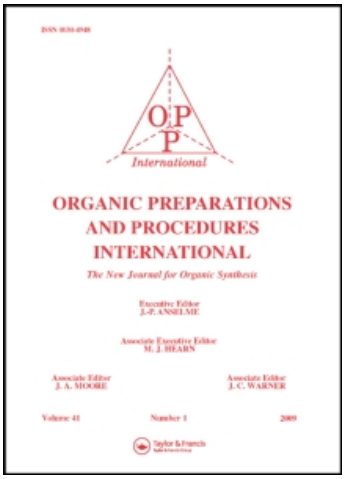


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A FACILE ONE POT SYNTHESIS OF 3-SUBSTITUTED-1,2,4-TRIAZOLO[4,3-B][4,1,2]BENZOTHIADIAZINE-8-ONES

B. Radha Rani[a]; M. F. Rahman[a]; U. T. Bhalerao[a]
[a] Indian Institute of Chemical Technology, Hyderabad, India

To cite this Article Rani, B. Radha , Rahman, M. F. and Bhalerao, U. T.(1991) 'A FACILE ONE POT SYNTHESIS OF 3-SUBSTITUTED-1,2,4-TRIAZOLO[4,3-B][4,1,2]BENZOTHIADIAZINE-8-ONES', Organic Preparations and Procedures International, 23: 2, 157 — 162
To link to this Article: DOI: 10.1080/00304949109458303
URL: http://dx.doi.org/10.1080/00304949109458303

ORGANIC PREPARATIONS AND PROCEDURES INT. 23 (2), 157-162 (1991)

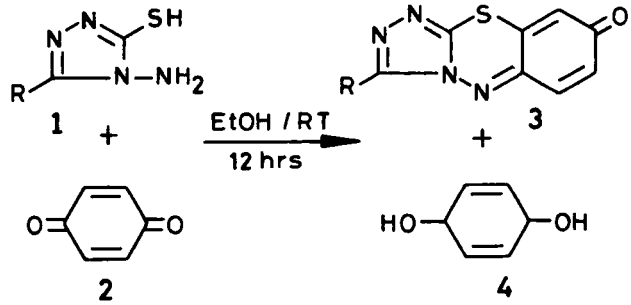
A FACILE ONE POT SYNTHESIS OF 3-SUBSTITUTED-1,2,4-TRIAZOLO[4,3-b][4,1,2]BENZOTHIADIAZINE-8-ONES†

B. Radha Rani, M. F. Rahman* and U. T. Bhalerao

Indian Institute of Chemical Technology, Hyderabad 500 007, INDIA

Many biologically active s-triazolocycloalkyl thiadiazines and s-triazolobenzocycloalkyl thiadiazines have been reported from substituted triazoles and α-haloketones.[1] We now report a facile one-pot synthesis of 3-substituted-1,2,4-triazolo[4,3-b][4,1,2]benzothiadiazine-8-ones by reaction of 5-substituted-4-amino-3-mercapto-1,2,4-triazole with excess of p-benzoquinone. This reaction involves Michael addition, dehydration followed by oxidation in one step.

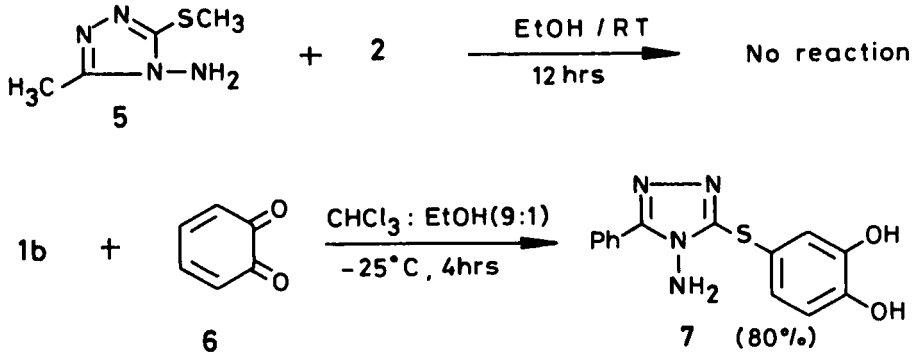
Treatment of 5-methyl-4-amino-3-mercapto-1,2,4-triazole (**1a**)[2] with two molar equivalents of p-benzoquinone (**2**) in ethanol at room temperature for 12 hrs gave an orange crystalline compound (**3a**) along with hydroquinone (**4**). The product **3a** has mass M^+ 218 and strong carbonyl absorption at 1700 cm^{-1} in its IR spectrum. The presence of three vinyl protons and a C-CH_3 signal in ^1H NMR spectrum suggests the occurrence of addition and dehydration followed by oxidation. These characteristics confirmed the structure of **3a** as 3-methyl-



a) R = Me
b) R = C_6H_5
c) R = 4-$MeOC_6H_4$
d) R = 4-ClC_6H_4
e) R = $C_6H_5CH_2$

1,2,4-triazolo[4,3-b][4,1,2]benzothiadiazine-8-one. Using the same conditions, compounds **3a-e** were synthesised from known substituted triazoles **1a-e** (R=CH_3, phenyl, p-methoxyphenyl, p-chlorophenyl and benzyl)[2,3] and p-benzoquinone. Their characteristics are listed in Table 1.

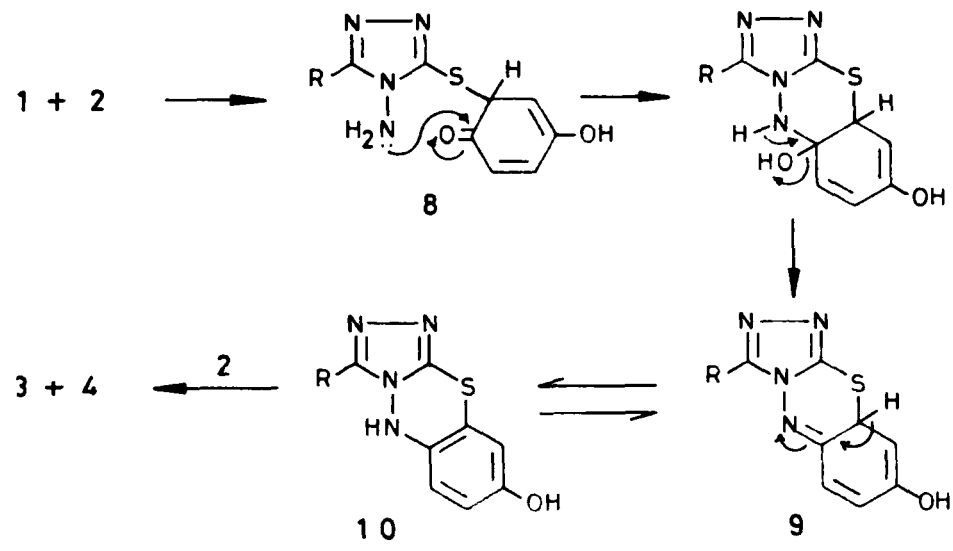
The inability of S-methylated triazole 5 to react with 2 clearly indicates that the initial addition occurred via the thiol group and not through -NH_2. Additional proof of Michael addition via thiol but not through -NH_2 group was obtained when **1b** was reacted with freshly prepared o-benzoquinone (6).[4] The product was characterised as a simple catechol addition product of the thiol group (7). In this case cyclisation was not expected as the carbonyl group is not in proximity with the amino group.



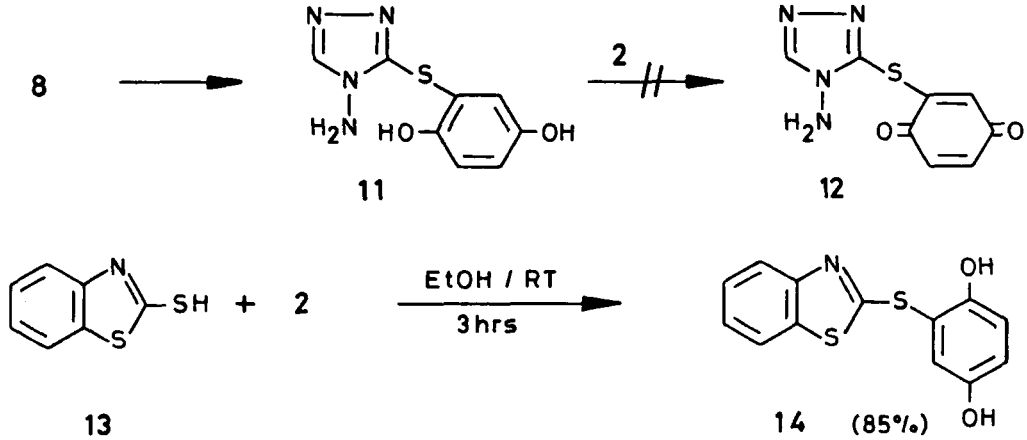
Use of equimolar proportions of 1 and 2 resulted in only 50% conversion of triazole 1 together with hydroquinone (4), whereas two moles of 2 resulted in complete conversion of triazole 1. This clearly indicates the use of a second mole of p-benzoquinone (2) in the oxidation of intermediate 10 and itself undergoing reduction to hydroquinone (4). All these observations clearly support the formation of product 3 by initial Michael addition of thiol on p-benzoquinone followed by condensation and oxidation.

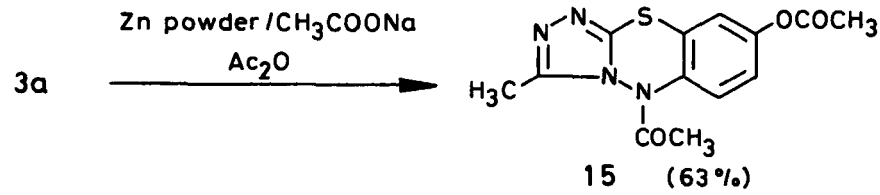
TABLE 1. Analytical and Spectral Data of Compounds **3a-e.**

Cmpd	mp (°C)	Mass (70eV) m/z(%)	IR(KBr) (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J(Hz)	Elemental Analyses Calcd (Found) C	H	N
3a	212	218 (M^+, 100)	1700	7.57(1H of C-6,d,J=9.8) 6.75 (2H of C-7 & C-9, d), 2.01 (3H, s, C-3 methyl)	49.55 (49.69	2.75 2.80	25.67 25.60)
3b	198	280 (M^+, 100)	1710	8.12-8.14 (2H, m, o-phenyl protons), 7.53-7.58 (4H, m, three phenyl protons & one proton of C-6), 6.83 (1H of C-7, d, J=9.63), 6.74 (1H of C-9, s)	60.00 (60.12	2.85 2.81	19.98 19.92)
3c	194	310 (M^+, 100)	1700	8.08 (2H, d, m to $-OCH_3$), 7.07 (2H, d, o to $-OCH_3$), 7.53 (1H of C-6, d, J=9.9), 6.80 (1H of C-7, d, J=9.40), 6.73 (1H of C-9, s), 3.90 (3H, s, $-OCH_3$).	58.07 (58.27	3.22 3.18	18.05 18.12)
3d	220	314 (M^+, 100)	1690	8.1 (2H, d, m to -Cl), 7.53 (3H, d, o to -Cl & one proton of C-6), 6.83 (1H of C-7, d, J=9.63), 6.75 (1H of C-9, d)	53.43 (53.47	2.22 2.29	17.79 17.81)
3e	193	294 (M^+, 100)	1695	7.28-7.39 (5H, m, phenyl protons), 7.46 (1H of C-6, d, J=10.05), 6.78 (1H of C-7, d, J=9.69), 6.68 (1H of C-9, s), 4.40 (2H, s, $-CH_2C_6H_5$)	61.23 (61.33	3.39 3.44	19.03 19.07)



The possibility of hydroquinone intermediate **11** being oxidised to quinone **12** is also ruled out as the hydroquinone derivatives are known to be stable.[5] Such a stable hydroquinone intermediate of 2-mercaptobenzothiazole[6] (**14**) was prepared and did not undergo further oxidation. Compound **3a** was derivatized to 3-methyl-5,6-N,O-diacetyl-1,2,4-triazolo[4,3-b][4,1,2]benzothiadiazine (**15**) by reductive acetylation in presence of zinc powder and anhydrous sodium acetate in acetic anhdyride. ^{1}H NMR and mass spectral data satisfactorily confirmed the structure of compound (**15**).





15 (63%)

EXPERIMENTAL SECTION

All the melting points were taken on a Mettler FP51 capillary melting point apparatus and are uncorrected. IR spectra were measured with a Perkin Elmer model 710B recording spectrophotometer with polystyrene as a standard, reported values are given in the cm^{-1}. Mass spectra were measured on micromass 7070H model. ^1H NMR spectra were recorded on a Bruker AM 300 spectrometer at 300 MHz with TMS as internal standard. All new compounds gave satisfactory elemental analysis, obtained from Perkin Elmer AD-2Z, Autobalance.

3-substituted-1,2,4-triazolo[4,3-b][4,1,2]benzothiadiazine-8-ones (3).- General procedure.- To a solution of 5-substituted-4-amino-3-mercapto-1,2,4-triazole (10 mmol) in ethanol (60 mL) p-benzoquinone (1.08g, 10 mmol) was added and stirred at room temperature for 12 hrs. The solvent was evaporated and the crude product was chromatographed on a silica gel column (200 mesh) to obtain pure crystalline product.

5-Phenyl-4-amino-3(3',4'-dihydroxyphenyl)thio-1,2,4-triazole (7).- 5-Phenyl-4-amino-3-mercapto-1,2,4-triazole (1.92g, 10 mmol) and o-benzoquinone (1.08g, 10 mmol) were dissolved in chloroform and ethanol (9:1) solvent mixture and stirred for 4 hrs at -25°. The white solid which separated from the reaction mixture was filtered and recrystallised from methanol, 2.4 g (80%), mp. 248°. IR (KBr): 3320, 3140 cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.84 (1H, d, 5'H, J = 8Hz), 6.88 (1H, d, 6'H, J = 8Hz), 6.97 (1H, s, 2'H), 7.51-8.00 (5H, m, Ar-H), 9.4 (2H, s, 2-OHs, exchanged with D_2O), 6.14 (2H, s, $-NH_2$, exchanged with D_2O). MS:m/z 300(M^+).

Anal. Calcd. for $C_{14}H_{12}N_4O_2S$: C, 56.02; H, 3.99; N, 18.65
Found: C, 56.14; H, 3.94; N, 18.61

2-(2',5'-Dihydroxyphenyl)thiobenzothiazole (14).- Equimolar proportions of 2-mercapto benzothiazole (0.835g, 5 mmol) and p-benzoquinone (0.54g, 5 mmol) were mixed in ethanol (40 mL) and stirred for 3 hrs. The separated solids were filtered and recrystallised from ethanol. 1.16 g (85%), mp. 228°. IR

(KBr): 3330 (broad) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.7 (1H, s, 6'H), 6.96 (2H, s, 3' & 4'H), 7.29-7.8 (4H, m, aromatic protons), 9.15 (2H, br, -OHs, exchanged with D_2O). MS: m/z 275 (M^+).

Anal. Calcd. for $C_{13}H_9NO_2S_2$: C, 56.72; H, 3.26; N, 5.08
Found: C, 56.81; H, 3.22; N, 5.12

3-Methyl-5,8-N,O-diacetyl-1,2,4-triazolo[4,3-b][4,1,2]benzothiadiazine (15).- To a suspension of **3a** (0.654g, 3 mmol) in pure acetic anhydride (2.5 mL) and zinc powder (0.5g), powdered anhydrous sodium acetate (0.1g) was added. The reaction mixture was warmed until the colour of quinone disappears and then boiled for a minute. Further, glacial acetic acid (2 mL) was added and boiled to dissolve the product and then solution was decanted from the zinc acetate and zinc powder. The residue was washed with hot glacial acetic acid (3 x 2 mL) and decanted. The solutions were combined and solvent was distilled off under reduced pressure. The resulting oily residue was poured into ice cold water, the separated solids (**15**) filtered, dried and recrystallised from benzene, 0.57g (63%), mp. 103°. ^1H NMR ($CDCl_3$): δ 2.18 (3H, s, C-3 methyl), 2.32 (3H, s, -NCOCH_3), 2.47 (3H,s, -OCOCH_3), 7.14-7.59 (3H, m, aromatic protons). MS: m/z 304 (M^+).

Anal. Calcd. for $C_{13}H_{12}N_4O_3S$: C, 51.33; H, 3.94; N, 18.41
Found: C, 51.54; H, 3.85; N, 18.39

Acknowledgement.- The authors are thankful to Dr.D.S. Iyengar and Dr. M. Pardhasaradhi for their useful discussions. One of us (BRR) is thankful to CSIR and Director, IICT for providing financial assistance.

REFERENCES

† IICT Communication No.2561

1. a) W. L. Albrecht and F. W. Sweet, U. S. Patent 3,954,983; C. A., **85**, 78172g (1976); b) W. L. Albrecht, U. S. Patent 3,954,984; C. A., **85**, 78173h (1976); c) W. L. Albrecht and W. D. Jones, U. S. Patent 3,954,981; C. A., **85**, 177501v (1976); d) W. L. Albrecht, W. D. Jones and F. W. Sweet, J. Heterocyclic Chem., **15(2)**, 209 (1978).
2. K. T. Potts and R. M. Huseby, J. Org. Chem., **31**, 3528 (1966).
3. J. R. Reid and N. D. Heindel, J. Heterocyclic Chem., **13**, 925 (1976).
4. F. A. Hoechst, German Patent 1,126,852; C. A., **57**, 8504 (1962).
5. El-Barbary and A. Ahmed, Croat. Chem. Acta., **58(1)**, 71 (1985); C. A., **104**, 168414c (1986).
6. H. Zinner and K. Neindorf, Chem. Ber., **89**, 1012 (1956).

(Received June 6, 1990; in revised form October 30, 1990)