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Cyclopenta[*b*]pyrroles from Triazines: Synthetic and Mechanistic Studies†

Long Ye,‡ Makhluf J. Haddadin,§ Michael W. Lodewyk,‡ Andrew J. Ferreira,‡ James C. Fettinger,‡ Dean J. Tantillo,‡ and Mark J. Kurth*,‡

Department of Chemistry, University of California, One Shields Avenue, Davis, California 95616, and Department of Chemistry, American University of Beirut, Lebanon

mjkurth@ucdavis.edu

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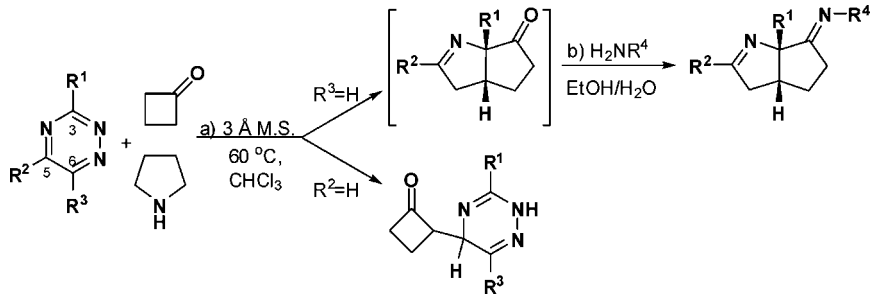
ABSTRACT



The pyrrolidine-mediated reactions of 3,5-disubstituted 1,2,4-triazines with cyclobutanone lead to cyclopenta[*b*]pyrroles, which can be derivatized into hydrazones and oximes. The cyclopenta[*b*]pyrrole ring system likely arises through a tandem [4 + 2] cycloaddition/cycloreversion/ring rearrangement reaction. In contrast, 3,6-disubstituted 1,2,4-triazines undergo a simple nucleophilic 1,4-addition with cyclobutanone to give 1:1 adducts.

An important synthetic application of substituted 1,2,4-triazines is their reaction as azadienes in inverse electron demand Diels−Alder reactions to generate substituted pyridines.[1,2] Analogously, 1,2,4,5-tetrazines are known to react with electron-rich enes to give substituted pyridazines.[3] However, in previous work from our laboratory, we did not obtain the expected pyridazine derivative **5** by the reaction of tetrazine **3** with cyclobutanone enolate **2**.[4−6] Rather, instead of intermediate **4** eliminating water to aromatize (→ **5**), diazocinone **6** was obtained through a ring-expansion reaction (Scheme 1).[4,5]

Attempts to extend this reaction to produce an eight-membered heterocycle containing a sulfur and two nitrogen atoms by reacting **3** with thietanone **7** and base (Scheme 1)

† Dedicated to Professor Jeremiah P. Freeman on the occasion of his 80th birthday and for his excellent service to *Organic Syntheses*.

‡ University of California, Davis.

§ American University of Beirut.

(1) For reviews of inverse electron-demand Diels−Alder reactions using azadienes, see: (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (c) Boger, D. L.; Weinreb, S. N. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987; Organic Chemistry Monograph Series, Vol. 47. (d) Kametani, T.; Hibino, S. In *Advances in Heterocyclic chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1987; Vol. 42, p 246.

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(5) Lodewyk, M. W.; Kurth, M. J.; Tantillo, D. J. *J. Org. Chem.* **2009**, *74*, 4801.

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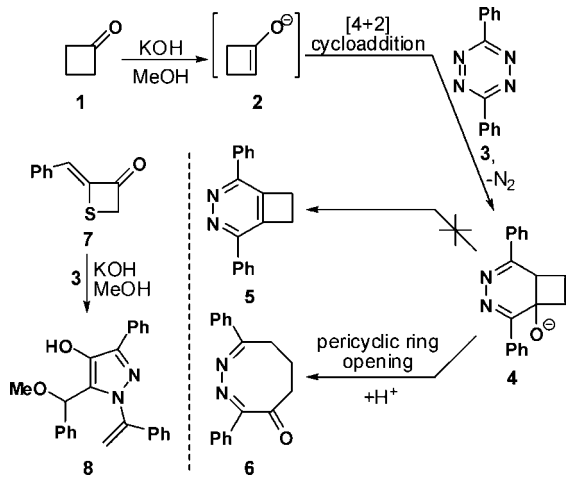
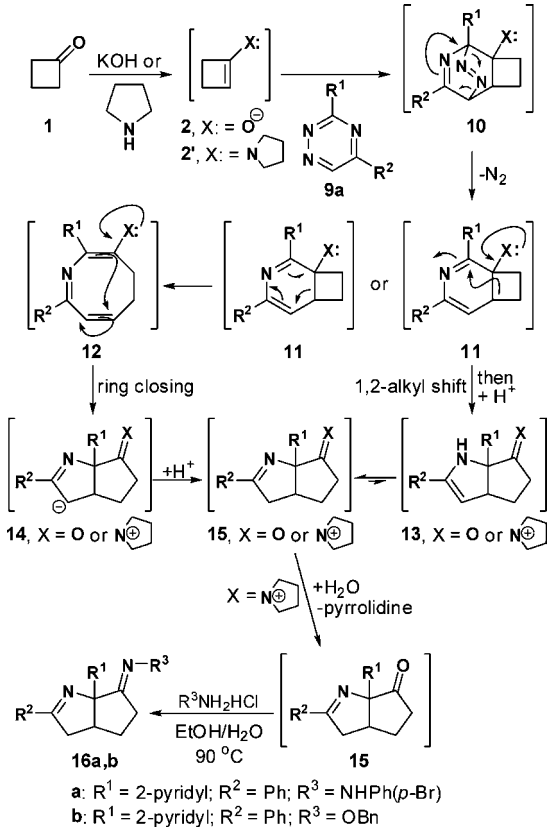
Scheme 1. Tetrazine-Based Reaction Cascades Leading to Diazocinone **6** and Pyrazole **8**



led to substituted pyrazole **8**.[6] In light of our results in Scheme 1 as well as the report by Taylor et al. that triazine **9a** (Scheme 2) undergoes an inverse electron demand

Scheme 2. Mechanistic Possibilities for Formation of Cyclopenta[*b*]pyrrole Derivatives



Diels−Alder reaction with the pyrrolidine enamine of cyclopentanone,[2b] we investigated the reaction of 3,5-disubstituted 1,2,4-triazines (**9**) with cyclobutanone. Upon addition of **9a** to a mixture of cyclobutanone and pyrrolidine, nitrogen extrusion occurred as evidenced by the formation of gas bubbles.[7] Analysis of the reaction mixture by mass spectrometry indicated the presence of components with [M + H^+] = 277 and 330, which could correspond to the eight-membered ring system **12** (X = O^- and *N*-pyrrolidine, respectively). Attempted purification of the crude mixture on a silica or alumina column led only to decomposition. In anticipation of the potential ketone functionality that would result from tautomerization of the desired azocine **12** (X = OH), the crude product mixture was reacted with (Br-Ph)$NHNH_2$·HCl (or $BnONH_2$·HCl) in the hope that a more stable hydrazone (or oxime) of ring-expanded azocine **12** could be isolated and characterized.[8] We were surprised to discover that, instead of obtaining the anticipated hydrazone or oxime of **12**, hydrazone **16a** and oxime **16b** derivatives of the cyclopenta[*b*]pyrrole ring system **15** were formed.

Establishing the structure of **16** was challenging. Efforts to obtain X-ray quality crystals of hydrazone **16a** were unsuccessful under a variety of conditions. ^{1}H NMR spectra of **16a** and **16b** indicated the presence of seven aliphatic protons, which excluded the possibility of **12**. Analysis of the HSQC and COSY spectra of **16a** and **16b** indicated the connectivity of the three CH_2 and CH groups in the bicyclic structure of **16**. The final cyclopenta[*b*]pyrrole structure was arrived at by analyzing the ^{1}H−^{13}C long-range coupling peaks in the HMBC spectra of **16** (see Supporting Information). The results of ^{1}H NMR calculations at the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) level are consistent with assignment of a *cis* rather than a *trans* configuration for **16** (see Supporting Information for details). Finally, we were able to obtain X-ray quality crystals of the (*E*)-oxime **16d**, and to our delight, the resulting crystal structure (Figure 1)

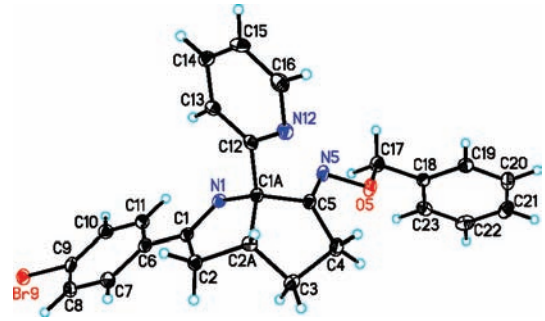


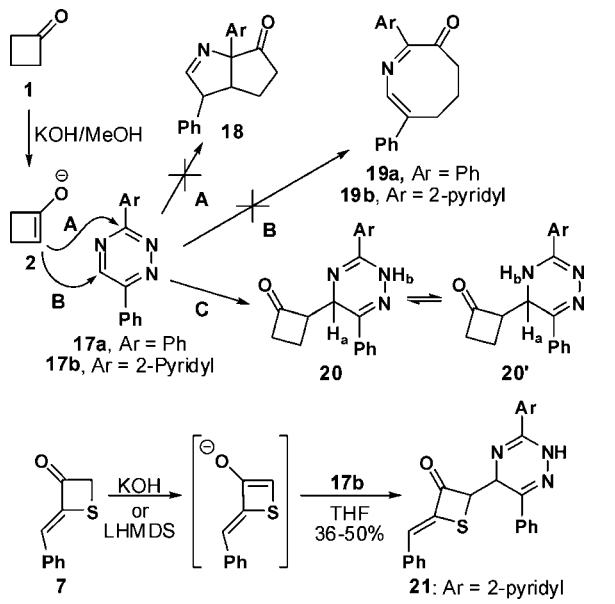
Figure 1. X-ray structure of the (*E*)-isomer of oxime **16d**.

confirmed our NMR-derived structural and stereochemical assignments (see Supporting Information for the crystal structures of both (*E*)-**16d** and (*Z*)-**16d**).

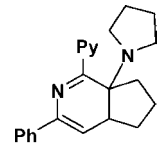
(7) Dry chloroform (1 mL) and 3 Å molecular sieves were added to a mixture of pyrrolidine (22 μL, 0.26 mmol) and cyclobutanone (320 μL, 4.3 mmol) in a sealable thick-wall test tube. Triazine **9a** (200 mg, 0.86 mmol) was then added to the above solution after it was stirred for 10 min. After bubbling stopped, the tube was sealed, and the reaction was stirred at 60 °C for 3−5 h and monitored by LC/MS.

We also wondered if 3,6-disubstituted 1,2,4-triazine (**17**) would react with enolate **2** to give a cyclopenta[*b*]pyrrole (e.g., **18**; pathway **A**, Scheme 3) or an azocinone (e.g., **19**; pathway **B**, Scheme 3). Analysis of the reaction mixture from 1,2,4-triazine **17a** by LC/MS revealed that unreacted starting material was a major component in the mixture, accompanied by a trace amount of what appeared to be an addition product according to its molecular ion ($[M + H^+] = 304$). However, when a 1,2,4-triazine with an electron-withdrawing 2-pyridyl at the C3 position (**17b**) was reacted with cyclobutanone enolate **2**, a mixture of tautomeric adducts **20** and **20′** resulted (pathway **C**, Scheme 3). The tautomeric nature of these addition products is evidenced by two sets of doublets (H_a, 5.43 and 5.35 ppm) and two sets of broad singlets (H_b, 10.21 and 10.06 ppm) in the ^{1}H NMR of these isolated products as well as their co-eluting LC/MS peak with $[M + H^+] = 305$. Indeed, nucleophilic addition to **17b** is precedented.[9] An analogous addition product was observed upon reaction of thietanone **7** with triazine **17b** in the presence of KOH (Scheme 3). Adduct **21** was fully charaterized by ^{1}H NMR, ^{13}C NMR, LC/MS, and X-ray crystallography (see Supporting Information). When LHMDS was used as base instead of KOH, the yield of **21** increased from 36% to 50%; presumably because the non-nucleophilic LHMDS is less likely to add to **17b**.

Scheme 3. Reactions of 3,6-Disubstituted 1,2,4-Triazines



Intrigued by the unexpected formation of cyclopenta[*b*]-pyrrole analogues **16a** and **16b** (Scheme 2), we set out to examine the possible mechanisms by which these products are formed. The first question regards the role of pyrrolidine. One possibility is that this amine reacts with cyclobutanone to form the corresponding enamine (**2′** in Scheme 2). This species could then participate as an electron-rich dienophile in a cycloaddition with triazine **9** to form intermediate **10** and, by loss of N_2, **11** (X = *N*-pyrrolidinyl).[10] This scenario is supported by Taylor's observation of **22** in a closely related reaction.[2b] Alternatively, pyrrolidine may simply function as a base and form small quantities of enolate **2** (protonated pyrrolidine is more acidic than cyclobutanone by ~10 pK_a units), which through reaction with **9** would give **11** (X = O^-). Previously **2**, generated using KOH/methanol, was shown to react in a similar manner with a 1,2,4,5-tetrazene.[4−6] In fact, employing KOH/methanol, while not effective in preparative reactions, does result in the reaction of cyclobutanone with **9** to give **12** (X = OH) and/or **15** as evidenced by LC/MS of the crude reaction mixture. However, no reaction was observed when DBU was used as base.



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Whether intermediate **11** is formed with X = O^- or X = *N*-pyrrolidinyl, there are at least two possible paths by which it can be converted to **15**. As depicted in Scheme 2, **11** may undergo a substituent-accelerated six-electron, electrocyclic ring-opening reaction to form the eight-membered system **12**,[5] which could then contract into **14**. Alternatively, a direct 1,2-alkyl shift may occur, as predicted previously for related systems,[5] to produce **13**, a tautomer of **15**. In order to gain additional insight into these possibilities, density functional theory calculations (B3LYP/6-31+G(d,p); see Supporting Information for details) were employed to probe the key steps outlined in Scheme 2. As shown in Figure 2 (see Supporting Information for additional structures), transition state structures corresponding to the **11** → **12** → **14** pathway for species derived from both **2** and **2′** were located. However, transition state structures for direct 1,2-alkyl shifts for either the enamine or enolate systems could not be located.[11] These observations lead us to conclude that the reaction likely occurs via a stepwise ring-opening/ ring-closing sequence.[12] Our calculations suggest that the enolate version of **12** would face lower barriers to form **14** than would the enamine version (Figure 2). On balance, although neither the enolate nor enamine pathways can be definitively ruled out, we favor the enolate mechanism.

(8) After the relative amount of triazine starting material no longer decreased as indicated by LC/MS, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was redissolved in ethanol and mixed with hydrazine or O-Bn hydroxyamine hydrochloride in a 90% ethanol/10% water solution. This mixture was refluxed for 2 h, the solvent was then removed, and the crude product was dried in DCM over Na_2SO_4, followed by chromatographic purification (silica gel with gradient hexane/ethyl acetate elution).

(9) Konno, S.; Ohba, S.; Sagi, M.; Yamanka, M. *Chem. Pharm. Bull.* **1987**, *35*, 1378.

(10) On the basis of calculations on a related system, it is possible that **10** is not a true minimum on the potential energy surface for this reaction.[5]

(11) Note here that additional calculations (see Supporting Information) revealed that structure **15** (X = O) is at least 20 kcal/mol lower in energy than neutral tautomers of structure **12**.

(12) See Supporting Information for discussion related to this same possibility for the tetrazine-derived systems studied in ref 5.

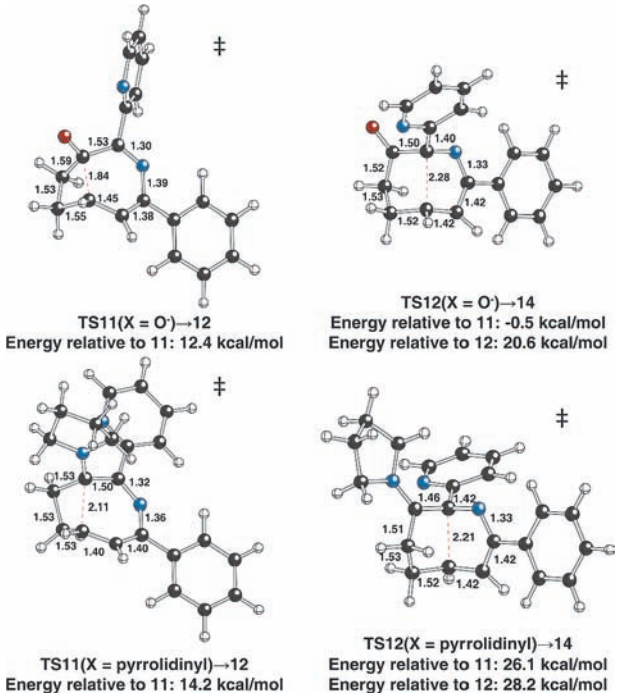
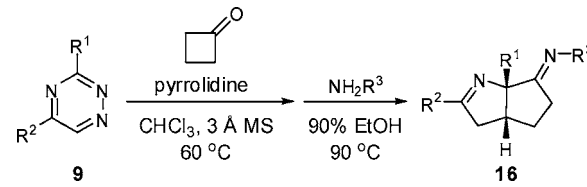


Figure 2. Computed transition state structures (selected distances shown in angstroms).

Encouraged by these observations and the definitive identification of **16a** and **16b**, we carried out the tandem cycloaddition and ring rearrangement reaction on a short series of 1,2,4-triazines (Table 1). We found that an electron-withdrawing group at R^1 is required to form the cyclopenta[*b*]pyrrole ring system. Pyridyl and ester groups at R^1 enable this reaction, with the ester analogue reacting faster than the pyridyl analogue. The moderate to low yields observed can be attributed to an incomplete cascade reaction, rather than inefficient hydrazone or oxime formation, and the relative instability of **15** under basic conditions as evidenced by LC/MS analysis of crude product mixtures. Although hydrazone and oxime formation proceed in comparable yields (Table 1, entry 1 vs entry 2), we focused on the formation of oximes because of their better solution stability. Two additional triazines were employed in this reaction: 3-(methylthio)-5-phenyl-1,2,4-triazine and 3-(methylsulfonyl)-5-phenyl-1,2,4-triazine. The former did not react, and the latter resulted in a complex product mixture.

Table 1. Examples of Tandem Cycloaddition and Ring Rearrangement (**9** → **16**)



entry	code	R^1	R^2	R^3	yield[a]
1	**16a**	2-pyridyl	Ph	NHPh(*p*-Br)	50
2	**16b**	2-pyridyl	Ph	BnO	48
3	**16c**	2-pyridyl	naphthenyl	BnO	42
4	**16d**	2-pyridyl	(*p*-Br)Ph	BnO	44[b]
5	**16e**	EtOC(O)	Ph	BnO	38

[a] Percent isolated yield. [b] Including both *E*- and *Z*-oxime isomers.

In summary, we have demonstrated that cyclopenta[*b*]-pyrroles **16** can be formed via a one-pot, tandem cycloaddition/cycloreversion/ring rearrangement reaction starting from 3,5-disubstituted 1,2,4-triazines and cyclobutanone.

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Supporting Information Available: Full experimental details, characterization data (^{1}H NMR, ^{13}C NMR, LC/MS, and HRMS) for all new compounds, 2D NMR data for **16a** and **16b**, crystallography data (CIF files) for (*E*)-**16d**, (*Z*)-**16d**, and **21**, and details on quantum chemical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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