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Transannular anti-Michael addition: formation of 4*H*-pyrazolo[5,1-*c*]thiazines

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M.J.H. dedicates this work to Dr. Mary Kasparian for her distinguished career of chemistry teaching and high standards at the American University of Beirut

Abstract—The reaction of 2-(diphenylmethylene)thietan-3-one (**2**) with 1,2,4,5-tetrazines (**3a–c**) in KOH/MeOH/THF gives 4*H*-pyrazolo[5,1-*c*]thiazines (**7a–c**). This novel condensation reaction proceeds via the intermediacy of an 8-(diphenylmethylene)-2*H*-1,4,5-thiadiazocin-7(8*H*)-one (**5**), which undergoes a multi-step rearrangement including a rare anti-Michael addition.

The synthesis of multiply-substituted pyrazoles has received considerable attention because of their diverse applications in both the pharmaceutical and the agrochemical industries.[1] In a serendipitous way, we became interested in the synthesis of fully substituted pyrazoles and recently reported the finding that thietanone **1** reacts, under mild basic conditions in an alcoholic solvent, with 1,2,4,5-tetrazines **3a–c** to yield pyrazole **6a–c** (Scheme 1).[2] We hypothesized that the formation of pyrazole **6** proceeded through the ring contraction/desulfurizaton of intermediate **5**. This hypothetical 8-benzylidene-2*H*-1,4,5-thiadiazocin-7(8*H*)-one forms in analogy to the reaction of cyclobutanone with **3**, which under similar conditions yields isolable 1,2-diazocin-4-ones (**5′** in Scheme 1).[3] It is believed that this multi-step transformation of **5** to **6** is initiated by the Michael addition of an alkoxide ion (generated from solvent; $R^2 = CH_3$, CH_2CH_3, CH_2CH_2OH) to the benzylidenone moiety.

Based upon these insights, the purpose of this work was to manipulate the starting thietanone in such a way that the resulting 1,4,5-thiadiazcinone derivative (**5**) would be stable. It was envisaged that introduction of an additional phenyl ring at the *exo*-cyclic double bond (e.g., thietanone **2**) would lead to isolable analogs of **5** ($R^1 = C_6H_5$) by retarding the rate of alkoxide addition to the now more hindered Michael acceptor. The requisite 2-(diphenylmethylene)thietan-3-one (**2**) was prepared[4] as outlined in Scheme 2.

In the event, reaction of **2** with 1,2,4,5-tetrazine **3a** delivered a stable product consistent in molecular weight with the targeted 1,4,5-thiadiazcinone **5a** ($R^1 = C_6H_5$). However, there were a number of surprising findings in the spectral data of this product vis-à-vis the anticipated 1,4,5-thiadiazcinone—principal among these being the presence of an unexchangeable, sharp one proton singlet in its ^{1}H NMR at 5.85 δ in addition to the absence of methylene protons as confirmed by the lack of ^{13}C NMR alkyl carbons holding protons. 1,2,4,5-Tetrazines **3b** and **3c** gave similar products. Fortunately, the product from the reaction of **2** with **3c** gave X-ray crystallographic quality crystals, which established the product as 4*H*-pyrazolo[5,1-*c*]thiazine **7c** (Fig. 1).

4*H*-Pyrazolo[5,1-*c*]thiazines **7a–c** are fully substituted pyrazoles wherein a sulfur-containing heteroring occupies two positions on the pyrazole ring. We conjecture that 2*H*-1,4,5-thiadiazocin-7(8*H*)-one is indeed formed

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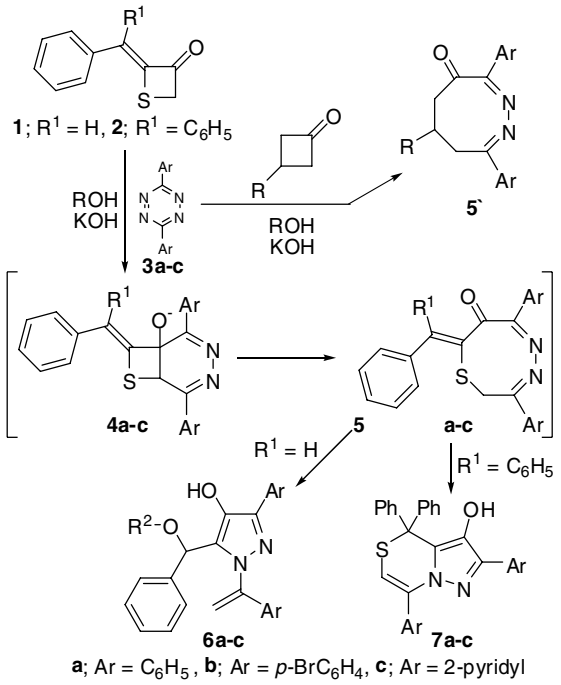
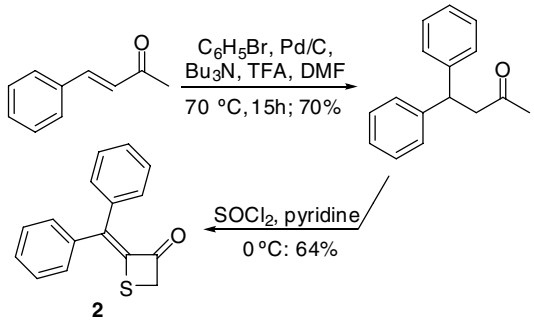


Scheme 1. 1,4,5-Thiadiazocinones (**5**) → pyrazoles (**6**; $R^1 = H$) and pyrazolo[5,1-*c*]thiazines (**7**; $R^1 = C_6H_5$).



Scheme 2. Preparation of thietan-3-one **2**.

and subsequently tautomerizes to 4*H*-1,4,5-thiadiazocin-7(8*H*)-one (e.g., **5a** → **8** as outlined in Scheme 3). This enamine intermediate then undergoes a transannular anti-Michael addition to the diphenylmethylenone moiety to give **9**. The ring opening via thiolate elimination delivers 1*H*-pyrazol-4(5*H*)-one **10** and the subsequent intramolecular thiolate Michael addition gives the observed 4*H*-pyrazolo[5,1-*c*]thiazine (**7a**). Clearly, our switch from benzylidenone-containing **1** to diphenylmethylenone-containing **2** met the initial objective of precluding alkoxide Michael addition and subsequent formation of pyrazole **6**. However, the inherent steric encumbrance of the diphenylmethylenone moiety drives the conversion of, for example, [**5a**] to **7a**, the thermodynamic product of this reaction.

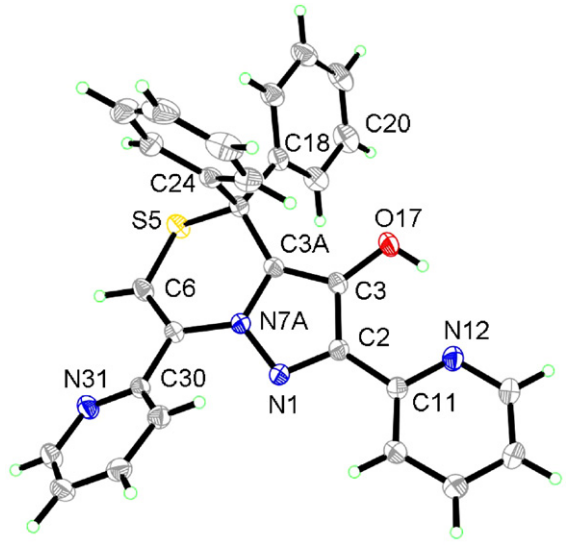
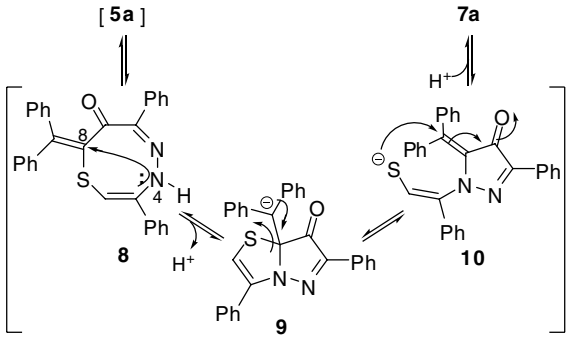


Figure 1. Atomic displacement ellipsoid plot (70% probability) of **7c**. With the exception of S5 and C6, the central, fused heterocycle is planar. S5 and C6 are 1.11 and 0.54 Å out of plane, respectively.



Scheme 3. Proposed mechanism for [**5a**] → **7a**.

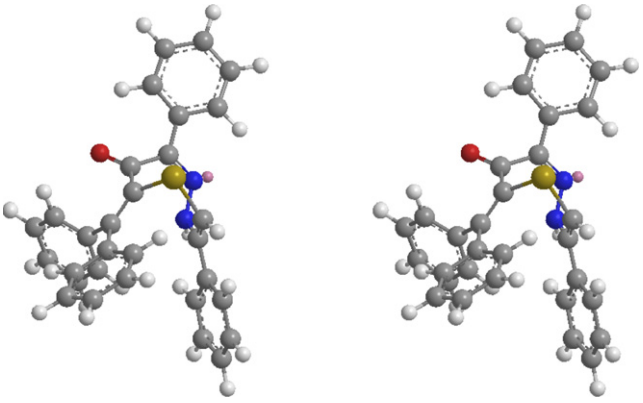
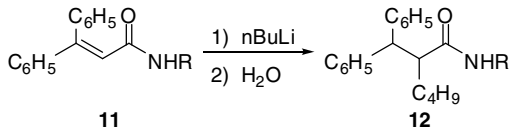


Figure 2. A stereoview of the preferred conformation of 4*H*-1,4,5-thiadiazocin-7(8*H*)-one **8**.

As illustrated in Figure 2, enamine **8** adopts a crown-like conformation in which steric interactions between the diphenylmethylene and carbonyl moieties are minimized by causing the C=C and C=O to become significantly noncoplanar. Furthermore, this conformation places the enamino nitrogen (e.g., N4 in **8**) in close proximity to C8 and hence well positions it for a transannular anti-Michael addition to form the pyrazolo[5,1-*b*]thiazol-7(7a*H*)-one] intermediate **9**. The ring opening to **10** and subsequent Michael addition delivers **7**. This



Scheme 4. Anti-Michael addition to acrylamide **11**.

anti-Michael attack by the enamino nitrogen at C8 is, to some extent, analogues to the recent synthesis of some annulated pyrazoles from a cyclocondensation of arylhydrazines with α-oxoketene.[1a] It is of relevance to point out that anti-Michael addition examples predominantly involve additions to triple bonds[5] with anti-Michael additions to double bonds being quite rare.[6] While we were preparing this manuscript, Suzuki and co-workers reported another example of an anti-Michael addition reaction to a C,C-double bond.[6c] Our finding which, to our knowledge constitutes the third report of an anti-Michael addition to a double bond, bears a close resemblance to the reported addition of *n*-BuLi to enamido **11** to give **12** (Scheme 4).[6a]

In conclusion, we have demonstrated (i) a synthesis of the unknown 4*H*-pyrazolo[5,1-*c*]thiazine heterocycle, (ii) the second example of a transannular reaction in an eight-membered S,N,N-heterocycle,[7] and (iii) discovered another example of the rare anti-Michael addition to a C,C-double bond.

Representative procedure for **2** + **3a**–**c** → **7a**–**c**: *Preparation of 2,7-bis(4-bromophenyl)-4,4-diphenyl-4H-pyrazolo[5,1-c][1,4]thiazin-3-ol* (**7b**). To a mixture of thietanone **2** (45 mg, 0.18 mmol) and tetrazine **3b** (140 mg, 0.36 mmol) in THF (6 mL) was added 5% KOH/MeOH (2 mL). The mixture was stirred for 10 min at which time TLC showed complete disappearance of thietanone **2**. Another three portions of thietanone (3 × 0.18 mmol) were added over a 5 min interval. The mixture was then diluted with water and made slightly acidic with 3 N HCl (in case of the reaction with 3,6-di-2-pyridyl-[1,2,4,5]tetrazine **2c**, the work-up was not made acidic) and extracted with DCM (3×). The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to dryness. Flash chromatography with 10–15% EtOAc/hexane delivered **7b** as a brown oil (114 mg, 52 %).

Compound **7a**: (56%) IR (neat) 3527 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.9 (2H, br d, $J = 8.4$ Hz), 7.4 (18H, m), 5.9 (1H, s), 3.1 (1H, br s). ^{13}C NMR ($CDCl_3$) δ 57.2, 103.7, 125.0, 126.8, 127.9, 128.2, 128.5, 128.8, 128.9, 129.1, 129.6, 132.1, 134.4, 135.7, 139.3, 139.9, 140.3.

Compound **7b**: (52%) IR (neat) 3522 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.7 (2H, d, $J = 8.8$ Hz), 7.4–7.3 (14H, m), 7.2 (H, d, $J = 8.8$ Hz), 5.8 (1H, s), 3.1 (1H, br s). ^{13}C NMR ($CDCl_3$) δ 57.8, 104.6, 122.0, 123.0, 125.1, 128.3, 129.1, 129.2, 129.5, 130.3, 131.0, 131.5, 131.7, 133.1, 135.8, 138.1, 139.0, 140.0.

Compound **7c**: (52%) IR (neat) H-bonded OH 3400–3300 cm^{-1} (w). ^1H NMR ($CDCl_3$) δ 8.6 (1H, d, $J = 4.8$ Hz), 8.3 (1H, d, $J = 4.8$ Hz), 7.8 (1H, d, $J = 8.0$ Hz), 7.7 (2H, m), 7.6 (1H, d, $J = 8.0$ Hz), 7.4 (4H, m), 7.3–7.2 (7H, m), 7.1 (1H, m), 6.8 (1H, s). ^{13}C NMR ($CDCl_3$) δ 57.6, 110.4, 119.3, 122.4, 123.1, 123.7, 124.7, 128.1, 128.2, 129.8, 135.8, 136.1, 137.0, 137.5, 140.0, 141.1, 147.3, 149.4, 151.5, 153.7. X-ray data: colorless, triclinic, space group $P\bar{1}$; $a = 6.5984(3)$, $b = 9.4762(5)$, $c = 18.8062(10)$ Å, $\alpha = 86.689(1)$, $\beta = 87.781(1)$, $\gamma = 71.694(1)°$, $V = 1114.27(10)$ $Å^3$, $T = 93(1)$ K, $Z = 2$; 7150 reflections; $R = 0.0418$ for 6006 with $I > 2\sigma(I)$, $R = 0.0515$ for all. Data collection: Bruker SMART Apex 2 diffractometer. Solution and refinement: SHELXS97 and SHELXL97.[8]

Acknowledgments

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