Mannich-type reaction of tetrahydropyridine-2-thiolates with primary amines and α-substituted propanals

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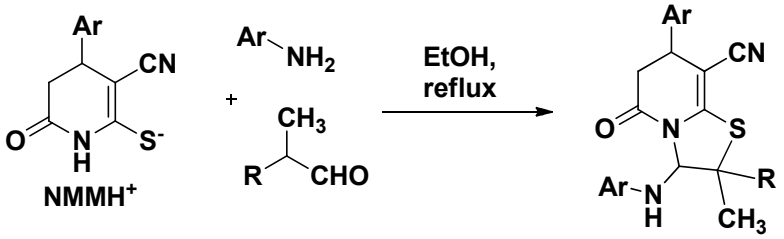
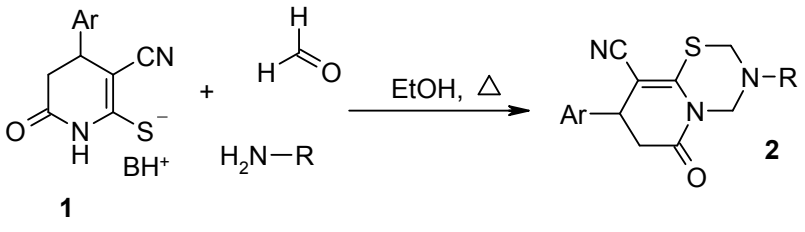
Abstract: The Mannich-type reaction of *N*-methylmorpholinium 4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates with 2-R-propanals (ocean propanal, isobutyraldehyde) and primary aromatic amines afforded 7-aryl-2-R-2-methyl-arylamino-5-oxo-2,3,6,7-tetrahydro-5*H*-thiazolo[3,2-*a*]pyridine-8-carbonitriles in modest yields; the structure of a key compound was confirmed by X-ray crystal structure analysis. The mechanism of the reaction is discussed.

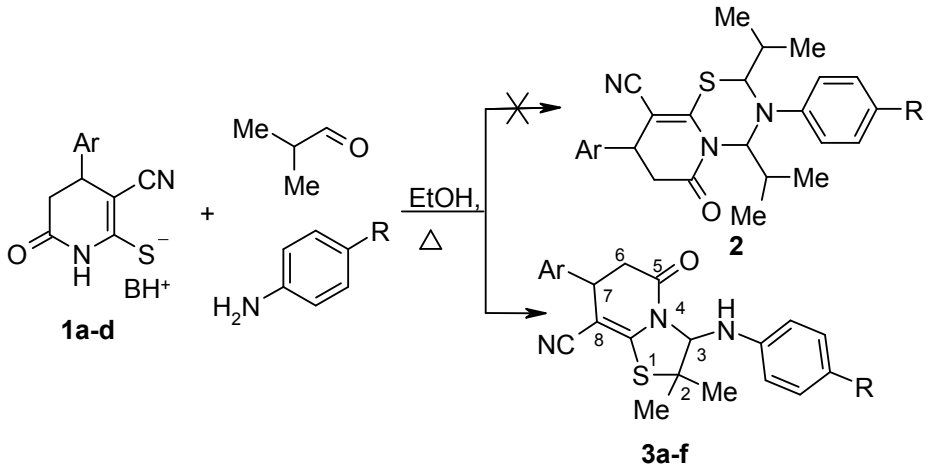
Keywords: Pyridine-2-thiolates, aminomethylation, X-ray studies, bis(pyrid-2-yl)disulfides, Mannich reaction, thiazolopyridines, heterocyclization.



We have previously shown that certain 2-mercaptopyridines (6-oxo-1,6-dihydropyridine-2-thiolates [2, 3] and 4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates **1** [4]) readily form condensed 1,3,5-thiadiazines when treated with $HCHO–RNH_2$.



Continuing our studies in this area we have attempted to synthesize novel pyrido[2,1-b][1,3,5]thiadiazines by treating the model tetrahydropyridine-2-thiolates **1** with isobutyraldehyde and primary aromatic amines. As expected, it was found that isobutyraldehyde was less active than HCHO in reaction with thiolates **1** and primary amines. Hence brief heating of isobutyraldehyde with pyridine-2-thiolates **1** and amines does not give the products of aminoalkylation, whereas a mixture of the thiolate **1**, HCHO, and an amine readily forms high yields of pyrido[2,1-b][1,3,5]thiadiazines **2** [4] under the same conditions. Carrying out the reaction under harsher conditions (refluxing for 4-5 h or more) led to an unexpected result: 7-aryl-3-arylamino-2-dimethyl-5-oxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-a]pyridine-8-carbonitriles **3a-f** were obtained as only isolated products instead of pyrido[2,1-b][1,3,5]thiadiazines.

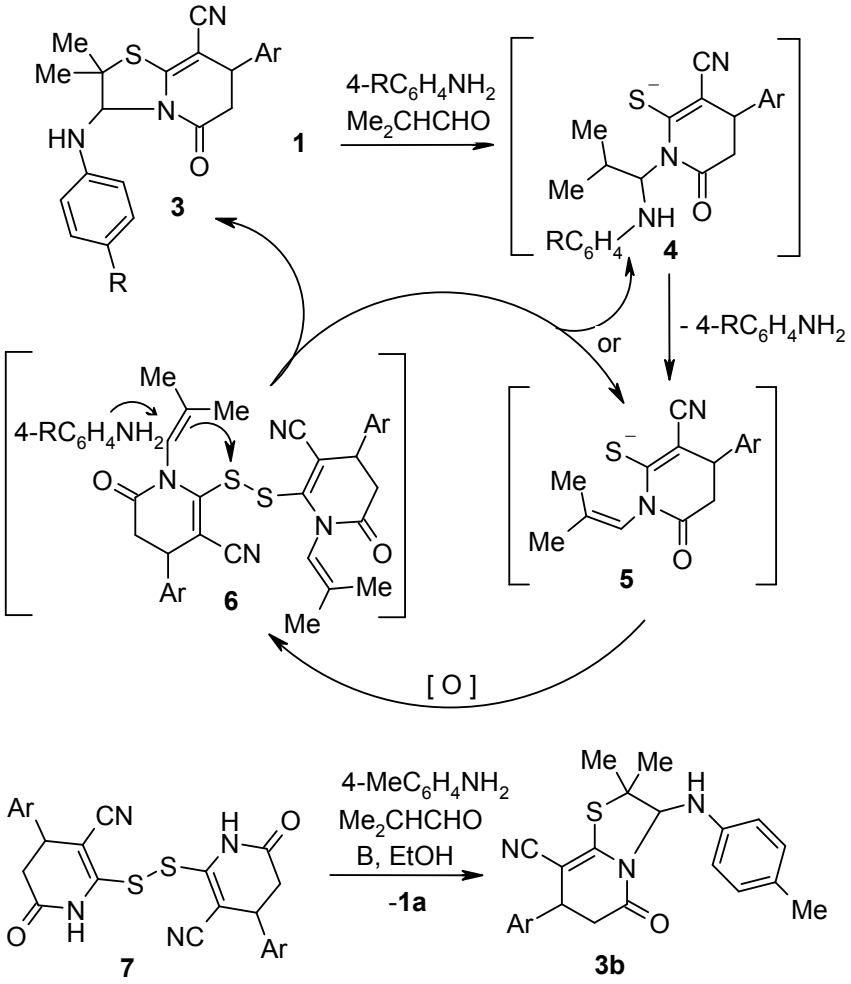


1a, **3a**,**b** Ar = 4-$MeOC_6H_4$; **1b**, **3c** Ar = 4-$MeSC_6H_4$; **1c**, **3d** Ar = 2-$EtOC_6H_4$; **1d**, **3e**,**f** Ar = 2-furyl; **3 a** R = MeO; **b**–**e** R = Me; **f** R = AcNH; $NMMH^+$ = *N*-methylmorpholinium

Compounds **3a-f** are white or faintly colored, finely crystalline powders which are readily soluble in acetone, ethyl acetate, and DMSO, moderately soluble in refluxing EtOH, and poorly soluble in cold EtOH. The structure of compounds **3a-f** was proved by their ^{1}H NMR and IR spectra and by HPLC-MS analysis. The ^{1}H NMR spectra show two sets of signals for the 7-Ar and 3-NHC_6H_4R aromatic substituents and a characteristic ABX pattern for the C(7)–C(6)H_2 fragment while the signals of *i*-Pr and CONH fragments are absent. In place of the two doublets for the methyl groups and methine proton multiplet for the $(CH_3)_2CH$ fragment only two sharp singlets were observed upfield. Two single-proton doublets were observed in the range 5.71-6.28 ppm and these can be assigned to the signals of the C(3)H–NHAr fragment.

The proposed reaction mechanism includes the *N*-aminoalkylation of the thiolates **1** followed by desamination of the condensation product **4** to form enamide **5** and oxidation to disulfide **6** by atmospheric oxygen. Noteworthy that the possible formation of such bis(pyrid-2-yl)disulfides under similar conditions and the ease of S–S bond cleavage in the presence of C-nucleophiles has been confirmed experimentally [5]. Subsequent intramolecular thiolation of the enamide C=C bond leads to the cleavage of a thiolate ion (compound **4** or **5**) and formation of the final product **3**. The low yields (18-38%) of the target products **3** are probably resulted from the multi-step cascade process and non-optimal reaction conditions.

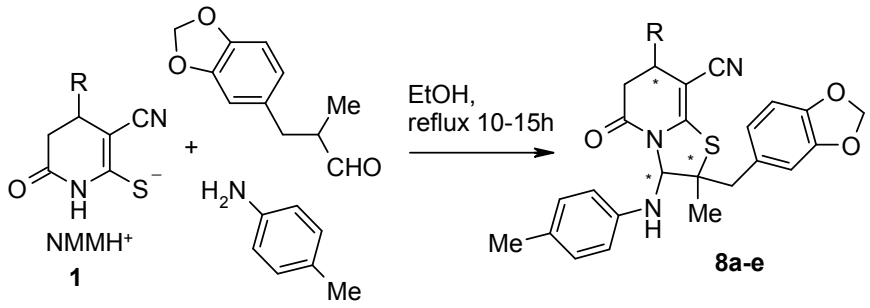
The proposed mechanism is also supported by the observation that bis(pyrid-2-yl)disulfide **7** (prepared by oxidation of thiolate **1a**) also gives the thiazolopyridine **3b** (yield 56% calculated on disulfide **7**) when treated with excess of isobutyraldehyde and *p*-toluidine under analogous conditions.



Ar = 4-$MeOC_6H_4$; B = *N*-methylmorpholine

To continue our efforts in this field, we next examined the reaction of thiolates **1** with the model amine, *p*-toluidine, and another accessible α,α-

disubstituted aldehyde – 3-(1,3-benzodioxol-5-yl)-2-methylpropanal (ocean propanal). Thus, when the reagents were heated in EtOH under reflux, thiazolopyridines **8a-e** were obtained in low (up to 46%) yields:



NMM = N-methylmorpholine;
8: R = 4-$MeOC_6H_4$ (**a**); R = 2-$EtOC_6H_4$ (**b**); R = 2-furyl (**c**); R = 4-BrC_6H_4 (**d**); R = 4-$PhCH_2O$-3-$MeOC_6H_3$ (**e**).

Evidently, the structure of an aldehyde component is a crucial factor that determines the specifics of the reaction: on the one hand, α,α-disubstituted aldehydes are able to form stable and active enamide/enamine species, on the other – they almost cannot react by self-condensation to form competing side products. The unusual fact of the formation of thiazolopyridine core in the aminomethylation process clearly reveals the specific character of the reaction of pyridine-2-thiolates with α,α-disubstituted aldehydes that differs from the analogous Mannich-type reactions with other aldehydes. Presumably, the modest yields of thiazolopyridines **8** are due to the multi-step mechanism of the reaction and competing side reactions. Since both ocean propanal and thiolates **1** are racemates, the products have three chiral centers and are isolated as a complex mixture of diastereoisomers which cannot be easily separated. Compounds **14** are easily soluble in Me_2CO, EtOAc, DMSO and hot MeCN but sparingly soluble in alcohols. The structure of compounds **14a-e** was confirmed by ^{1}H NMR, ^{13}C APT NMR, IR, mass-spectrometry and LCMS data. The analysis of NMR spectra of compounds **14** revealed a complex mixture presumably due to the formation of diastereomers based on the presence of three stereogenic centers. In the IR spectra, the presence of a secondary amine moiety was confirmed by the appearance of the intense and sharp absorption bands exhibited at ν 3330 cm^{-1}. The IR spectra also revealed the conjugated nitrile adsorption bands and lactam C=O bands. The mass spectra showed peaks [M+H]+ and [M–$ArNH_2$]+.

Since it was difficult to elucidate the structure of compounds **8** unequivocally from the spectral data, the structure of thiazolo[3,2-*a*]pyridine **8c** has been studied by X-ray single crystal methods (Fig. 1). The compound **8c** is a racemate (space group *P*21/*c*); the relative configuration of stereo centers was determined as 2*R**,3*S**,7*R**. In the bicyclic core, the cycle N1-C5-C6-C7-C8=C8A

has a *sofa* conformation with C6 lying 0.526(2) Å out of the plane of the remaining atoms (standard deviation 0.082 Å). The fragment S1-C2-C3-N1-C8A has an envelope conformation with C3 out of the plane of the other thiazole ring atoms by 0.520(2) Å. The lengths of bonds C–S & C–N have the expected values. In a crystal, molecules of **8c** form centrosymmetric dimers, which are linked by hydrogen bonds N3-H3…N2 (N3…N2 3.034(2) Å, N3-H3…N2 160.5(17)°).

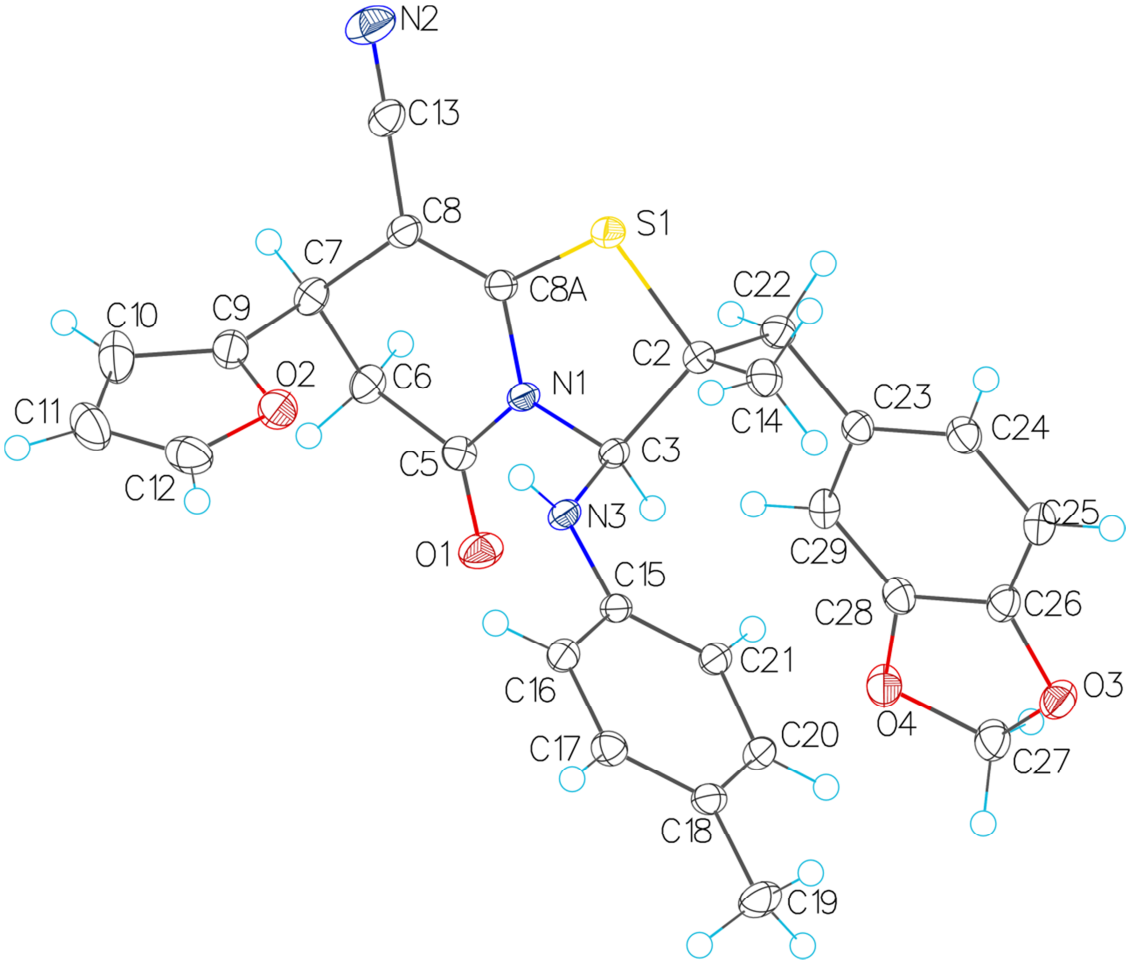


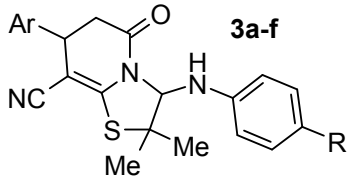
Figure 1. The structure of compound **8c**. Vibrational ellipsoids are shown at the 50% probability level.

In summary, we have demonstrated that the Mannich reaction of N-methylmorpholinium 4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridin-2-thiolates **1** with 2-R-propanals and primary amines leads to the unexpected formation of functionalized thiazolo[3,2-a]pyridines. The structures of the new compounds was unambiguously confirmed by spectral data and X-ray analysis. As far as we know, the reaction demonstrates a new approach towards the construction of thiazolo[3,2-a]pyridine ring system. Further studies to expand the scope of the reaction and optimize the conditions are currently underway and will be published elsewhere.

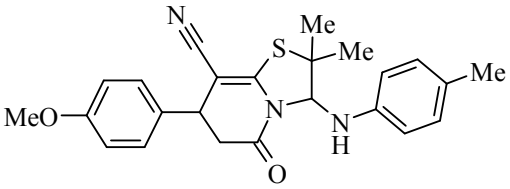
Typical experimental procedures

Starting thiolates **1** were obtained by the known method [6-10] as follows: a mixture of an aromatic aldehyde (0.05 mol), finely powdered cyanothioacetamide [11] (5.0 g, 0.05 mol), EtOH (35-40 mL) and 5-7 drops of N-methylmorpholine were stirred until cyanothioacetamide had dissolved and yellow (or orange) crystalline 3-aryl-2-cyanoprop-2-enethioamide started to precipitate. Then Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (7.5 g, 0.052 mol) and N-methylmorpholine (8.3 mL, 0.075 mol) were added, and the mixture was gently refluxed for 2−4 h. The solution was evaporated to a syrup, whereupon it was treated with acetone (50 mL). The light yellow (or beige) precipitate of the corresponding thiolate **1** was filtered off and washed with cold EtOH and acetone. The compounds were used without further purification.

Thiazolo[3,2-a]pyridine-8-carbonitriles 3a-f.



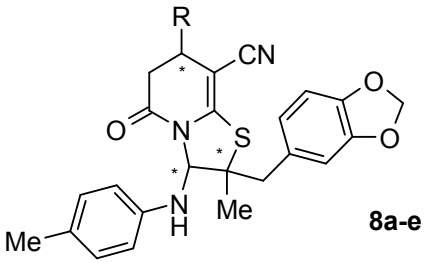
A mixture of the thiolate **1a-d** (2.5 mmol), isobutyraldehyde (1.5 ml, 16.5 mmol), and a primary amine (2.7 mmol) in ethanol (15 ml) was refluxed for 4-5 h in a flask fitted with a condenser. The product was evaporated to two thirds of the initial volume and left for 72 h at 25 ºC. The precipitate formed was filtered off and washed with ethanol and petroleum ether to give analytically pure samples of the thiazolopyridines **3a-f**.



2,2-Dimethyl-3-[(4-methylphenyl)amino]-7-(4-methylsulfanylphenyl)-5-oxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-*a*]pyridine-8-carbonitrile (3c). Yield 0.41 g (38%), white powder, mp 220-222 ºC. IR spectrum, ν, cm^{-1}: 3320 (NH), 2195 (C≡N), 1697 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.51 (3H, s, 2-CH_3); 1.63 (3H, s, 2- CH_3); 2.18 (3H, s, ArCH_3); 2.43 (3H, s, SCH_3); 2.50-2.52 (1H, m, *cis*-H-6); 3.17-3.21 (1H, m, *trans*-H-6); 3.91 (1H, dd, ^3J = 7.5, ^3J = 1.8, H-7); 5.86 (1H, d, ^3J = 10.9, H-3); 6.18 (1H, d, ^3J = 10.9, NH); 6.85 (2H, d, ^3J = 8.5, H Ar); 6.88 (2H, d, ^3J = 8.5, H Ar); 7.07 (2H, d, ^3J = 8.5, H Ar); 7.10 (2H, d, ^3J = 8.5, H Ar). Mass spectrum, *m/z* (I_{rel}, %): 436 $[M+H]^+$ (26), 329 $[M-ArNH_2]^+$ (52), 287 [M-

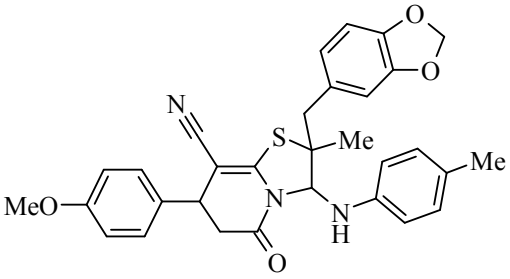
CH_2O-$ArNH_2]^+$ (100), 161 $[ArN{=}CHMe_2]^+$ (10). Found, %: C 65.90; H 5.81; N 9.78. $C_{24}H_{25}N_3OS_2$. Calculated, %: C 66.17; H 5.78; N 9.65.

Thiazolo[3,2-a]pyridine-8-carbonitriles 8a-e.



8a-e

p-Toluidine (330 mg, 3.08 mmol) and ocean propanal (1.7 mL, 10.2 mmol) were added to the suspension of thiolate **1a-e** (2.4 mmol) in the mixture of EtOH (12 mL) and water (2 mL). The mixture was heated under reflux for 10-15 h. The heavy red oil formed was separated by decantation and then dissolved in boiling *n*-BuOH (20 mL). The solution was left to stand at 25 °C in a loosely stoppered flask. The crystalline solid which slowly (1-3 months) precipitate from the solution was filtered off and recrystallized from either BuOH or *i*-PrOH–MeCN.



2-(1,3-Benzodioxol-5-ylmethyl)-7-(4-methoxyphenyl)-2-methyl-3-[(4-methylphenyl)amino]-5-oxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-a]pyridine-8-carbonitrile 14a, mixture of diastereomers. White crystalline solid, yield was 46% (*n*-BuOH). IR spectrum (nujol): 3330 (NH), 2195 (C≡N), 1680 (C=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6), δ 1.41-1.53 (m, 3H, 2-CH3), 2.12-2.15 (m, 3H, ArMe), 2.29-2.42 (m, 1H, *cis*-H-6), 2.84-2.94 (m, 1H, 2-CH_2Ar), 3.04-3.12 (m, 1H, 2-CH_2Ar), 3.16-3.26 (m, 1H, *trans*-H-6), 3.69-3.75 (m, 3H, OCH_3), 3.85-3.92 (m, 1H, H-7), 5.93-6.04 (m, 3H, H-3 & OCH_2O signals overlapped), 6.25 (d, ~0.32H, ^3J =9.4, NH), 6.36 (d, ~0.36H, ^3J =10.7, NH), 6.47 (d, ~0.22H, ^3J =11.0, NH), 6.67-6.95 (m, 9H, H Ar), 7.08 (d, ~1.23H, ^3J =8.3, H Ar), 7.16 (d, ~0.71H, ^3J =8.3, H Ar). LCMS, *m/z* (ES-API): 1080.3 $[2M+H]^+$, 540.8 $[M+H]^+$, 433.6 $[M-ArNH_2]^+$. MS (EI, 70 eV) *m/z* (*I*, %): 539 $[M]^+$ (22), 280 (23), 135 [3,4-(OCH_2O)-$C_6H_3CH_2]^+$ (100), 118 (24), 107 (14). Anal. Calcd for $C_{31}H_{29}N_3O_4S$: C 69.00; H 5.42; N 7.79. M = 539.66. Found: C 69.31; H 5.54; N 7.65.

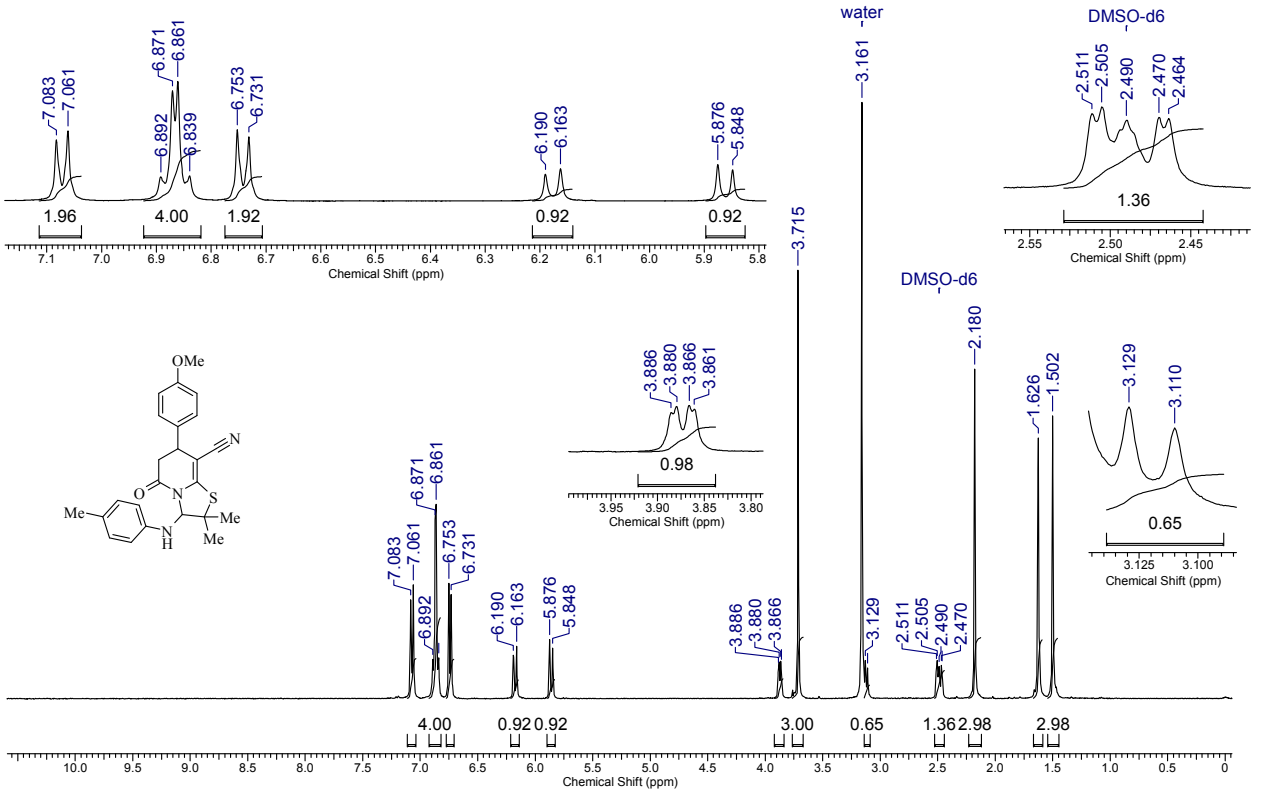


Fig. 2. ^{1}H NMR (400.4 MHz) of 2,2-Dimethyl-7-(4-methoxyphenyl)-3-[(4-methylphenyl)amino]-5-oxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-*a*]pyridine-8-carbonitrile (**3b**).

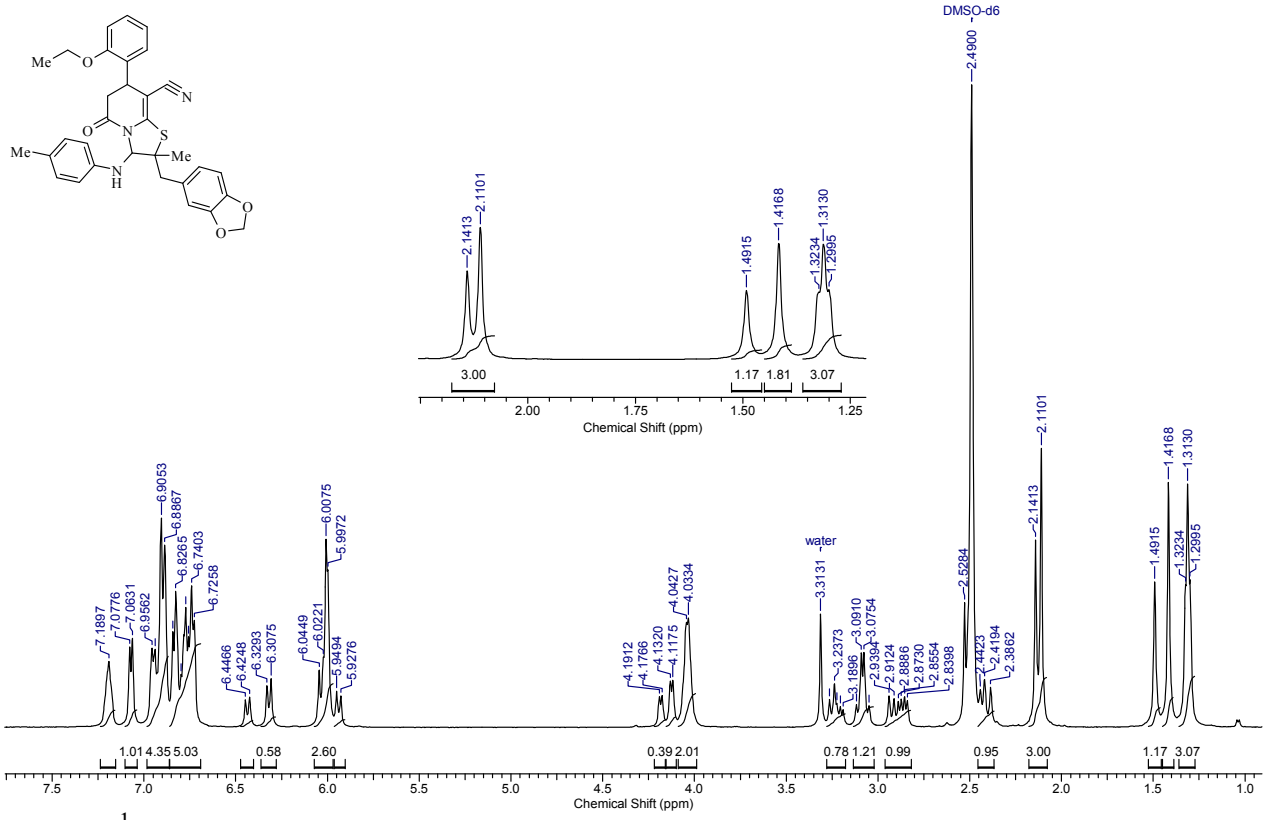


Fig. 3. ^{1}H NMR (500 MHz, DMSO-d_6) of 2-(1,3-benzodioxol-5-ylmethyl)-7-(2-ethoxyphenyl)-2-methyl-3-[(4-methylphenyl)amino]-5-oxo-2,3,6,7-tetrahydro-5 *H*-thiazolo[3,2-*a*]pyridine-8-carbonitrile (**8b**) (*mixture of diastereomers*)

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