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Design and Synthesis of Pyrrolotriazepine Derivatives: An Experimental and Computational Study

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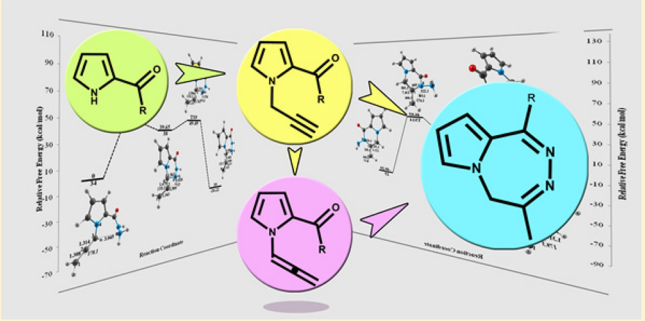
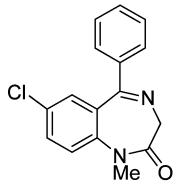
Supporting Information

ABSTRACT: The pyrrole derivatives having carbonyl groups at the C-2 position were converted to *N*-propargyl pyrroles. The reaction of those compounds with hydrazine monohydrate resulted in the formation of 5*H*-pyrrolo[2,1-*d*][1,2,5]-triazepine derivatives. The synthesis of these compounds was accomplished in three steps starting from pyrrole. On the other hand, attempted cyclization of a pyrrole ester substituted with a propargyl group at the nitrogen atom gave, unexpectedly, the six-membered cyclization product, 2-amino-3-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as the major product. The expected cyclization product with a seven-membered ring, 4-methyl-2,3-dihydro-1*H*-pyrrolo[2,1-*d*]-[1,2,5]triazepin-1-one was formed as the minor product and was converted quantitatively to the major product. The formation mechanism of the products was investigated, and the results obtained were also supported by theoretical calculations.

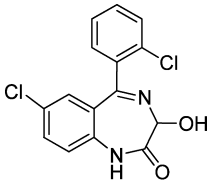


INTRODUCTION

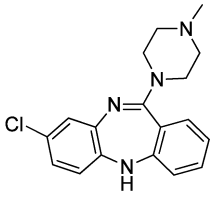
Nitrogen-containing heterocycles have attracted considerable attention, particularly due to their wide range of pharmacological activities. Benzodiazepines are among the most widely prescribed drugs for the treatment of anxiety and related disorders.[1] Further extensive investigation of seven-membered ring N-heterocycles led to the development of a number of pharmacologically active agents directed against the other diseases, such as cancer, HIV, and cardiac arrhythmia.[2]



1 Diazepam

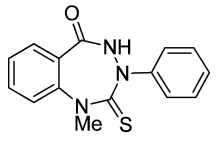


2 Lorazepam



3 Clozapine

Triazepine is a seven-membered heterocyclic compound with three nitrogen atoms, where the position of nitrogen atoms can vary. Various benzene-fused triazepine and triazepinone derivatives were synthesized, and furthermore, it was shown that a variety of biological activities and synthetic routes have been established for the related benzotriazepines.[3]



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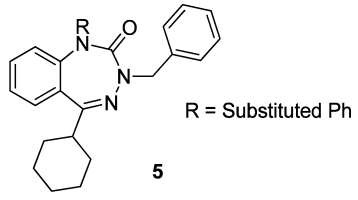

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For example, 2-thioxobenzotriazepinone derivative **4** was subjected to a ptosis test using clozapine (**3**) as a reference drug to evaluate its antipsychotic activity. It was found that **4** has the same antipsychotic activity as the reference drug clozapine, but with lesser side effects.[4] On the other hand, some 1,3,4-benzotriazepine derivatives, such as **5**, were found to be suitable as a nonpeptide parathyroid hormone-1 receptor (PTH1R) antagonist.[5] Recent 3D QSAR studies of various 1,3,4-

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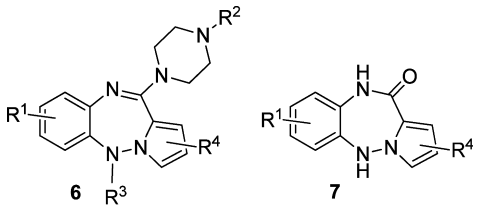
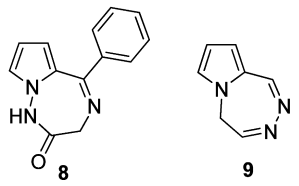
benzotriazepine derivatives showed their activity as a *cholecystokinin* (CCK_2) receptor antagonist.[6]

Because of the interest directed toward investigating the synthesis and activity of benzene-fused triazepine derivatives, we were interested in the synthesis of pyrrole-fused triazepine and triazepinone derivatives.



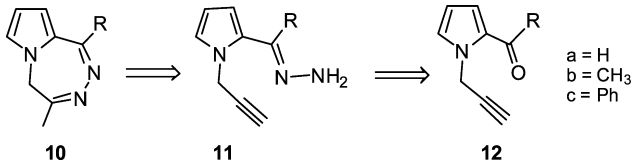


Pyrrolotriazepine derivatives are rarely found in the literature. Benzopyrrolotriazepine derivatives **6** and **7** are reported to be useful as neuroleptic agents in the treatment of psychotic disturbances, such as schizophrenia.[7,8] Unfortunately, in the literature, only a single pyrrole condensed triazepine skeleton **8** is reported. Some substituted derivatives of **8** showed analgesic activity in mice and anxiolytic and anticonvulsant activities.[9] In view of these important observations, we herein report a synthetic methodology leading to the synthesis of derivatives of a new class of compound, 5*H*-pyrrolo[2,1-*d*][1,2,5]triazepine **9**.

RESULTS AND DISCUSSION

Our planned approach to **10** involved metal-free cyclization of pyrrole hydrazone derivatives **11**, synthesized by the reaction of acylpyrroles **12** having an alkyne moiety attached to the nitrogen atom of pyrrole with hydrazine. The retrosynthesis is summarized in Scheme 1.

Scheme 1. Retrosynthesis of Pyrrolotriazepine Derivatives



For the synthesis of pyrrole-fused triazepine derivatives, the starting materials were prepared according to the literature. Pyrrole carbonyl compounds were prepared by application of the Vilsmeier reaction.[10] As depicted in Scheme 2, treatment of the heterocyclic building blocks **14a**–**14c** with propargyl bromide afforded the alkyne derivatives **12a**–**12c**.[11,12]

To the best of our knowledge, the facile construction of this new pyrrole-fused triazepine skeleton has not been previously explored. Heating of synthesized propargyl derivatives **12a**–**12c** with hydrazine monohydrate in methanol at reflux temperature produced the desired cyclization products **10a**–**10c**, which were isolated in good yields (63–69%) after chromatographic purification. The structures were determined by NMR spectral data. Full assignment of ^{1}H and ^{13}C NMR spectra was done in the case of **10a** using 1D- and 2D-NMR spectra (DEPT, COSY, HSQC, and HMBC). In particular, the HSQC and HMBC spectra of **10a** supported the proposed structure. The proton signals of H-5 and H-5′ appearing at 5.70 and 4.34 ppm correlate with the methylene carbon (C-5) at 53.8 ppm. Furthermore, a correlation between the C-1 and H-9 proton and the C-5 and H-7 proton in the HMBC spectrum supports the proposed structure. The other correlations are also in agreement with the structure **10a**.

A tentative mechanism of the formation of **10a**–**10c** is outlined in Scheme 3. It is proposed that the first step is the formation of hydrazones **11a**–**11c**. We assume that the terminal nitrogen atom of hydrazone cannot attack the triple bond because of the increased electron density. However, the terminal alkyne can undergo base-catalyzed isomerization[15] to give the terminal allenes **15a**–**15c**, where the hydrazine/H_2O mixture acts as a base. Since the central carbon in the allene moiety is electropositive, nucleophiles can easily attack this carbon atom, as depicted in Scheme 3. To support this proposal, the corresponding allene was synthesized independently and submitted to the cyclization reaction under the same reaction conditions (Scheme 4).

Propargyl aldehyde **12a** was reacted with NaH in DMF at 0 °C; the isomerized allene **18a** was isolated as the main product in 94% yield (Scheme 4). The structure was determined by NMR spectral data. The allenic proton =CH− resonated at 8.05 ppm as a triplet and the =C=CH_2 protons at 5.44 as a doublet. The measured coupling constant between the allenic protons of ^4J = 6.6 Hz clearly indicated the formation of an allene structure. Furthermore, the resonance frequencies observed at 202.0, 98.6, and 87.4 ppm in the ^{13}C NMR spectrum fully supported the formation of an allene structure. The isolated allene **18a** was reacted with hydrazine monohydrate under the same reaction conditions as reported for the reaction with alkynes, and the same cyclization product **10a** was formed in 65% yield. This finding supported the formation of an allenic structure as an intermediate in the formation of pyrrole-fused triazepine derivatives **10a**–**10c**.

After successful completion of the synthesis of triazepine derivatives **10a**–**10c**, we turned our attention to the synthesis of pyrrolotriazepinone scaffold **19**. Thus, triazepine derivative **10a** was submitted to SeO_2 oxidation in dioxane (Scheme 5). Unfortunately, only dicarbonyl compound **20** was formed as an isolable product in 62% instead of the targeted oxidation product **19**. The structure of dicarbonyl compound **20** was established beside the spectral data by independent synthesis of **20** by the reaction of pyrrole aldehyde **14a** with chloroacetone in the presence of K_2CO_3. Reaction of dicarbonyl compound **20** with hydrazine monohydrate provided the cyclization product **10a** in 51% yield.

1-(2-Oxopropyl)-1*H*-pyrrole-2-carbaldehyde (**20**) looks to be formed by hydrolysis of the starting material **10a**. However, it has been shown that triazepine **10a** is stable under the reaction conditions. We proposed the following mechanism for the formation of **20** (Scheme 6).

It is proposed that SeO_2 undergoes a [2 + 4] cycloaddition reaction with the diazine unit in **10a** to form a selenino lactone **21**. This intermediate can easily undergo nitrogen extrusion, which is observed during the reaction. At the final step, oxidation of C−Se to a C−O bond takes place. This mechanism is strongly supported by a recent observation that 1,3-diene systems form *syn*-1,2- and *syn*-1,4-diols upon reaction

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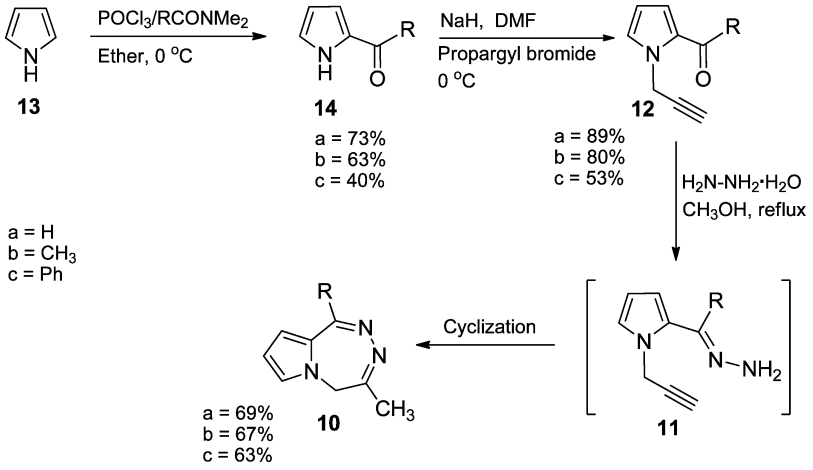
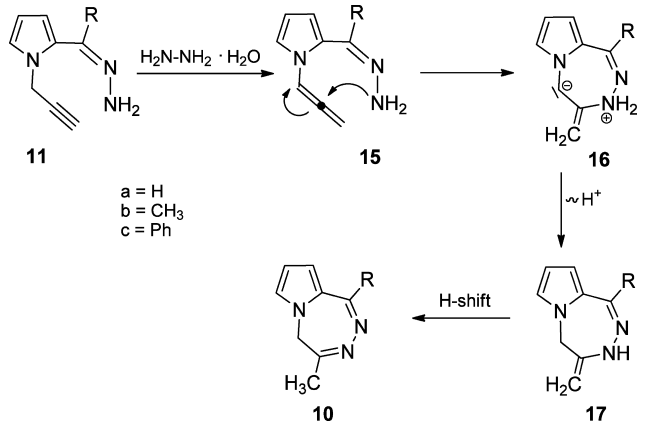
Scheme 2. Synthesis of Pyrrole-Fused Triazepines



Scheme 3. Mechanism for the Formation of Pyrrolotriazepine Derivatives 10a–10c



with SeO_2, where the involvement of cyclic selenites is proposed.[16]

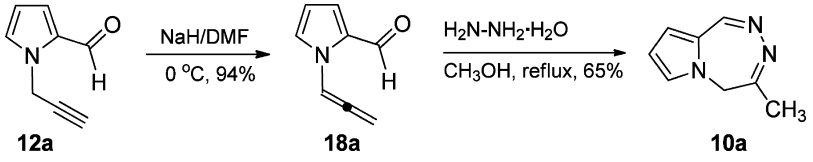
After failure of the oxidation reaction of **10a** with selenium dioxide to give triazepinone derivatives, we turned our attention to construction of the desired heterocyclic scaffold by intramolecular ring cyclization reaction of a propargyl ester **24**[17] with hydrazine monohydrate. The key compound, propargyl ester **24**, was synthesized in high yield from the reaction of methyl 1*H*-pyrrole-2-carboxylate **23**[18] with propargyl bromide in the presence of NaH as a base (Scheme 7). The next step was to investigate cyclization to the corresponding triazepinone derivative **26**. Indeed, this expected product **26** was formed only in 16% yield. However, a cyclization product **25** with a pyrrolopyrazinone structure was formed as the major product in 62% yield. The structures were proven by NMR spectral data. Further structural proof of the presence of a $-NH_2$ group was obtained when the product **25** was reacted with benzaldehyde in methanol. Two regioisomeric condensation products were formed in a ratio of 9:1. Careful examination of the reaction mixture did not reveal the formation of any trace of **26**. Finally, to test the feasibility of converting the allene **28** to **25**, the propargyl ester **24** was isomerized to the corresponding allene **28** in the presence of NaH in DMF. The allene **28** was obtained in high yield and submitted to cyclization reaction with hydrazine monohydrate. Again, the six-membered cyclization product **25** was formed as the sole product in 96% yield. It was interesting to observe that the cyclization reaction took place with the less reactive nitrogen atom, which is in conjugation with the carbonyl group.

Furthermore, we noted that the triazepinone derivative **26** was smoothly rearranged to the six-membered ring isomer **25** in quantitative yield upon standing at room temperature in chloroform for 3 days. The calculations show that the isomer **25** is 4.28 kcal/mol more stable than the isomer **26** in methanol. We assume that this rearrangement is catalyzed by the trace amount of acid present in chloroform. A tentative mechanism for the rearrangement is given in Scheme 8. The more nucleophilic nitrogen atom in **29** may attack the carbonyl group to form a diaziridine intermediate **30**, which can easily rearrange to the six-membered ring **25** during the regeneration of the carbonyl group.[19]

Finally, we focused our attention on cyclization of ketoester **31**, synthesized by reaction of **23** with chloroacetone in the presence of K_2CO_3. The reaction of **31** with hydrazine monohydrate at the reflux temperature of methanol resulted in the formation of diazine derivative **32** (Scheme 9). The desired product **26** was not formed. Because of the difference in reactivity of the carbonyl groups in **31**, intermolecular condensation was preferred over the intramolecular cyclization reaction.

Theoretical Calculations. Formation of pyrrolotriazepine **10**, pyrrolopyrazine **25**, and pyrrolotriazepinone **26** derivatives was computationally investigated in an effort to clarify the mechanism. Geometrical parameters of reactants, intermedi-

Scheme 4. Isomerization of 12a to Allene 18a and Its Reaction with Hydrazine



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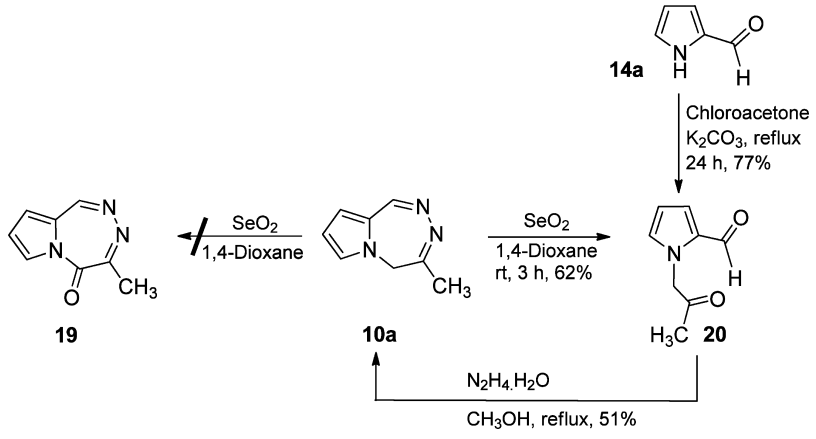
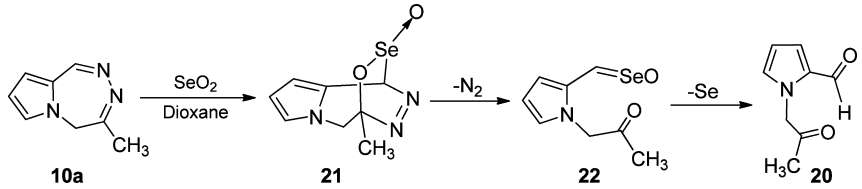
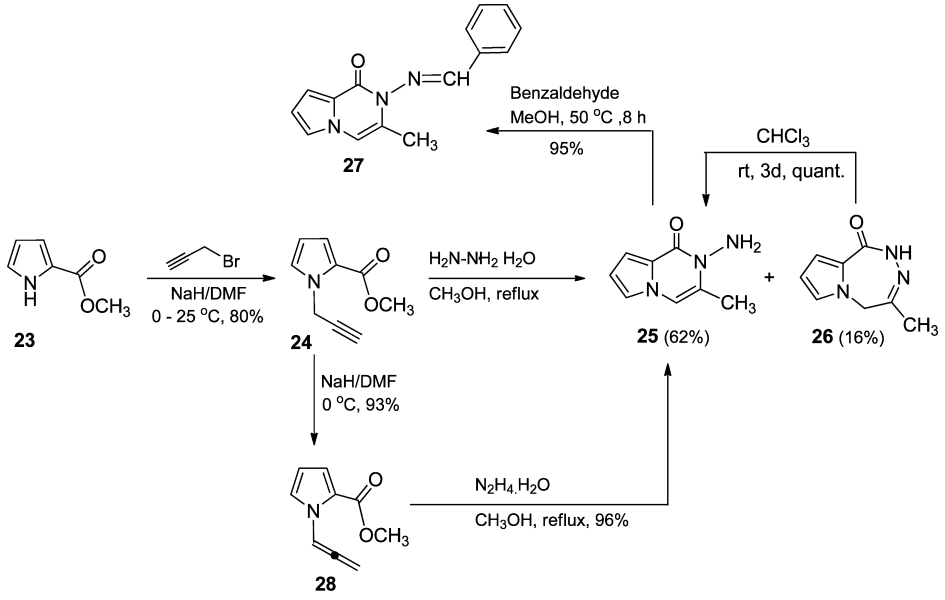
Scheme 5. Oxidation of Pyrrolotriazepine 10a with SeO_2



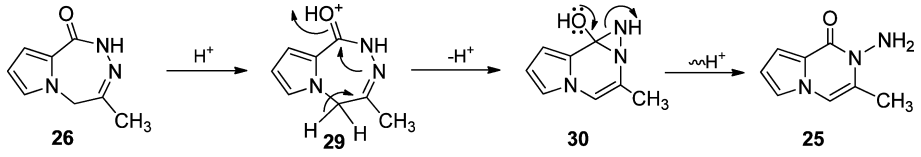
Scheme 6. Tentative Mechanism for the Formation of 20



Scheme 7. Reaction of Pyrrolepropargyl Ester 24 with Hydrazine



Scheme 8. Tentative Mechanism for Rearrangement of 26 to 25



ates, transition states (**TS**), and products were fully optimized in the gas phase (for isolated molecules) with the hybrid density functional B3LYP[20,21] (Becke-3-parameter–Lee–Yang–Parr) method using the 6-31+G(d,p) basis set implemented in Gaussian 09,[22] for all structures, except otherwise indicated. The solvent effect was considered implicitly employing the polarizable continuum[23] model (PCM)[23,24] with single-point energy calculations at the optimized geometries of B3LYP/6-31+G(d,p), namely, PCM/B3LYP/6-31+G(d,p)//B3LYP/6-31+G(d,p). All possible cyclization pathways have been considered in order to shed light

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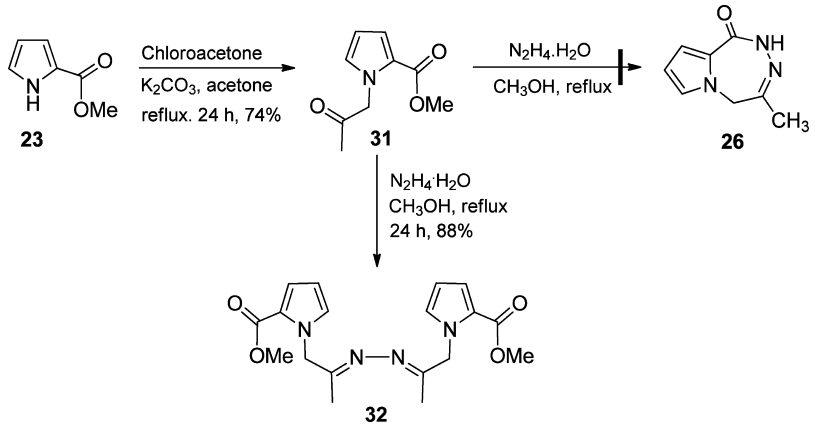
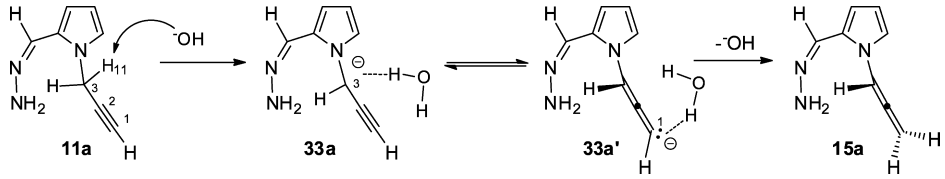
Scheme 9. Reaction of Methyl *N*-Acetonylpyrrolecarboxylate 31 with Hydrazine



Scheme 10. Mechanism for the Propargyl−Allene Isomerization



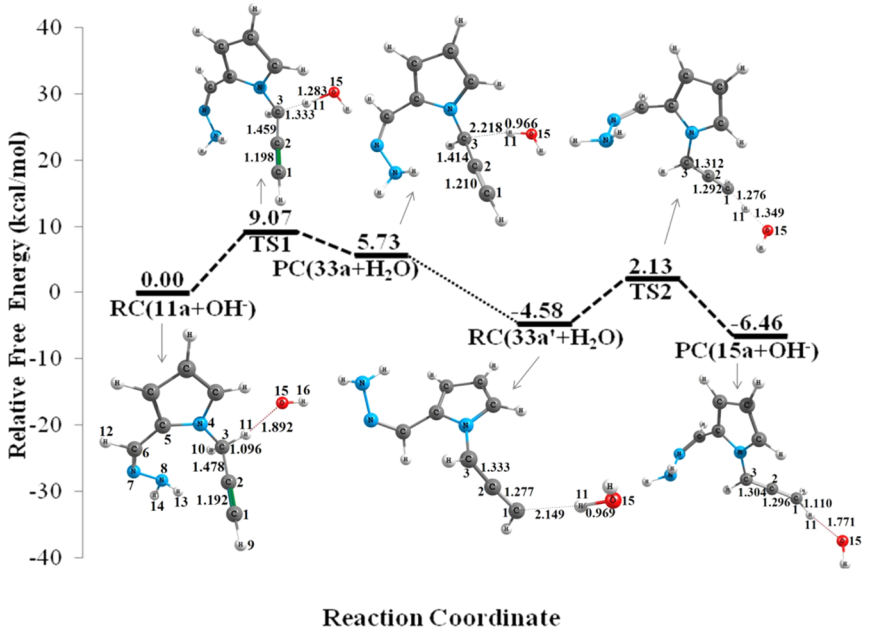


Figure 1. Potential energy profile related to the propargyl−allene isomerization at the PCM/RHF/6-31+G(d))//RHF/6-31+G(d) level in methanol. (Polarization effect of the solvent was considered implicitly.) Distances are given in angstroms; angles are in degrees.

on the mechanism. Computational details are given in the Supporting Information.

Propargyl−Allene Isomerization. Prior to the cyclization mechanism, we first modeled the propargyl−allene isomerization from **11a** to **15a** proposed in Scheme 3. Prototropic isomerization processes generally consist of two-stage transformations including carbanions as intermediates.[25] In unsubstituted MeC≡CH, although the most acidic proton is known to be the proton attached to the sp-hybridized carbon atom, the process also depends on the relative stability of the anions formed, and proton abstraction from the sp^3-hybridized carbon atom is sometimes possible. In addition, in heteropropargyl systems, allene isomers can be more stable than the propargyl isomer.[26] The B3LYP/6-31+G(d,p) calculations show that the allene isomer **15a** is about 8.23 and 7.43 kcal/mol (in the gas phase and methanol, respectively) more stable than the propargyl isomer **11a**. Vitkovskaya et al.[25] proposed a propargyl−allene isomerization mechanism that includes the abstraction of a proton with a hydroxide ion from the sp^3-hybridized carbon atom. Similarly, we assume that propargyl−allene isomerization starts with the abstraction of H-11 attached to the sp^3-hybridized carbon atom by a hydroxide ion (formed from the proton abstraction of water by hydrazine) (Scheme 10). The resulting anion is stabilized by the electron-

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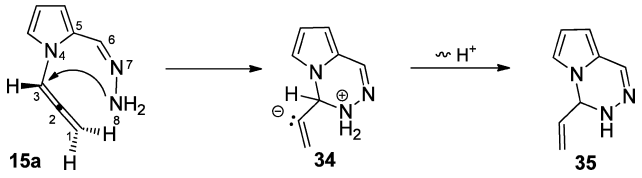
withdrawing effect of the adjacent pyrrole nitrogen as well as the intermolecular hydrogen bonding with water. The potential energy profile of this two-step process was obtained using RHF/6-31+G(d) since the B3LYP/6-31+G(d,p) method could not optimize the desired transition states (Figure 1).

In the first step, one of the methylene protons is abstracted by a hydroxide ion, forming a complex between **33a** and H_2O. Product complex PC (**33a** + H_2O) is less stable compared to reactant complex RC (**33a′** + H_2O) due to the interactions of H_2O with different carbon atoms, namely, with C-3 in **33a** and with C-1 in **33a′**. In the second step, the carbanion **33a′** abstracts a proton from H_2O to generate the corresponding allene **15a**. The small activation energies in Figure 1 and experimental evidence for the conversion of **18a** to **10a** (Schemes 10 and 4) strongly support our proposal (Scheme 3) that cyclization takes place through allene intermediate **15a**.

Cyclization of 15a. According to the experimental proposal in Scheme 3, the cyclization process occurs via the nucleophilic attack of N8 on the most electrophilic carbon C-2 on the allene moiety to give **10a**. Mulliken charges calculated at the B3LYP/6-31+G(d,p) level on atoms C-3, C-2, and C-1 are −0.160, 0.224, and −0.603, respectively. However, since the attack of N8 on the less electropositive carbon C3 leads to the formation of a stable six-membered ring **35**, we also investigated this reaction, and it is described below (Scheme 11). The Gibbs free activation barrier associated with the cyclization step was found to be 51.82 and 41.78 kcal/mol in the gas phase and methanol, respectively (for the potential energy profile, see the Supporting Information).

Scheme 11. Formation Mechanism of 35



Formation of 10a from 15a. After the formation of allene structure **15a**, the nucleophilic attack of N8 on the C2 atom via **TS3** takes place, and subsequent proton transfer, followed by a 1,3-H shift, leads to the desired product as described below. During the formation of the C2−N8 bond, the bond distance changed from 4.226 to 1.520 Å, where the elongation of the C2−C3 bond from 1.314 to 1.394 Å and of the C1−C2 bond from 1.308 to 1.368 Å in **15a** and **16a**, is observed (Figure 2). This indicates the transfer of π-bond electrons to both C1 and C3 carbon atoms. The Gibbs free activation energy barrier was found to be 30.46 and 28.65 kcal/mol in the gas phase and methanol, respectively.

The next step is the proton transfer from N8 to the C3. For this process, the explicit consideration of solvent molecules plays an important role because the solvent molecules may function as a proton channel.[26,27] Therefore, this step was modeled with the assistance of methanol, which was used as a solvent in our experimental study. The Gibbs free energy barrier with respect to **15a** was predicted to be 26.33 kcal/mol in methanol. The last step (1,3-H shift from N8 to C1) was also modeled with the assistance of methanol and exhibited a more stable transition state. Collectively, the first step is the rate-determining step, and the formation of triazepine **10a** is plausible as experimentally observed.

Reaction of 24 with Hydrazine. We assume that the first step is the formation of hydrazide **36**, formed from the reaction of **28** with hydrazine, followed by a cyclization reaction. For those reactions, there are two possible nucleophilic centers in **36**, namely, N7 and N8, and three possible electrophilic centers of the allene moiety, namely, C1, C2, and C3. Mulliken charges of C1, C2, and C3 in **36** (−0.693, 0.308, and −0.059) show that C1 is much less electrophilic than C3 and C2. Therefore, the C1 position of the allene is not susceptible to the nucleophilic attack of N8, leading to the eight-membered

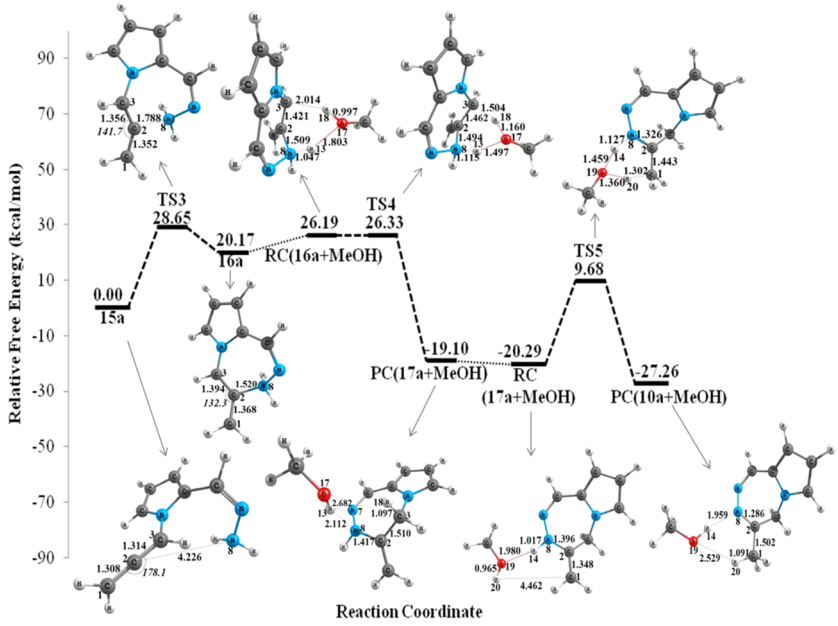


Figure 2. Potential energy profile related to formation of pyrrolotriazepine derivative **10a** at the PCM/B3LYP/6-31+G(d,p)//B3LYP/6-31+G(d,p) level in methanol. The effect of methanol was considered both implicitly and explicitly. (Relative energies shown for **15a**, **TS3**, and **16a** include Gibbs free energy of methanol.)

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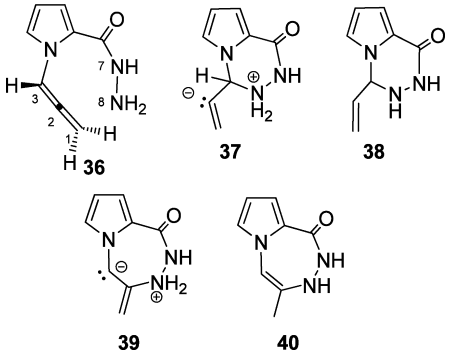
heterocyclic product not being taken into account. Thus, nucleophilic attacks of the more nucleophilic N8 on C2 and C3 centers were investigated. The nucleophilic attack of the less nucleophilic atom N7 on the most electrophilic center of the allene moiety, which results in the formation of a six-membered product **25**, is also considered.



Formation of 38. The first step is the formation of the unstable zwitterionic intermediate **37** and exhibits a high Gibbs free energy barrier (49.49 kcal/mol) in methanol (for the potential energy profile, see the Supporting Information). Thus, the path from **36** to **38** is not plausible since transition states of both steps are quite unstable, leading to high barriers.

Formation of 26. This path is proposed based on the intramolecular attack of N8 to C2 of **36**. The first step includes cyclization of **36**, giving rise to a seven-membered heterocyclic intermediate with activation energies of 34.03 and 31.63 kcal/mol in the gas phase and methanol, respectively (Figure 3). As N8 attacks with its lone pair of electrons on the electron-deficient C2 of the allene moiety, the C5−N4−C3−C2 dihedral angle alters from 11.2° in **36** to −164.3° in **39**. The C1−C2−C3 angle decreased from 178.2° to 143.2° and 136.7° in **36**, **TS6**, and **39**, respectively, which demonstrated the change in the hybridization of C2. From the attack of N8 on C2 in **36**, the isomeric triazepinone derivative **40** might also form. However, the calculations show that **26** was about 10.59 kcal/mol more stable than **40** in methanol.

The second step of the formation of triazepinone derivative **26** takes place via the six-membered transition state **TS7** with the assistance of methanol. The Gibbs free energy barrier with respect to **36** was predicted to be 34.00 kcal/mol in methanol. The third step was initially optimized without the assistance of methanol, and the activation barrier was found to be quite high (50.02 kcal/mol in the gas phase). Thus, it was also modeled with the assistance of methanol via six-membered **TS8**. The activation barrier decreased to 34.18 and 29.91 kcal/mol in the gas phase and methanol, respectively. This step had a higher activation barrier compared to the first and second steps; however, when the overall reaction coordinate is considered, the rate-determining step is considered to be the second step, with an energy barrier of 34.0 kcal/mol relative to the reactants. The overall process is quite exergonic, with an energy of 33.05 kcal/mol.

Formation of 25. The reaction starts with a nucleophilic attack of the N7 on the C2 of the allene moiety. According to the Mulliken charges, N7 (−0.244) is less nucleophilic than N8 (−0.670). However, we also modeled this path because it was expected to produce a stable six-membered structure **25**, which was experimentally observed to be the main product.

The first step of the formation of pyrrolopyrazine has 32.89 kcal/mol activation barrier in methanol, whereas the transition state **TS10** involving the methanol-assisted proton transfer from N7 to C1 is 33.70 kcal/mol higher than the initial reactant. The overall process is quite exergonic with an energy of 37.26 kcal/mol in methanol. Considering the comparable relative energies in Figures 3 and 4, we presume that formation of both **26** and **25** is plausible at the reflux conditions in methanol. However, **25** is thermodynamically more stable than **26** by 4.28 kcal/mol. The fact that **26** smoothly rearranges to **25** in chloroform at room temperature supports this finding.

In conclusion, a practical three-step synthesis for *5H*-pyrrolo[2,1-*d*][1,2,5]triazepine derivatives has been developed

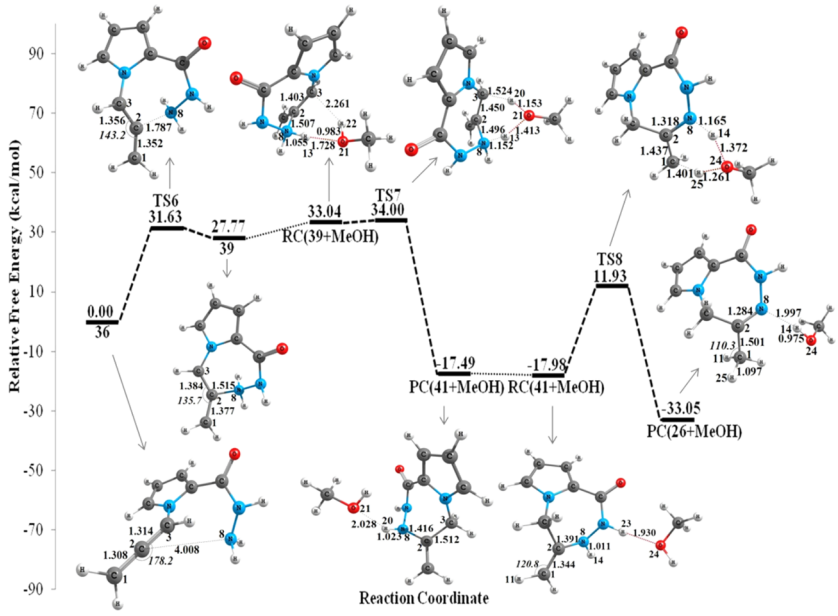


Figure 3. Potential energy profile related to formation of pyrrolotriazepinone derivative at the PCM/B3LYP/6-31+G(d,p)//B3LYP/6-31+G(d,p) level in methanol. The effect of methanol was considered both implicitly and explicitly. (Relative energies shown for **36**, **TS6**, and **39** include Gibbs free energy of methanol.)

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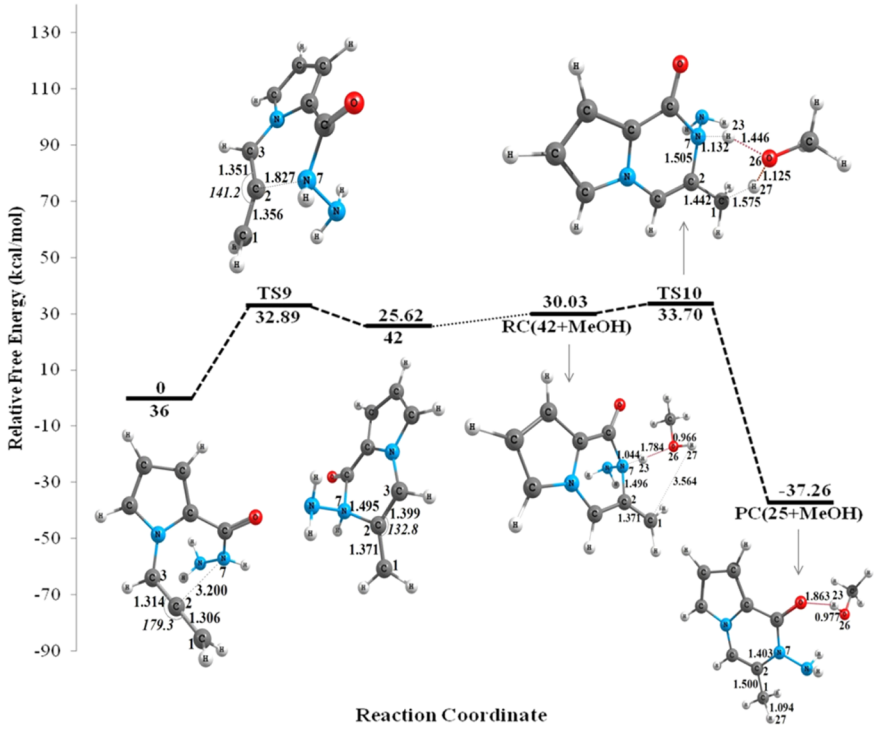

Figure 4. Potential energy profile related to formation of pyrrolopyrazine derivative at the PCM/B3LYP/6-31+G(d,p)//B3LYP/6-31+G(d,p) level in methanol. The effect of methanol was considered both implicitly and explicitly. (Relative energies shown for **36**, **TS9**, and **42** include Gibbs free energy of methanol.)

starting from pyrrole. The pyrrole derivatives having carbonyl groups at the C-2 position were converted to *N*-propargyl pyrroles. The reaction of those compounds with hydrazine monohydrate resulted in the formation of 5*H*-pyrrolo[2,1-*d*][1,2,5]triazepine derivatives. Mechanistic studies indicated that the propargyl group first undergoes isomerization to give the corresponding allene, which can be trapped by nucleophilic attack of the nitrogen atom of the initially formed hydrazones. On the other hand, the reaction of ester **24** with hydrazine monohydrate gave, unexpectedly, the six-membered cyclization product **25** as the major product. However, the desired cyclization product **26** was formed in 16% yield, which rearranged to the thermodynamically more stable compound **25**. The formation mechanism of the products was investigated, and the results obtained were also supported by theoretical calculations.

EXPERIMENTAL SECTION

1-(Prop-2-yn-1-yl)-1*H*-pyrrole-2-carbaldehyde (12a). To a stirred solution of $POCl_3$ (23.1 g, 0.15 mol) and DMF (12.0 g, 0.16 mol) in dry ether (100 mL) was added pyrrole (**13**) (10.0 g, 0.15 mol) dropwise at 0 °C. The mixture was stirred at room temperature for 16 h. After completion of the reaction, the saturated solution of $NaHCO_3$ was added until a basic medium was obtained. The reaction mixture was extracted with EtOAc (4 × 25 mL). The extracts were washed with brine (3 × 15 mL) and dried over $MgSO_4$, and the solvent was evaporated to give 1*H*-pyrrole 2-carbaldehyde (10.35 g, 73%) (**14a**), which was used without further purification for the next step. To a solution of pyrrole-2-carbaldehyde (10.35 g, 0.11 mol) (**14a**) in DMF (85 mL) was added NaH (60%, 4.32 g, 0.18 mol) at 0 °C portionwise over 1 h. The resulting mixture was stirred at 0 °C for 0.5 h, and to the reaction flask was added a solution of propargyl bromide (17.02 g, 0.14 mol) in DMF (30 mL) dropwise over 0.5 h. The reaction mixture was stirred at room temperature for 16 h, and after adding water (50 mL), the mixture was extracted with EtOAc (4 × 25 mL). The extracts were washed with brine (6 × 15 mL), dried over $MgSO_4$, and evaporated. The crude product was chromatographed on silica gel eluting with hexane/EtOAc (5/1) to give **12a** as a yellow liquid (11.01 g; isolated yield: 75%; crude yield: 89%).[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (bd, J = 1.2 Hz, 1H, CHO), 7.20−7.19 (m, 1H, H-5), 6.90 (dd, $J_{5,4}$ = 4.0, $J_{3,4}$ = 1.6 Hz, 1H, H-3), 6.22 (dd, $J_{4,3}$ = 4.0, $J_{4,5}$ = 2.4 Hz, 1H, H-4), 5.14 (d, J = 2.6 Hz, 2H, CH_2), 2.39 (t, J = 2.6 Hz, 1H, C≡CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5, 131.1, 130.4, 124.9, 110.1, 77.8, 74.4, 38.1.

1-(1-(Prop-2-yn-1-yl)-1*H*-pyrrol-2-yl)ethanone (12b). To a stirred solution of $POCl_3$ (16.2 g, 0.1 mol) and dimethyl acetamide (DMA) (10.44 g, 0.12 mol) in dry ether (100 mL) was added pyrrole (10.0 g, 0.15 mol) dropwise at 0 °C. The mixture was stirred at room temperature for 16 h. The reaction mixture was worked up as described above to give the acetyl compound **14b** (6.98 g, 63%), which was used without further purification for the next step. To a solution of **14b** in DMF (75 mL) was added NaH (60%, 2.53 g, 0.11 mol) at 0 °C portionwise over 1 h. The resulting mixture was stirred at 0 °C for 0.5 h, and to the reaction flask was added a solution of propargyl bromide (80% in xylene, 10.21 g, 0.086 mol) in DMF (30 mL) dropwise over 0.5 h. The reaction mixture was stirred at room temperature for 16 h, and after adding water (50 mL), the mixture was extracted with EtOAc (4 × 25 mL). The extracts were washed with brine (4 × 15 mL), dried over $MgSO_4$, and evaporated. The crude product was chromatographed on silica gel eluting with hexane/EtOAc (5/1) to give **12b** as an orange-yellow liquid (6.45 g; isolated yield: 69%; crude yield: 80%).[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, $J_{5,4}$ = 2.4 Hz, $J_{5,3}$ = 2.0 Hz, 1H, H-5), 6.92 (dd, $J_{3,4}$ = 4.0 and $J_{3,5}$ = 2.0 Hz, 1H, H-3), 6.12 (dd, $J_{4,3}$ = 4.0 and $J_{4,5}$ = 2.4 Hz, 1H, H-4), 5.15 (d, $J_{6,8}$ = 2.6 Hz, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.36 (t, $J_{8,6}$ = 2.6 Hz, 1H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 129.0, 128.2, 119.5, 107.6, 77.2, 72.9, 37.8, 26.1.

Phenyl(1*H*-pyrrol-2-yl)methanone (14c). Pyrrole (4.7 g, 70 mmol), phosphorylchloride (10.7 g, 70 mmol), and *N*,*N*-dimethylbenzamide (10.44 g, 70 mmol) were dissolved in ethylene chloride (25 mL) in a 100 mL round-bottom flask. The resulting mixture was stirred at 60 °C for 18 h. After cooling to room temperature, water and

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a solution of K_2CO_3 were added slowly to the reaction mixture until the pH of the solution reached a value of pH = 7. The mixture was extracted with ethyl acetate (3 × 30 mL). After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with hexane/ethyl acetate (2:1) to give dark green crystals of **14c**,[13] (mp 74−75 °C; Lit. 78−79 °C[14]) (7.2 g, 40%), which were used for the next reaction.

Phenyl(1-(prop-2-yn-1-yl)-1*H*-pyrrol-2-yl)methanone (12c). Pyrrole derivative **14c** (1.0 g, 5.86 mmol) was dissolved in dimethylformamide (DMF) (30 mL). NaH (0.14 g, 5.86 mmol) was added to the solution, and the mixture was stirred in a ice bath for 30 min. Gas evolution was observed. After completion of the reaction, propargyl bromide (0.87 g, 6.2 mmol) in DMF (5 mL) was added dropwise at room temperature, and the solution was stirred for 24 h. Water was (50 mL) added, and the solution was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was evaporated to give a crude product (1.12 g), which was purified by column chromatography eluting with EtOAc/hexane (4:1). As the first fraction, the pyrrole derivative **12c** was isolated as a dark brown liquid (0.65 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.71 (m, 2H, aromatic), 7.45 (tt, J = 7.4 and 1.3 Hz, 1H, aromatic), 7.39−7.34 (m, 2H, aromatic), 7.22 (dd, J = 2.6 and 1.7 Hz, H-5), δ 6.70 (dd, J = 4.0 and 1.7 Hz, 1H, H-3), 6.14 (dd, J = 4.0 and 2.6 Hz, 1H, H-4), 5.22 (d, J = 2.5 Hz, 2H, CH_2), 2.38 (t, J = 2.5 Hz, 1H, C≡CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.4, 137.4, 129.2, 127.4, 126.8, 125.7, 121.2, 106.4, 75.9, 71.7, 36.3; IR (ATR, cm^{-1}) 1622, 1574, 1524, 1407, 1343, 1237, 1139, 1081, 1024; HRMS Calcd for $C_{14}H_{11}NO$ $[M + H]^+$: 210.0913; Found: 210.0904.

Phenyl(1-(propa-1,2-dien-1-yl)-1*H*-pyrrol-2-yl)methanone (18c). The second fraction gave the allene derivative (0.27 g, 22%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (t, J = 6.5 Hz,1H, HC═C═C), 7.71−7.69 (m, 2H, aromatic), 7.44 (tt, J = 7.3 and 1.3 Hz, 1H, aromatic), 7.37−7.33 (m, 2 H, aromatic), 7.17 (dd, J = 2.8 and 1.6 Hz, H-5), 6.68 (dd, J = 3.9 and 1.6 Hz, 1H, H-3), 6.15 (dd, J = 3.9 and 2.8 Hz, 1H, H-4), 5.42 (d, J = 6.5 Hz, 2H, C═C═CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 186.4, 139. 7, 131.7, 129.7, 129.2, 128.1, 127.7, 124.2, 110.1, 99.4, 87.0; IR (ATR, cm^{-1}) 1623, 1573, 1446, 1407, 1340, 1239, 1023; HRMS Calcd for $C_{28}H_{22}N_2NaO_2$ $[2M + Na]^+$: 441.1580; Found: 441.1599.

4-Methyl-5*H*-pyrrolo[2,1-*d*][1,2,5]triazepine (10a). To a solution of carbaldehyde **12a** (0.5 g, 3.7 mmol) in methanol (7 mL) was added hydrazine monohydrate (0.92 g, 18.5 mmol). The reaction mixture was heated at reflux temperature for 48 h. After completion of the reaction, water (20 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL), and then the extracts were dried over $MgSO_4$. Evaporation of the solvent and purification of the yellow residue by silica gel chromatography with hexane/EtOAc (1/1) as eluent afforded a yellow powder **10a** (0.38 g 69%) (mp 219−221 °C) from chloroform/hexane (5/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H, H-1), 6.68 (dd, $J_{7,8}$ = 2.4 and $J_{7,9}$ = 2.0 Hz, 1H, H-7), 6.21 (dd, $J_{9,8}$ = 4.0 and $J_{9,7}$ = 2.0 Hz, 1H, H-9), 6.05 (dd, $J_{8,9}$ = 4.0, $J_{8,7}$ = 2.4 Hz, 1H, H-8), 5.70 (bd, A-part of AB-system, J = 18.0 Hz, 1H, H-5), 4.34 (bd, B-part of AB-system, J = 18.0 Hz, 1H, H-5′), 1.62 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3 (C-4), 151.3 (C-1), 129.8 (C-7), 127.1 (C-10), 120.4 (C-9), 109.4 (C-8), 53.8 (C-5), 19.3 (CH_3); IR (ATR, cm^{-1}) 2914, 1623, 1590, 1525, 1463, 1421, 1361, 1257, 1243, 1213, 1078, 1025, 966, 905; HRMS Calcd for $C_8H_{10}N_3$ $[M + H]^+$:148.0869; Found: 148.0873.

1,4-Dimethyl-5*H*-pyrrolo[2,1-*d*][1,2,5]triazepine (10b). Acetylpyrrole (0.8 g, 5.44 mmol) and hydrazine monohydrate (1.36 g, 27.2 mmol) in methanol (10 mL) were reacted as described above (see the synthesis of **10a**). Chromatography of the residue and purification of the yellow residue by silica gel chromatography eluting with hexane/EtOAc (1/1) as eluent afforded yellow cubic crystals (0.36 g, 41% isolated yield; 0.59 g, 67% crude yield) (mp 239−240 °C) from chloroform/hexane (5/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (dd, $J_{7,8}$= 2.4 and $J_{7,9}$ = 1.7 Hz, 1H, H-7), 6.48 (dd, $J_{9,8}$ = 3.9 and $J_{9,7}$ = 1.7 Hz, 1H, H-9), 6.10 (dd, $J_{8,9}$ = 3.9 and $J_{8,7}$ = 2.4 Hz 1H, H-8), 5.28 (d, A-part of AB-system, J = 19.0 Hz, 1H, H-5), 4.57 (d, B-part of AB-system, J = 19.0 Hz, 1H, H-5′), 1.81 (s, 3H, CH_3), 1.71 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 159.4, 130.4, 128.5, 115.7, 108.5, 53.4, 20.0, 13.9; IR (ATR, cm^{-1}) 2918, 1619, 1566, 1460, 1420, 1398, 1359, 1331, 1247, 1089, 1037, 982, 907; HRMS Calcd for $(C_9H_{12}N_3)$ $[M + H]^+$: 162.1025; Found: 162.1016.

4-Methyl-1-phenyl-5*H*-pyrrolo[2,1-*d*][1,2,5]triazepine (10c). To a solution of **12c** (1.02 g, 5.84 mmol) in *n*-propanol (20 mL) was added hydrazine monohydrate (2.75 g, 70%, 55 mmol). The reaction mixture was heated at reflux temperature for 48 h. After completion of the reaction, the solvent was evaporated and the residue was chromatographed on a silica gel column eluting with EtOAc/*n*-hexane (1:1) to give the triazepine derivative **10c** (0.71 g, 63%) (orange solid, mp 132−134 °C) from chloroform/hexane (5/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.77 (m, 2H, aromatic), 7.40−7.31 (m, 3H, aromatic), 6.72 (dd, $J_{7,8}$ = 2.6 and $J_{7,9}$ = 1.4 Hz, 1H, H-7), 6.33 (dd, $J_{9,8}$ = 3.9 and $J_{9,7}$ = 1.4 Hz, 1H, H-9), 6.26 (dd, $J_{8,9}$ = 3.9 and $J_{8,7}$ = 2.6 Hz, 1H, H-8), 4.40 (s, 2H, CH_2), 2.13 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 151.2, 137.6, 130.4. 129.6, 128.2, 126.3, 121.2, 113.7, 110.0, 49.1, 23.3; IR (ATR, cm^{-1}) 3125, 3000, 2924, 1611, 1539, 1403, 1328, 1270, 1074; HRMS Calcd for $C_{14}H_{13}N_3$ $[M + H]^+$: 224.1182; Found: 224.1172.

1-(Propa-1,2-dien-1-yl)-1*H*-pyrrole-2-carbaldehyde (18a). To a solution of propargyl carbaldehyde (**12a**) (0.133 g, 1 mmol) in DMF (3 mL) was added NaH (0.038 g, 1.6 mmol) at 0 °C portionwise. The resulting mixture was stirred at room temperature for 3 h. Water (10 mL) was then added, and the mixture was extracted with EtOAc (2 × 10 mL). The combined extracts were washed with brine (4 × 10 mL), dried over $MgSO_4$, and evaporated. The crude product was chromatographed on silica gel eluting with hexane/EtOAc (4/1) to give a yellow viscous liquid (0.111 g, 83%; crude yield 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, J = 1.0 Hz, 1H, CHO), 8.06 (t, $J_{6,8}$ = $J_{6,8'}$ = 6.6 Hz, 1H, ═CH), 7.14 (m, 1H, H-5), 6.90 (dd, $J_{3,4}$ = 4.0 and ve $J_{3,5}$ = 1.4 Hz, 1H, H-3), 6.23 (dd, $J_{4,3}$ = 4.0 and $J_{4,5}$ = 2.6 Hz, 1H, H-4), 5.44 (d, J_{86} = 6.6 Hz, 2H, =CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8 (═C═), 179.8 (CHO), 130.8, 128.0, 125.4, 111.2, 98.6, 87.4; IR (ATR, cm^{-1}) 2925, 1650, 1528, 1476, 1402, 1368, 1336, 1313, 1218, 1074; HRMS Calcd for $(C_{16}H_{14}N_2O_2Na)$ $[2M + Na]^+$: 289.0948; Found: 289.0977.

Reaction of 1-(Propa-1,2-dien-1-yl)-1*H*-pyrrole-2-carbaldehyde (18a) with Water. To a solution of allene **18a** (0.1 g, 0.75 mmol) in methanol (7 mL) was added water (0.135 g, 7.5 mmol). The resulting mixture was heated at reflux temperature for 8 h. After removal of the solvent, the residue was analyzed by NMR spectroscopy. The starting material was recovered unchanged.

Cyclization of Allene 18a with Hydrazine. A solution of allene **18a** (0.2 g, 1.51 mmol) and hydrazine monohydrate (0.31 g, 7.52 mmol) in methanol (7 mL) was heated at reflux temperature for 36 h. After completion of the reaction (controlled by TLC), the solvent was evaporated and water (10 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL), and organic extracts were washed with brine (2 × 10 mL) and dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography using hexane/ethylacetate (1/1). The cyclization product, 4-methyl-5*H*-pyrrolo[2,1-*d*][1,2,5]triazepine (**10a**) (143 mg, 65%), was isolated. The spectral data of this compound matched exactly with data of those compounds obtained by the reaction of **12a** with hydrazine.

Reaction of Pyrrolotriazepine 10a with SeO_2. To a solution of pyrrolotriazepine **10a** (0.2 g, 1.36 mmol) in 1,4-dioxane (5 mL) was added SeO_2 (0.45 g, 4.08 mmol) portionwise over 10 min at rt. The reaction mixture was stirred for 3 h at rt. During this period, the color of the reaction mixture was changed from yellow to purple and gas evolution was observed. The purple-colored precipitate formed during the reaction was filtered off, and the solvent was evaporated. Crude product was purified by silica gel column chromatography eluting with hexane/EtOAc (4/1) to give 1-(2-oxopropyl)-1*H*-pyrrole-2-carbaldehyde **20** as colorless needle-like crystals (127 mg, 62%) (mp 60−61 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (d, $J_{9,5}$ = 1.2 Hz, 1H, CHO), 6.93 (dd, $J_{3,4}$ = 4.0 and $J_{3,5}$ 1.6 = Hz, 1H, H-3), 6.78 (ddd, $J_{5,6}$ = 2.5, $J_{5,7}$ =1.6 and $J_{5,9}$ = 1.2 Hz, 1H, H-5), 6.25 (dd, $J_{4,3}$ = 4.0 and $J_{4,5}$ = 2.5 Hz, 1H, H-4), 5.02 (s, 2H, CH_2), 2.16 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 179.8, 132.1, 131.4, 124.6, 110.3, 57.9, 26.9; IR (ATR,

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cm^{-1}) 2938, 2797, 1718, 1645, 1526, 1479, 1397, 1362, 1320, 1222, 1172, 1077; HRMS Calcd for ($C_8H_{10}NO_2$) [M + H]$^+$: 152.0706; Found: 152.0712.

1-(2-Oxopropyl)-1*H*-pyrrole-2-carbaldehyde (20). To a solution of 1*H*-pyrrole-2-carbaldehyde **14a** (0.95 g, 10 mmol) in acetone (20 mL) was added chloroacetone (1.02 g, 11 mmol) and K_2CO_3 (1.4 g, 10 mmol). The reaction mixture was heated at reflux temperature for 24 h. After cooling to room temperature, the solid was filtered off and the solvent was evaporated. The residue was extracted with EtOAc (3 × 10 mL), and extracts were dried over $MgSO_4$ and evaporated. The crude product was chromatographed on a silica gel column eluting with hexane/EtOAc (4/1) to give dicarbonyl compound **20** as white needles (1.16 g, 77%) (mp 61−62 °C) from chloroform/hexane (5:1).

Reaction of 1-(2-Oxopropyl)-1*H*-pyrrole-2-carbaldehyde with Hydrazine: Synthesis of 4-Methyl-5*H*-pyrrolo[2,1-*d*]-[1,2,5]triazepine (10a). To a solution of 1-(2-oxopropyl)-1*H*-pyrrole-2-carbaldehyde (**20**) (0.3 g, 2 mmol) in methanol (7 mL) was added hydrazine monohydrate (0.3 g, 6 mmol). The reaction flask was heated at reflux temperature for 36 h. After completion of the reaction, water (10 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL), and organic extracts were washed with brine (3 × 10 mL). After evaporating the organic solvent, the residue was purified by silica gel column chromatography eluting with hexane/EtOAc(1/1) to give the cyclization product **10a** (149 mg, 51%). The spectral data of this compound were identical with those of the product obtained by reaction of **12a** with hydrazine.

Methyl 1-(Prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxylate (24). To a solution of methyl 1*H*-pyrrole-2-carboxylate (**23**)[16] (16.19 g, 0.13 mol) in DMF (50 mL) was added NaH (4.99 g, 0.21 mol) portionwise at 0 °C over 0.5 h. The reaction mixture was stirred at room temperature for 1 h. To this solution was then added a solution of propargyl bromide (20.11 g, 0.17 mol) in DMF (15 mL) dropwise, and the resulting mixture was stirred at room temperature for 18 h. Water (50 mL) was added, and the mixture was extracted with EtOAc (6 × 25 mL). Organic extracts were washed with brine (4 × 15 mL) and dried over $MgSO_4$. Evaporation of solvent gave propargyl-pyrrole-2-carboxylate (**24**)[17] as an orange-colored liquid (16.89 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, J = 2.8 and 1.8 Hz, 1H, H-5), 6.90 (dd, J = 4.0 and 1.8 Hz, 1H, H-3), 6.11 (dd, J = 4.0 and 2.8 Hz, 1H, H-4), 5.10 (d, J = 2.5 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 2.36 (t, J = 2.5 Hz, 1H, C≡CH); ^{13}C NMR (100 MHz, $CDCl_3$) 161.5, 127.9, 121.6, 118.5, 108.6, 78.2, 73.7, 51.1, 38.1.

Reaction of Methyl 1-(Prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxylate (24) with Hydrazine. Progargyl-pyrrole-2-carboxylate (**24**) (0.7 g, 4.3 mmol) in methanol (15 mL) was reacted with hydrazine monohydrate (1.51 g, 30.1 mmol). The reaction mixture was heated at reflux temperature for 36 h. After cooling to room temperature, the solvent was removed and the residue was chromatographed on a silica gel column eluting with hexane/EtOAc (2/1) to give **25** (437 mg, 62%, isolated yield) as the first fraction.

2-Amino-3-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (25). Colorless needles, mp 190−192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (ddd, $J_{8,7}$ = 3.9, $J_{8,6}$ = 1.5, and $J_{8,4}$ = 1.1 Hz, 1H, H-8), 6.98 (dd, $J_{6,7}$ = 2.5 and $J_{6,8}$ = 1.5 Hz, 1H, H-6), 6.73 (qui, $J_{4,CH3}$ = $J_{4,8}$ = 1.1 Hz, 1H, H-4), 6.46 (dd, $J_{7,8}$ = 3.9 and $J_{7,6}$ = 2.5 Hz, 1H, H-7), 4.44 (bs, 2H, NH_2), 2.21 (d, $J_{11,4}$ = 1.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 124.7, 120.9, 115.6, 110.2, 107.7, 102.8, 14.2; IR (ATR, cm^{-1}) 3302, 3193, 3094, 2924, 1674, 1607, 1475, 1380, 1329, 1245, 1033; HRMS Calcd for ($C_8H_9N_3NaO$) [M + Na]$^+$: 186.0638; Found: 186.0636.

4-Methyl-2,3-dihydro-1*H*-pyrrolo[2,1-*d*][1,2,5]triazepin-1-one (26). **26** was isolated as the second fraction (0.112 g, 16% isolated yield) as colorless needles, which rearranged quantitatively to **25** upon standing in chloroform at room temperature for 3 days. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (bs, 1H, NH), 7.08 (dd, J = 4.0 and 1.8 Hz, 1H), 6.76 (dd, J = 2.3 and 1.8 Hz, 1H), 6.28 (dd, J = 4.0 and 2.3 Hz, 1H), 4.62 (s, 2H, CH_2), 2.15 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 156.7, 126.1, 124.3, 117.5, 110.2, 49.1, 23.2.

2-(Benzylideneamino)-3-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (27). To a solution of pyrrolopyrazine derivative **25** (80 mg, 0.49 mmol) in ethanol (5 mL) was added benzaldehyde (53 mg, 0.5 mmol). The mixture was heated at 50 °C for 8 h. After completion of the reaction, the solvent was evaporated and yellowish powder was purified by column chromatography on silica gel eluting with hexane/EtOAc (7/1) to give the condensation product **27** as bright yellow crystals (0.117 g, 95%) (mp 123.5−125 °C). (E/Z mixture, 9/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H, N=CH), 7.75 (bdd, J = 7.3 and 1.7 Hz, 2H, aromatic), 7.41−7.37 (m, 3H, aromatic), 7.06 (ddd, $J_{8,7}$ = 4.0, $J_{8,6}$ = 1.5 and $J_{8,4}$ = 1.1 Hz, 1H, H-8), 6.98 (dd, $J_{6,7}$ = 2.5 and $J_{6,8}$ = 1.5 Hz, 1H, H-6), 6.78 (qui, $J_{4,CH3}$ = 1.1 = $J_{4,8}$ Hz, 1H, H-4), 6.46 (dd, $J_{7,7}$ = 4.0 Hz, $J_{7,6}$ = 2.5 Hz, 1H, H-7), 2.24 (d, $J_{CH3,4}$ = 1.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 161.6, 154.3, 134.2, 131.3, 128.7, 128.2, 127.0, 123.6, 117.9, 112.4, 111.6, 105.3, 17.0; IR (ATR, cm^{-1}) 3104, 2924, 1684, 1622, 1525, 1480, 1407, 1358; HRMS [M + H] Calcd for $C_{15}H_{14}N_3O$: 252.1131; Found: 252.1135

Methyl 1-(Propa-1,2-dien-1-yl)-1*H*-pyrrole-2-carboxylate (28). Propargyl-pyrrole-2-carboxylate **25** (0.163 g, 1 mmol) was reacted with NaH (0.038 g, 1.6 mmol) as described above. The rearranged product allene **28** was isolated as a colorless viscous liquid (0.138 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (t, J = 6.6 Hz, 1H, C=C=CH), 7.05 (dd, J = 2.7 and 1.9 Hz, 1H, H-5), 6.93 (dd, J = 3.9 and 1.9 Hz, 1H, H-3), 6.14 (dd, J = 3.9 and 2.7 Hz, 1H, H-4), 5.43 (d, J = 6.6 Hz, 2H, =CH_2), 3.7 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 161.5, 125.8, 121.6, 119.0, 109.8, 98.8, 86.8, 51.2; IR (ATR, cm^{-1}) 3010, 2985, 1715, 1601, 1595, 1510, 1490, 1440, 1396, 1331, 1295, 1230, 1187, 1070, 985, 910; HRMS Calcd for $C_{18}H_{18}N_2NaO_4$ [2M + Na]: 349.1159; Found: 349.1194.

Cyclization of Allene 28 with Hydrazine. A solution of allene **28** (0.2 g, 1.23 mmol) and hydrazine monohydrate (0.31 g, 6.14 mmol) in methanol (7 mL) was heated at reflux temperature for 36 h. After completion of the reaction, the solvent was evaporated and water (10 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL), and organic extracts were washed with brine (2 × 10 mL). Organic extracts were dried with $MgSO_4$ and evaporated. The residue was purified with column chromatography using hexane/ethylacetate (1/1) to give 2-amino-3-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (**25**) (193 mg, 96%) as the sole product. The spectral data of these compound matched with those obtained by the reaction of hydrazine with propargyl derivative **24**.

Methyl 1-(2-Oxopropyl)-1*H*-pyrrole-2-carboxylate (31). To a solution of methyl 1*H*-pyrrole-2-carboxylate (**23**) (1.25 g, 10 mmol) in acetone (20 mL) was added chloroacetone (1.02 g, 11 mmol) and K_2CO_3 (1.4 g, 10 mmol). The reaction mixture was heated at reflux temperature for 24 h. After cooling to room temperature, the solid was filtered off, and solvent was evaporated. The residue was extracted with EtOAc (3 × 10 mL), and extracts were dried with $MgSO_4$ and evaporated. The crude product was chromatographed on a silica gel column eluting with hexane/EtOAc (4/1) to give ketoester **31** as a colored viscous liquid (1.34 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dd, $J_{3,4}$ = 4.0 and $J_{3,5}$ = 1.8 Hz, 1H, H-3), 6.70 (dd, $J_{5,4}$ = 2.8 and $J_{5,3}$ = 1.8 Hz, 1H, H-5), 6.11 (dd, $J_{4,3}$ = 4.0 and $J_{4,5}$ = 2.8 Hz, 1H, H-4), 4.9 (s, 2H, CH_2), 3.7 (s, 3H, OCH_3), 2.1 (s, 3H, CH_3);^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 161.7, 129.5, 121.9, 118.2, 108.7, 60.3, 51.1, 26.7; IR (ATR, cm^{-1}) 3011, 2925, 1775, 1680, 1595, 1510, 1488, 1410, 1395, 1310, 1288, 1066, 1010, 990; HRMS Calcd for ($C_9H_{12}NO_3$) [M + H]$^+$: 182.0811; Found: 182.0834.

Reaction of Methyl 1-(2-Oxopropyl)-1*H*-pyrrole-2-carboxylate (31) with Hydrazine. To a solution of methyl 1-(2-oxopropyl)-1*H*-pyrrole-2-carboxylate (**31**) (0.4 g, 2.21 mmol) in methanol (7 mL) was added hydrazine monohydrate (0.33 g, 6.63 mmol). The reaction mixture was heated at reflux temperature for 24 h. After completion of the reaction, water (20 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The extracts were washed with brine (3 × 10 mL), dried over $MgSO_4$, and evaporated to give the diazine derivative **31** as a yellow viscous liquid (0.35 g, 88%).

Dimethyl 1,1′-((2*E*,2′*E*)-Hydrazine-1,2-diylidenebis(propan-1-yl-2-ylidene))bis-(1*H*-pyrrole-2-carboxylate) (32). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dd, $J_{3,4}$ = 3.9 and $J_{3,5}$ = 1.9 Hz, 2H, H-

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3), 6.80 (dd, $J_{5,4}$ = 2.6 and $J_{5,3}$ = 1.8 Hz, 2H, H-5), 6.11 (dd, $J_{4,3}$ = 3.9 and $J_{4,5}$ = 2.6 Hz, 2H, H-4), 5.01 (s, 4H, CH_2), 3.74 (s, 6H, CH_3), 1.61 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 147.1, 128.9, 122.3, 118.2, 108.7, 53.9, 51.1, 11.5; IR (ATR, cm^{-1}) 2949, 1699, 1534, 1471, 1438, 1409, 1365, 1331, 1259, 1217, 1196, 1178, 1110, 1082; HRMS Calcd for ($C_{18}H_{22}N_4NaO_4$) $[M + Na]^+$: 381.1533; Found: 381.1529.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra (^{1}H and ^{13}C) for all new compounds and tables of atom coordinates and absolute energies of the calculated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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