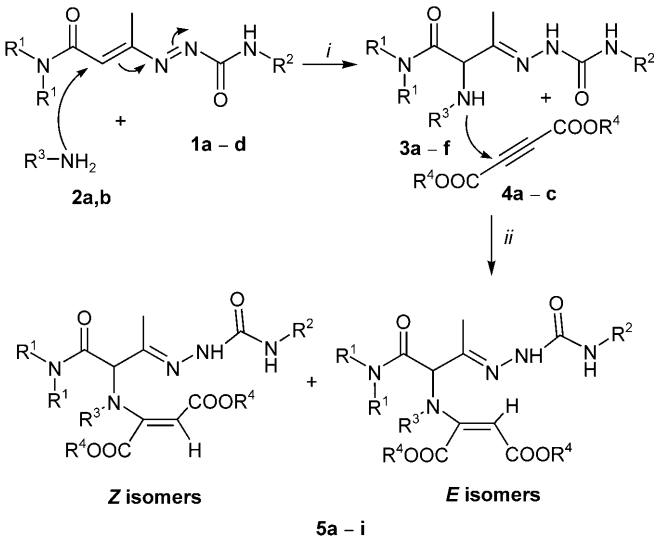
Keywords: alkynes; 1,2-diaza-1,3-butadienes; hydroamination; Lewis acids; Michael addition; pyrroles

Pyrroles are among the most studied heterocyclic ring systems due to their diverse biological activities and applications in materials science.[1,2] As a consequence, much attention has been paid to their preparation by classical methods such as the Knorr,[3] Hantzsch,[4] and Paal–Knorr[5] syntheses. However, these approaches usually present significant limitations in terms of substituents that can be introduced, the substitution pattern, or regioselectivity. Several recent variations in the formation of pyrrole rings are based on metal-catalyzed reactions[6] and catalytic multicomponent coupling methodologies[7] which can improve usefully the classical synthetic approaches.

We have demonstrated that the reactions between 1,2-diaza-1,3-butadienes and carbonyl compounds[8] or enol silyl derivatives[9] represent useful and convenient entries to 1-aminopyrroles. Here, we report a new and flexible Knorr-related strategy for the construction of amply functionalized pyrroles. The typical Knorr approach utilizes α-amino ketones and carbonyl derivatives containing an activated methylene group as starting materials.[3] A variation of this synthesis provides for the use of alkynes as reagents rather than carbonyl compounds.[10] In our methodology, the α-amino ketones are replaced with α-aminohydrazones. Their easy and flexible preparation involves the 1,2-diaza-1,3-butadienes **1a–d** that readily react with different primary amines **2a**, **b** in tetrahydrofuran at room temperature in the case of **1a–c**, or under reflux for **1d** producing the desired α-aminohydrazones **3a–f**. The reaction takes place by means of 1,4-hydroamination (Michael-type) of the amino derivatives **2a**, **b** to the azo-ene system of the 1,2-diaza-1,3-butadienes **1a–d**. (Scheme 1, Table 1).[8b,11]

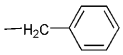
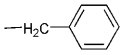
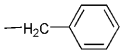
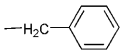
It is noteworthy that α-aminohydrazones are solid compounds and are appreciably more stable to storage and handling than α-amino ketones. In fact, no self-condensation of compounds **3** was observed.

In turn, the α-aminohydrazones **3a–f** reacted with dialkyl acetylenedicarboxylates **4a–c** in ethanol under reflux to give α-(*N*-enamino)-hydrazones **5a–i** in 2–



Scheme 1. Synthesis of the α-aminohydrazones **3a–f**, and α-(*N*-enamino)-hydrazones **5a–i**. *i*: THF, room temperature for **1a–c**; THF, reflux for **1d**. *ii*: EtOH, reflux.

Table 1. Yields of the α-aminohydrazones **3a–f**, α-(*N*-enamino)-hydrazones **5a–i** and pyrroles **8a–f**.

1	R^1	R^2	**2**	R^3	**3**	Yield [%][a]	**4**	R^4	**5**	*E* isomer Yield [%][b,c]	*Z* isomer Yield [%][b,c]	**8**	Yield [%][d]	Time [h]
1a	Me	H	**2a**		**3a**	83	**4a**	Et	**5a**	75	0	**8a**	87	0.5
1a	Me	H	**2b**		**3b**	91	**4a**	Et	**5b**	55	19	**8b**	90	0.5
1b	Me		**2a**		**3c**	97	**4a**	Et	**5c**	76	0	**8a**	91	0.6
1b	Me		**2a**		**3c**	97	**4b**	Me	**5d**	74	0	**8c**	86	0.5
1b	Me		**2a**		**3c**	97	**4c**	*t*-Bu	**5e**	66	0	**8d**	88	0.6
1b	Me		**2b**		**3d**	81	**4b**	Me	**5f**	68	25	**8e**	93	0.6
1b	Me		**2b**		**3d**	81	**4a**	Et	**5g**	80	14	**8b**	89	0.5
1c	Me		**2a**		**3e**	74	**4b**	Me	**5h**	56	0	**8c**	93	0.5
1d	Et	H	**2b**		**3f**	69	**4b**	Me	**5i**	57	28	**8f**	92	0.6

[a] Yield of the isolated purified compounds **3a–f** based on the 1,2-diaza-1,3-butadienes **1a–d**.
[b] Yield of the isolated purified compounds (*E*/*Z*) **5a–i** based on the hydrazones **3a–f**.
[c] The *E* and *Z* geometry was assigned on the basis of the chemical shifts of the vinylic proton and of the vicinal heteronuclear coupling constant between the esteric carbon and the vinylic ^{1}H nucleus.
[d] Yield of the isolated purified compounds **8a–f** based on α-(*N*-enamino)-hydrazones **5a–i**.

4 h as *E*/*Z* mixtures in good yields (Scheme 1, Table 1). The C=C bond geometry of compounds **5** was determined by NMR measurements, considering the vicinal heteronuclear coupling constant between the ester carbon and the vinylic proton. For the compound **5f**, chosen as a representative example, the *E* isomer was predominant (68%) showing a coupling constant of 9.3 Hz, while for the *Z* isomer (25%) the coupling constant value was 3.2 Hz, in good agreement with data reported in the literature.[12] Also the chemical shift of the vinylic proton can be diagnostic: 4.93 ppm for the (*Z*)-**5f** *versus* 5.20 ppm for the (*E*)-**5f** in complete agreement with the NMR data reported by Dolfini.[13] The same behaviour was observed for all compounds **5b**, **g**, **i** derived from the α-benzylaminohydrazones **3b**, **d**, **f**. The X-ray diffraction study of (*E*)-**5f** unambiguously supports the assigned structure. The compound **5f** crystallizes as an *N*-methylpyrrolidine solvate (Figure 1).[14] In the case of the α-(*N*-enamino)-hydrazones **5a**, **c–e**, **h**, derived from the α-cyclohexylaminohydrazones **3a**, **c**, **e**, the formation of only one isomer was observed. The heteronuclear coupling constant values between the ester carbon and the vinylic proton, that were in the range 10.4–12.0 Hz, confirmed the *E* configuration for these compounds.[12]

We then explored the conversion of the α-(*N*-enamino)-hydrazones **5a–i** into the corresponding pyrroles **8a–f** by acid-catalyzed intramolecular ring closure. The compound **5d** was chosen to test the catalytic activity by different types of Lewis/Brønsted acids in different solvents and temperatures (see Supporting Information). Among the different types of the tested acids, only the Lewis acids exhibited remarkable catalytic activity, and this occurrence is probably due to

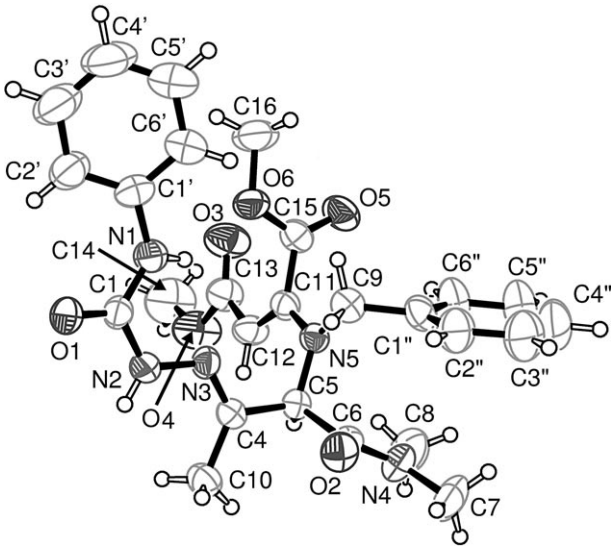
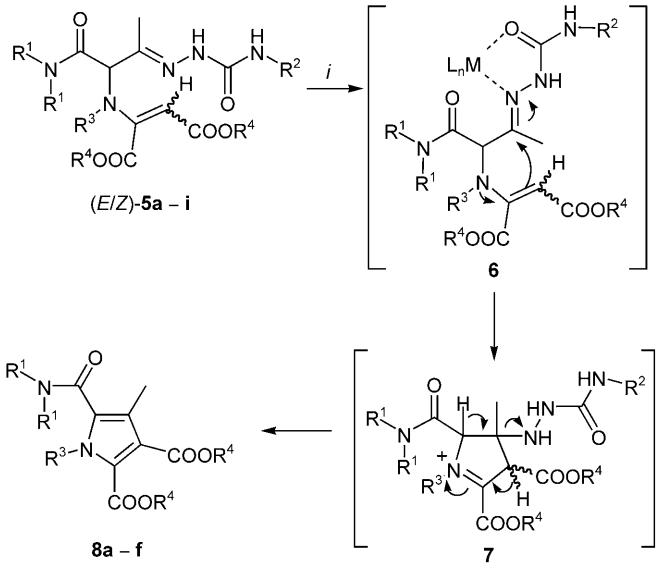
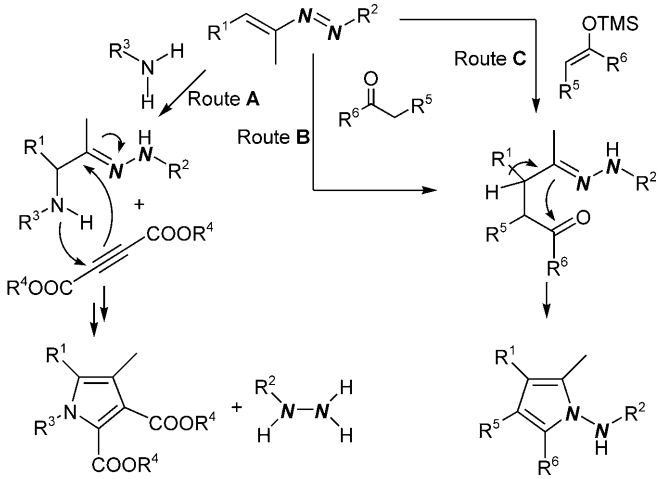


Figure 1. X-ray structure of compound (*E*)-**5f**·$C_5H_{11}N$. Ellipsoids for non-hydrogen atoms enclose 50% probability. *N*-Methylpyrrolidine has been omitted for clarity.



Scheme 2. Synthesis of the pyrroles **8a–f**. *i*: CH_2Cl_2, reflux, $Zn(TfO)_2$.



Scheme 3. Different approaches for the construction of pyrroles starting from 1,2-diaza-1,3-butadienes: Route **A** with primary amines and acetylenedicarboxylates. Route **B** with carbonyl compounds. Route **C** with enol silyl derivatives.

the chelation effect of the *N*-carbonylhydrazones towards metal catalysts (Scheme 2).[15] In particular, $ZnCl_2$, $Zn(TfO)_2$, $InCl_3$, $InBr_3$, $In(TfO)_3$ and $Yb(TfO)_3$ have furnished the best results in terms of yields (75–95%). Our choice of $Zn(TfO)_2$ was based on the lower reaction time (0.5 h) together with lower cost with respect to other tested catalysts. The choice of the solvent and temperature also played a crucial role. We have found that the use of dichloromethane under reflux is determinant in the Lewis acid-catalyzed ring closure. Thus, the use of these optimal conditions was extended to the conversion of the α-(*N*-enamino)-hydrazones **5a–i** into the corresponding pyrroles **8a–f**. The reaction proceeds by means of the intramolecular nucleophilic attack of the ene-amino carbon to the hydrazone moiety of the intermediate **6**, activated by coordination with the Lewis acid. This process produces the 4,5-dihydro-1*H*-pyrrole intermediates **7** that furnish the final aromatic 5-amidopyrroles **8**, by elimination of the hydrazino moiety (Scheme 2, Table 1). In this particular case, moreover, the Knorr equivalent starting α-amino-α-amido ketones are both not commercially available products and difficult to prepare by other methods.

Some differences in the construction of the pyrrole skeleton can be observed with respect to our previous synthesis. In fact, starting from 1,2-diaza-1,3-butadienes and carbonyl compounds[8] (Route **B**, Scheme 3) or enol silyl derivatives[9] (Route **C**, Scheme 3), we obtained *N*-substituted-aminopyrroles in which the pyrrole nitrogen is originally situated in the position two of the azo-ene system, while in this case the pyrrole nitrogen derives from the substituted amino reagents **2a**, **b** (Route **A**, Scheme 3). This fact permits an additional diversification site that can be easily introduced using a variety of amines.

In conclusion, this paper describes a smooth procedure to prepare α-(*N*-enamino)-hydrazones and then amply functionalized pyrroles. The advantage of the use of 1,2-diaza-1,3-butadienes as building blocks in the modelling of azaheterocycles is the stability and accessibility of the starting materials, as well as the mild conditions of the experimental procedures. Further investigations are presently in progress in order to improve the utility and application of this synthetic methodology.

Experimental Section

General Procedure for the Synthesis of α-Aminohydrazones 3a–f

To a solution of the 1,2-diaza-1,3-butadiene **1a–d** as a mixture of *E*/*Z* isomers (1.0 mmol) in tetrahydrofuran (10 mL), the cyclohexylamine **2a** or the benzylamine **2b** (1 mmol) was added. The reaction was allowed to proceed under magnetic stirring at room temperature for 2–4 h in the case of **1a–c**, or under reflux for 4 h in the case of **1d**, until the disappearance of the reagents (monitored by TLC). The solvent was then evaporated under reduced pressure. The products **3a–f** were purified by silica gel chromatography (elution mixture: ethyl acetate/cyclohexane) and they were crystallized from ethyl acetate (see Supporting Information).

3-[(Aminocarbonyl)hydrazono]-2-(cyclohexylamino)-*N*,*N*-dimethylbutanamide (3a): mp 124–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 0.77$–0.94 (m, 6H), 1.23–1.29 (m, 1H), 1.35–1.41 (m, 2H), 1.46–1.52 (m, 1H), 1.54 (s, 3H), 1.93–1.99 (m, 1H), 2.65 (s, 3H), 2.72 (s, 3H), 2.83 (brs, 1H), 3.99 (s, 1H), 5.86 and 6.21 (2 brs, 2H), 9.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 12.4$ (q), 24.7 (t), 24.8 (t), 26.0 (t), 33.1 (t), 33.4 (t), 36.0 (q), 36.9 (q), 54.7 (d),

61.8 (d), 147.9 (s), 159.0 (s), 170.6 (s) ppm; IR (nujol): ν_{max} = 3422, 3374, 3265, 3204, 1776, 1732, 1676 cm^{-1}; MS: *m/z* (%) = 283 (M^+) (16), 238 (74), 211 (100), 167 (31), 152 (11); anal calcd. for $C_{13}H_{25}N_5O_2$ (283.37): C 55.10, H 8.89, N 24.71; found: C 55.21, H 8.94, N 24.59.

General Procedure for the Synthesis α-(*N*-Enamino)-hydrazones 5a–i

To a solution of the α-aminohydrazones **3a–f** (1 mmol) in ethanol (20 mL) a stoichiometric amount of the dialkyl acetylenedicarboxylates **4a–c** (1 mmol) was added. The reaction mixture was refluxed for 2–4 h until the complete disappearance of the reagents (monitored by TLC). The solvent was then evaporated under reduced pressure. The products **5a–i** were purified by silica gel chromatography (elution mixture: ethyl acetate/cyclohexane) and they were crystallized from ethyl acetate. In the case of the α-(*N*-enamino)-hydrazones **5b**, **f**, **g**, **i** derived from the benzylamine **2b**, it was possible to separate the *E* and *Z* isomers, while for **5a**, **c–e**, **h**, derived from the cyclohexylamine **2a**, we have observed the exclusive formation of the *E* isomer (see Supporting Information).

Diethyl (2*E*)-2-({2-[(aminocarbonyl)hydrazono]-1-[(dimethylamino)carbonyl]propyl}(cyclohexyl)amino)but-2-enedioate (5a): mp 161–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.97–1.23 (m, 9H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.47–1.54 (m, 2H), 1.71–1.81 (m, 2H), 1.90 (s, 3H), 2.98 (s, 3H), 2.93 (s, 3H), 3.23–3.29 (m, 1H), 3.89–4.06 (m, 2H), 4.18–4.32 (m, 2H), 4.77 (s, 1H), 5.13 (s, 1H), 5.58 and 5.86 (2 brs, 2H), 9.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.8 (q), 14.2 (q), 25.4 (t), 25.8 (t), 26.0 (t), 30.9 (t), 31.1 (t), 35.9 (t), 37.0 (t), 59.1 (t), 61.4 (d), 61.8 (t), 64.0 (d), 91.2 (d), 144.0 (s), 153.1 (s), 157.8 (s), 166.0 (s), 167.4 (s), 167.8 (s); IR (nujol): ν_{max} = 3424, 3200, 1741, 1727, 1704, 1685, 1658 cm^{-1}; MS: *m/z* (%) = 453 (M^++1) (1), 408 (3), 378 (48), 349 (11), 334 (41), 306 (8), 262 (100), 239 (22), 193 (53); anal. calcd. for $C_{21}H_{35}N_5O_6$ (453.53): C 55.61, H 7.78, N 15.44; found: C 55.72, H 7.91, N 15.51.

General Procedure for the Synthesis of Pyrroles 8a–f

To a solution of the α-(*N*-enamino)-hydrazones **5a–i** (1.0 mmol) in dichloromethane (15 mL), a catalytic amount of $Zn(OTf)_2$ (0.2 mmol) was added. The reaction mixture was refluxed for 0.5–0.6 h, until the disappearance of the starting materials (monitored by TLC). The solvent was then evaporated under reduced pressure. The products **8a–f** were purified by silica gel chromatography (elution mixture: ethyl acetate/cyclohexane) and they were crystallized from ethyl acetate (see Supporting Information).

Diethyl 1-cyclohexyl-5-[(dimethylamino)carbonyl]-4-methyl-1*H*-pyrrole-2,3-dicarboxylate (8a): mp 143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.12–1.26 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.58–1.65 (m, 1H), 1.73–1.82 (m, 3H), 1.89–1.96 (m, 2H), 2.07 (s, 3H), 2.94 (s, 3H), 3.10 (s, 3H), 4.06–4.15 (m, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.32 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.2 (q), 13.9 (q), 14.2 (q), 24.9 (t), 26.0 (t), 26.3 (t), 31.3 (t), 33.2 (t), 34.7 (q), 38.1 (q), 59.8 (d), 60.1 (t), 61.6 (t), 116.1 (s), 118.8 (s), 126.7 (s), 127.7 (s), 162.9 (s), 164.4 (s), 164.5 (s) ppm; IR (nujol): ν_{max} = 1745, 1730, 1640 cm^{-1}; MS: *m/z* (%) = 378 (M^+) (45), 306 (100), 260 (71), 233 (100), 188 (67), 159 (100); anal. calcd. for $C_{20}H_{30}N_2O_5$ (378.46): C 63.47, H 7.99, N 7.40; found: C 63.29, H 8.04, N 7.51.

Supporting Information

Experimental details and spectroscopic characterization of all compounds are given in the Supporting Information.

Acknowledgements

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[14] CCDC 710574 contains the supplementary crystallographic data for the structure of **5f**·$C_5H_{11}N$ reported in 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.

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