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A novel approach to fused 1,2,4-triazines by intramolecular cyclization of 1,2-diaza-1,3-butadienes bearing allyl(propargyl)sulfanyl and cyclic *tert*-amino groups

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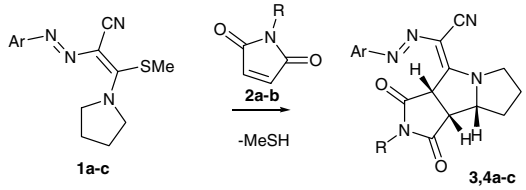
Abstract—3-Allyl- and 3-prop-1-ynylsulfanyl-2-arylazo-3-cycloalkylamino-acrylonitriles undergo cyclization under mild conditions to afford the novel heterocyclic systems 1,4,6,7,8,8a-hexahydropyrrolo[2,1-*c*][1,2,4]-triazine-4-thione, 1,4,6,7,9,9a-hexahydro-[1,4]oxazino[3,4-*c*][1,2,4]triazine and 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[2,1-*c*][1,2,4]triazine via a number of consecutive pericyclic reactions.

Recently, we have shown that 3-methylsulfanyl-2-arylazo-3-pyrrolidine-1-yl)acrylonitriles **1a**–**c** generated azomethine ylides under mild conditions.[1] The latter reacted by a 1,3-dipolar cycloaddition mechanism with *N*-substituted maleimides to form 4-methylene pyrrolizidines **3** and **4** (Scheme 1).

Herein, we report a novel intramolecular reaction of 3-alkylsulfanyl-2-arylazo-3-cycloalkylamino-acrylonitriles leading to 2,3,4,5-tetrahydro-[1,2,4]-triazines fused to pyrrolidine, piperidine, and morpholine rings. The starting allyl- and propargylsulfanyl-2-arylazo-3-(pyrrolidin-1-yl, piperidin-1-yl and morpholin-4-yl)acrylonitriles **5** and **6** were prepared by the alkylation of 2-arylhydrazono-3-cycloalkylamino-3-thioxopropionitriles with an excess of allyl- and propargyl bromides in the presence of KOH in 85–95% yields.

Surprisingly, it was found that on standing in $CHCl_3$ compounds **5** and **6** were gradually transformed into new products. We observed this process in benzene, acetone and acetonitrile at room and higher temperatures while optimal conditions involved heating of compounds **5** or **6** in acetonitrile at 40 °C.[2] Column chromatography of the final reaction mixtures allowed us to isolate pure 1-aryl-4-thioxo-[1,2,4]-triazine-3-carbonitriles **7a**–**f** as the main products in moderate yields (Scheme 2, Table 1).



1a Ar = 4-$NO_2C_6H_4$; **1b** Ar = 4-MeC_6H_4; **1c** Ar = 4-$MeOC_6H_4$
2a R = Me; **2b** R =Ph
3a R = Me, Ar = 4-$NO_2C_6H_4$; **3b** R = Me, Ar = 4MeC_6H_4, **3c** R = Me, Ar = 4-$MeOC_6H_4$
4a R = Ph, Ar = 4-$NO_2C_6H_4$; **4b** R = Ph, Ar = 4-MeC_6H_4; **4c** R = Ph, Ar = 4-$MeOC_6H_4$

Scheme 1.

The structural determination of compounds **7** was achieved from their analytical and spectral data. ^1H NMR spectra of products **7a**–**f** were considerably different in comparison to those of starting materials **5** and **6**.[3] There were no signals of protons due to the SR groups in the spectra of **7**. The number of protons of the

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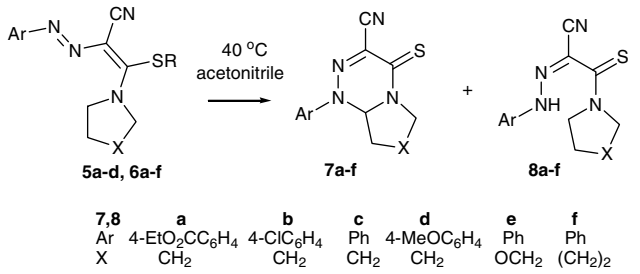


Scheme 2.

cycloalkylamine had decreased by one. The signals of the two protons of the cycloalkylamine were shifted downfield significantly in comparison with the starting materials. A doublet of doublets at δ 5.58 ppm ($J = 8.2$, 5.3 Hz) for **7a**–**d** and δ 6.40 ($J = 10.4$, 2.9 Hz) for **7e**–**f** corresponding to the proton on the bridging carbon of the heterocyclic system and a complex multiplet due to the remaining protons of the cyclic amino ring were registered in the spectra of compounds **7**. A strong shift (around 20 ppm) of the signal of the carbon connected to the sulfur atom, the small shifts of the signals of the aromatic carbon atoms (2–3 ppm), and strong downfield shifts for the signals of the α- and β-carbons of the cycloalkylamine were the main features of the ^{13}C NMR spectra of compounds **7** in comparison with **5** and **6**. Confirmation of the structures of compounds **7** was made on the basis of 2D HMBC and HSQC experiments. The assigned structures were further validated by single-crystal X-ray analysis (Fig. 1).[4]

It is worth noting that thioamides **8a**–**f** were isolated as minor products of side chain dealkylation in all the transformations of thioimidates **5** and **6** to **7**. The mechanism of the transformation of 3-allyl- and 3-prop-1-ynylsulfanyl-2-arylazo-3-cycloalkylamino-acrylonitriles **5** or **6** to fused 1,2,4-triazines **7** can be described in analogy to cyclizations relying on the so-called '*tert*-amino effect' (Scheme 3) as compounds **5** and **6** contain both *tert*-amino functions and a conjugated system.[5]

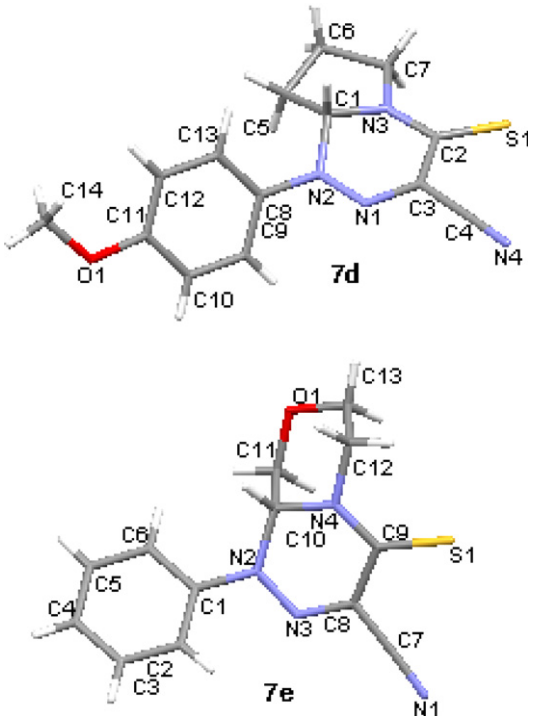


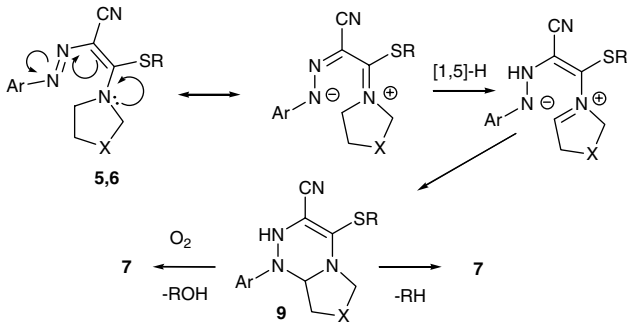
Figure 1. X-ray structures of **7d** and **7e.**

The cyclization according to this mechanism (Scheme 3) is accomplished by dealkylation of intermediate products **9** to form the final compounds **7**. As dry solvents were used and because the yields of the final products did not diminish when the reaction was carried out under argon (entries 8 and 12, Table 1) we conclude that the last step of the reaction may involve elimination of propene (for compounds **5**) or propyne (for compounds **6**) from intermediate **9** (formed via thio-Claisen rearrangement) rather than an oxidative reaction with the formation of propen(propyn)ols. Moreover, the use of sulfur as an oxidant did not lead to a change in the yield of the reaction (entry 10, Table 1). The formation of

Table 1. Investigation of the transformation of 3-allyl- and 3-prop-1-ynylsulfanyl-2-arylazo-3-cycloalkylamino-1-yl-acrylonitriles **5** and **6**

Entry	Substrate	Ar	X	R	Time (h)	Yield[a] **7** (%)	Yield[a] **8** (%)
1	**5a**	4-$EtO_2CC_6H_4$	CH_2	Allyl	40	51	3
2	**6a**	4-$EtO_2CC_6H_4$	CH_2	Propargyl	15	47	6
3	**5b**	4-ClC_6H_4	CH_2	Allyl	40	68	5
4	**6b**	4-ClC_6H_4	CH_2	Propargyl	9	60	12
5	**5c**	C_6H_5	CH_2	Allyl	60	55	6
6	**6c**	C_6H_5	CH_2	Propargyl	10	65	7
7	**5d**	4-$MeOC_6H_4$	CH_2	Allyl	40	55	17
8[b]	**5d**	4-$MeOC_6H_4$	CH_2	Allyl	40	70	7
9[c]	**5d**	4-$MeOC_6H_4$	CH_2	Allyl	40	55	17
10[d]	**5d**	4-$MeOC_6H_4$	CH_2	Allyl	40	53	11
11	**6d**	4-$MeOC_6H_4$	CH_2	Propargyl	10	60	11
12[b]	**6d**	4-$MeOC_6H_4$	CH_2	Propargyl	10	53	15
13	**6e**	C_6H_5	OCH_2	Propargyl	25	40	10
14	**6f**	C_6H_5	$(CH_2)_2$	Propargyl	20	37	10

[a] Isolated yields.
[b] Reaction carried out under argon.
[c] Reaction carried out with toluene-4-thiol.
[d] Reaction carried out with sulfur.



Scheme 3. The mechanism of triazine ring construction from **5** and **6** according to the *tert*-amino effect.

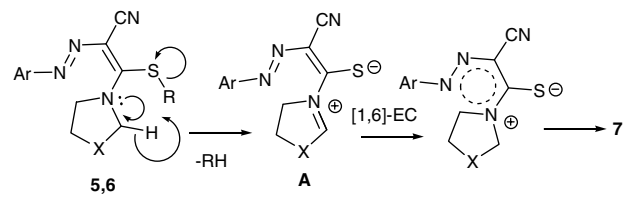
propene as the principal gas phase product of the reaction was confirmed by a GC-MS experiment.[6]

However, thio-Claisen rearrangements normally take place under more vigorous conditions and the rearrangement of 5-alkylsulfanyl-1,2,4-triazine-3-carbonitrile **9** should be hampered by the presence of a cyano group at position 3.[7]

An alternative mechanism involves the elimination of propene (propyne in the case of compounds **6**) to afford intermediate **A**, containing a conjugated hetero-hexatriene system (Scheme 4). The latter undergoes a 6π-electrocyclic reaction to furnish final product **7**. The allyl(propargyl)thio group along with active α-protons makes **5** and **6** well suited for the pericyclic group transfer reactions [8] to final products **7** by elimination of propene(propyne) or via intermediate allyl(propargyl) amination (via structure **A**). A radical mechanism was excluded because there were no new products detected when the reaction was carried out in the presence of toluene-4-thiol (entry 9, Table 1).

The main feature of the reported reaction is elimination of propene (propyne in the case of propargyl derivatives **6**) and the formation of a new C–N bond leading to novel 2,3,4,5-tetrahydro-[1,2,4]-triazine-5-thiones **7a**–**f**. Piperidine and morpholine derivatives **7e** and **f** are novel heterocyclic systems.

It is worth mentioning that annulated 1,2,4-triazines are present as important core structures in many biologically active compounds, both naturally occurring and synthetic.[9] Various condensed 1,2,4-triazines have found applications as pharmaceuticals, herbicides, pesticides, and dyes. For example, pyrrolo[2,1-*f*][1,2,4]triazines demonstrate inhibitory effects on the growth of a wide range of cancer cells.[10] Some pyrrazolo[5,1-*c*][1,2,4]triazines have acquired considerable importance because of their remarkable antitumor and antifungal activities.[11] Certain synthetic derivatives of imidazo[2,1-*c*][1,2,4]triazin-4(1*H*)-ones have revealed a strong affinity for tumor cells and have demonstrated antiproliferative properties and anticancer and antibacterial activities.[12]



Scheme 4. The mechanism of triazine ring construction via 6π-electrocyclization.

In conclusion, we have discovered a novel reaction, which represents a new approach for the synthesis of bicyclic tetrahydro-1,2,4-triazines.

Supplementary data

Supplementary data (copies of ^{1}H and ^{13}C spectra for compounds **7)**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.140.

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2. *General procedure for the transformation of* **5** and **6**: A solution of 0.5 mmol of **5** or **6** in 5 ml of acetonitrile was kept at 40 °C. The reaction progress was monitored by TLC (3:2:1∶∶chloroform:hexane:acetone). The solvent was evaporated and the oily residue purified by column chromatography (5:4:1∶∶chloroform:hexane:acetone, silica gel 0.075–0.035 mm).
3. *1-(4-Methoxyphenyl)-4-thioxo-1,4,6,7,8,8a-hexahydropyrrolo[2,1-c][1,2,4]triazine-3-carbonitrile* (**7d**): mp 125–127 °C; IR (KBr, cm^{-1}) 3440, 2960, 2930, 2880, 2840, 2220, 1605, 1500; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.90–2.03 (m, 3H, CH_2), 2.58–2.65 (m, 1H, CH_2), 3.79 (s, 3H, OMe), 3.68–3.87 (m, 2H, CH_2) 5.47 (dd, 1H, $J = 8.2$, 4.8 Hz, CH), 7.03 and 7.40 (AA′XX′, 4H, $J = 8.7$ Hz, Ar); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.3 (t, $J = 133.4$ Hz, CH_2), 31.0 (ddm, $J = 138.6$, 134.1 Hz, CH_2), 50.6 (tm, $J = 145.7$ Hz, CH_2), 55.5 (q, $J = 144.7$ Hz, OMe), 72.2 (dm, $J = 164.5$ Hz, CH), 114.3 (dd, $J = 161.0$, 5.3 Hz, 2CH–Ar), 115.1 (d, $J = 1.2$ Hz, CN), 120.6 (d, $J = 0.9$ Hz, C–CN), 125.0 (dd, $J = 162.3$, 5.4 Hz, 2CH–Ar), 134.9 (tt, $J = 9.2$, 2.5 Hz, C-Ar), 158.7 (C-Ar), 172.5 (t, $J = 1.8$ Hz, CS); MS (70 eV) *m/z* (%) 286 (M^+, 40.8); Anal. Calcd for $C_{14}H_{14}N_4OS$: C, 58.72; H, 4.93; N, 20.57%. Found: C, 57.19; H, 4.36; N, 20.39%.
   1-Phenyl-4-thioxo-1,4,6,7,9,9a-hexahydro-[1,4]oxazino[3,4-c]-[1,2,4]triazine-3-carbonitrile (**7e**): mp 165–167 °C; IR (KBr, cm^{-1}) 3440, 2980, 2960, 2840, 2220, 1600, 1540; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.59 (ddd, 1H, $J = 12.9$, 11.9, 3.1 Hz, CH_2), 3.67 (ddd, 1H, $J = 11.9$, 11.5, 1.8 Hz, CH_2), 3.78 (dd, 1H, $J = 11.2$, 2.9 Hz, CH_2), 3.90 (dd, 1H, $J = 11.5$, 3.1 Hz, CH_2), 3.99 (dd, 1H, $J = 11.2$, 10.4 Hz, CH_2), 5.02 (dd, 1H, $J = 12.9$, 1.8 Hz, CH_2), 6.45 (dd, 1H, $J = 10.4$, 2.9 Hz, CH), 7.32 (tt, 1H, $J = 6.6$, 1.8 Hz, Ph), 7.54-7.45 (4H, m, Ph). ^{13}C NMR (100 MHz, DMSO-d_6): δ 50.5 (ddd, $J = 146.0$, 143.1, 3.8 Hz, CH_2). 64.0 (tm, $J = 147.7$ Hz, CH_2), 65.0 (ddm, $J = 149.4$, 145.4 Hz, CH_2), 69.7 (dt, $J = 160.4$, 4.5 Hz, CH), 114.9 (s, CN), 117.1 (s, C–CN), 117.8 (dm, $J = 163.1$ Hz, 2CH–Ph), 126.4 (dt, $J = 165.2$, 7.5 Hz,

CH–Ph), 129.7 (dd, $J = 164.4$, 6.6 Hz, 2CH–Ph), 140.9 (t, $J = 6.9$ Hz, C–Ph), 174.4 (ddd, $J = 5.5$, 6.7, 3.1 Hz, CS); MS (70 eV) *m/z* (%) 272 (M^+, 10.5); Anal. Calcd for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57%. Found: C, 57.19; H, 4.36; N, 20.39%.

4. Crystal data for **7d** were measured with an *Xcalibur 3 CCD* (graphite monochromator, MoKα): $C_{14}H_{14}N_4OS$, $FW = 286.35$, orthorhombic, $a = 14.840(3)$, $b = 11.2764(9)$, $c = 8.3820(12)$ Å, $\alpha = 90.00°$, $\beta = 90.00°$, $\gamma = 90.00$ °, $V = 1402.7(4)$ Å^3, $T = 295(2)$ K, space group *Pna2(1)*, $Z = 4$ reflections were used in all calculations. $R = 0.0367$.
Crystal data for **7e** were measured with an *Xcalibur 3 CCD* (graphite monochromator, MoKα): $C_{13}H_{12}N_4OS$, $FW = 272.33$, triclinic, $a = 7.9097(8)$, $b = 8.1071(7)$, $c = 11.3649(7)$ Å, $\alpha = 100.870(6)°$, $\beta = 106.054(7)°$, $\gamma = 108.337(9)°$, $V = 633.72(9)$ Å^3, $T = 293(2)$ K, space group *P1*, $Z = 2$ reflections were used in all calculations. $R = 0.0367$. Crystallographic data for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC-649110 and CCDC-649111. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax:+44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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