Heteroatom Chemistry
Volume 5, Number 4, 1994

Stereospecific Synthesis of 6,7-Dihydro-5H-1,2,4-triazolo[3,4-b][1,3,4]Thiadiazines

Yehia A. Ibrahim,* Ahmed H. M. Elwahy, and Ayman E. M. El-Fiky

Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R. Egypt

Received 14 January 1994; revised 14 February 1994

ABSTRACT

The reaction of 3-mercapto-4-arylideneamino-1,2,4-triazoles **2b-d**, **3a-d** *with ethyl bromoacetate and/or phenacyl bromide in hot DMF and triethylamine affords the stereochemically pure 7-acyl-6-aryl-6,7-dihydro-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines* **4b-d**, **5a-d**, **6b,d** *in which the consecutive hydrogen atoms N(5)H-C(6)H-C(7)H are cis to each other. This stereochemistry was determined by ^1H NMR spectroscopy and confirmed by comparison with the spectrum of 3,6-diphenyl-6,7-dihydro-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine* **10**. *The latter was prepared by $NaBH_4$ reduction of 3,6-diphenyl-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine* **9**. *The reported reactions offer two interesting stereospecific syntheses of the condensed heterocyclic compounds.*

Many publications [1–7] and patents have described the syntheses and applications of s-triazolo-[3,4-b][1,3,4]thiadiazines. The most important synthetic route toward such a ring system was first reported by Hoggarth [1] and involves the alkylative-cyclocondensation of 3-mercapto-4-amino-1,2,4-triazoles with α-halocarbonyl compounds [1–7]. On the other hand, very little is known regarding the synthesis, chemistry, and applications of 6,7-dihydro-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines. Only two examples of the latter system were prepared by reduction of the corresponding triazolo[3,4-b][1,3,4]thiadiazines [2,8] in addition to a procedure that described the synthesis of the quaternary salts [9]. It is, therefore, quite interesting to explore additional synthetic routes toward such reduced heterocyclic systems.

In the present publication, a simple approach to the synthesis of reduced 1,2,4-triazolo[3,4-b][1,3,4] thiadiazines is described. Thus, during our attempted alkylation of 4-arylideneamino-3-mercapto-1,2,4-triazoles **2b-d**, **3a-d** with ethyl bromoacetate and/or phenacyl bromide in dimethylformamide (DMF) and triethylamine (TEA), the corresponding 6,7-dihydro-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines **4b-d**, **5a-d**, **6b,d** were obtained.

In contrast to the previous findings, compound **2a** reacted with ethyl bromoacetate and phenacyl bromide in hot DMF and TEA to afford only the corresponding S-alkylated derivatives **7a** and **8**, respectively.

The stereochemical purity of the products **4–6** was apparent from their ^1H NMR spectra (Table 1) measured in $CDCl_3$. All these products showed a well-resolved doublet for N^5H, a doublet for C^7H, and almost a triplet for C^6H. The NH signal slowly disappeared on addition of D_2O (complete exchange occurred after 24 hours), and consequently, C^6H became a doublet. From the coupling constants $^3J_{5,6}$ = 4.4–5.8 Hz, $^3J_{6,7}$ = 3.6–4.6 Hz for compounds **4b–d**, **5b–d** and $^3J_{5,6}$ = 6.3–6.6, $^3J_{6,7}$ = 4.7–5.2 Hz for compounds **6b,d**, these products were assigned the *cis* stereochemistry (Figure A). Such an assignment is substantiated by comparison with the ^1H NMR spectrum of 3,6-diphenyl-6,7-dihydro-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine **10** (Table 1) which was prepared by $NaBH_4$ reduction of 3,6-diphenyl-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine **9** [1]. In compound **10**, the large vicinal coupling ($^3J_{5,6}$ = 10.2, $^3J_{6,7_a}$ = 9.7 Hz) indicates the *trans* relationship of N^5-H, C^6-H and of C^6-H, C^7-H_a.

*To whom correspondence should be addressed.

1042-7163/94/$5.00 + .25

TABLE 1 ^{1}H NMR ($CDCl_3$) of Compounds **4b–d**, **5a–d**, **6b,d**, **10** (δ/J Hz)

	Thiadiazine Protons			
Compound	*C^5H* ($J_{5,6}$)	*C^6H*	*C^7H* ($J_{6,7}$)	*Other Protons*
4b	6.38 (d) (4.4)	4.95 (t)	4.40 (d) (3.6)	1.25 (t, 3H, CH_3), 4.25 (dq, 2H, CH_2), 7.2–8.1 (m, 10H, ArH's)
4c	5.92 (d) (4.5)	4.82 (t)	4.22 (d) (3.6)	1.3 (t, 3H, CH_3), 4.1–4.2 (m, 4H, OCH_2, CH_2Ph), 7.3 (m, 10H, ArH's)
4d	6.27 (d) (4.8)	4.95 (t)	4.37 (d) (4.0)	1.3 (t, 3H, CH_3), 3.8 (s, 3H, OCH_3), 4.26 (dq, 2H, OCH_2), 6.8–8.05 (m, 9H, ArH's)
5a	5.2 (s)	3.85 (s)	3.85 (s)	1.25 (t, 3H, CH_3), 4.2 (q, 2H, CH_2), 7.3, 7.52 (2d, 4H, ArH's), 8.47 (s, 1H, triazole-H)
5b	6.61 (d) (5.6)	4.88 (t)	4.43 (d) (4.6)	1.26 (t, 3H, CH_3), 4.23 (m, 2H, CH_2), 7.2–8.1 (m, 9H, ArH's)
5c	6.16 (d) (4.6)	4.76 (t)	4.26 (d) (3.8)	1.26 (t, 3H, CH_3), 4.1 (s, 2H, (CH_2Ph), 4.2 (dq, 2H, OCH_2), 7.2 (m, 9H, ArH's)
5d	6.58 (d) (5.8)	4.85 (t)	4.4 (d) (3.8)	1.24 (t, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.22 (dq, 2H, CH_2), 6.8–8.0 (m, 8H, ArH's)
6b	6.67 (d) (6.29)	5.11 (t)	5.5 (d) (4.72)	7.3–8.1 (m, 15H, ArH's)
6d	6.74 (d) (6.6)	5.06 (t)	5.57 (d) (5.2)	3.8 (s, 3H, OCH_3), 6.85–8.02 (m, 14H, ArH's)
10[a]	5.8 (d)	4.53 (dt)	3.55 (dd) (9.73) 3.35 (dd) (3.1)	7.4–8.0 (m, 10H, ArH's)

[a]The two protons of C^7H_2 each appear as dd as a result of the geminal coupling with the geminal coupling constant ^2J = 12.7 Hz.

On the other hand, the small vicinal coupling ($^3J_{6,7_e}$ = 3.1 Hz) indicates the *cis* relationship of C^6-H, C^7-H_e. Additional support for the stereochemistry of the products **4–6** comes from comparison with the reported triazolothiadiazinium bromides (Figure B) in which the consecutive hydrogen atoms -N^5H-C^6H-C^7H- were established to be *trans* to each other by X-ray diffraction analysis [9]. The latter compounds exhibit large vicinal coupling $J_{5,6}$, $J_{6,7}$ (9.1–11.6 Hz), which epimerize slowly in $CDCl_3$ solution into an equilibrium mixture of 60:40 of *trans* and *cis* isomers. The *cis* isomers are characterized by the small vicinal coupling ($J_{5,6}$, $J_{6,7}$ = 3.2–2.7 Hz) [9].

Compound **5a** does not show the splitting pattern of the thiadiazine protons but gives instead a singlet for N^5H (exchangeable) and a singlet (2H) for C^6H, C^7H at the same δ value (3.85). This behavior could be attributed to the rapid inversion of the N^5-H as a result of the absence of a substituent at the 3-position in this derivative.

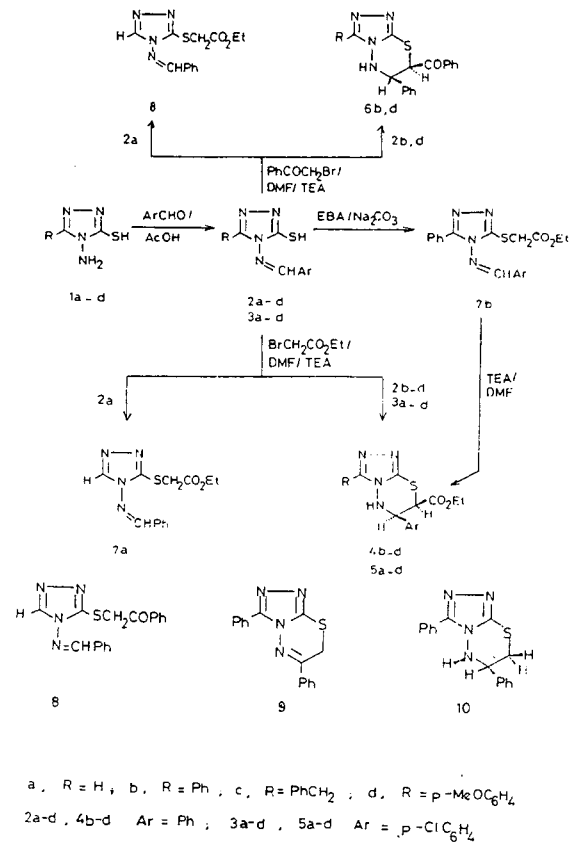
The stereospecificity of the present synthesis of the products **4–6** points to the involvement of a concerted cyclization step. Presumably, the reaction first proceeds via the formation of the S-alkylated derivative (B) followed by enolization under the basic reaction conditions, and then by an intramolecular ene-reaction [10]. Thus, the azomethine group acts as the ene part and the enol acts as the enophile part in the proposed intermediate C. This presumption finds supports from the following facts.

1. The intermediate **7b** when heated in DMF and TEA afforded **4b**. Compound **7b** was prepared by reacting **2b** with ethyl bromoacetate in aqueous sodium carbonate.
2. X-ray diffraction studies [11] showed that compound **2a** exists in the *anti*-form (A) (R = H) with the suitable stereochemistry required for this stereoselective formation of **4–6** arising via the proposed ene-reaction.

TABLE 2

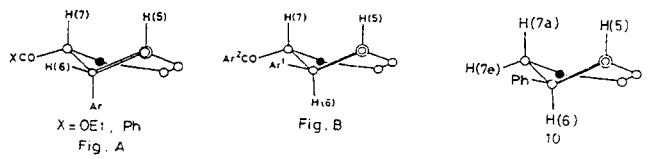
Compound	Mp (°C) (Yield %)	Formula (MW)	Anal. % Calcd/Found			
			C	H	N	S
2c	185–7	$C_{16}H_{14}N_4S$ (294.38)	65.28	4.79	19.03	10.89
	(85)		65.40	5.00	19.30	10.90
2d	178–80	$C_{16}H_{14}N_4OS$ (310.38)	61.92	4.55	18.05	10.33
	(89)		62.00	4.70	18.20	10.60
3a	237–9	$C_9H_7N_4C1S$ (238.70)	45.29	2.96	23.47	13.43
	(87)		45.30	3.00	23.70	13.60
3b	198–200	$C_{15}H_{11}N_4ClS$ (314.80)	57.23	3.52	17.80	10.19
	(90)		57.10	3.70	18.00	10.40
3c	177–9	$C_{16}H_{13}N_4ClS$ (328.83)	58.44	3.99	17.04	—
	(92)		58.20	4.20	17.20	—
3d	187–9	$C_{16}H_{13}N_4ClOS$ (344.83)	55.73	3.80	16.25	—
	(90)		55.40	3.60	16.20	—
4b	206–8	$C_{19}H_{18}N_4O_2S$ (366.45)	62.28	4.95	15.29	8.75
	(60)		62.40	5.20	15.40	9.00
4c	81–3	$C_{20}H_{20}N_4O_2S$ (380.47)	63.14	5.30	14.73	8.43
	(65)		63.30	5.60	14.50	8.60
4d	200–2	$C_{20}H_{20}N_4O_3S$ (396.47)	60.59	5.08	14.13	—
	(55)		60.40	5.10	14.40	—
5a	172–4	$C_{13}H_{13}N_4ClO_2S$ (324.79)	48.07	4.03	17.25	9.87
	(58)		48.10	4.20	17.40	10.10
5b	141–3	$C_{19}H_{17}N_4ClO_2S$ (400.89)	56.93	4.27	13.98	8.00
	(62)		56.70	4.30	14.00	8.30
5c	114–6	$C_{20}H_{19}N_4ClO_2S$ (414.92)	57.90	4.62	13.50	7.73
	(71)		58.10	4.40	13.30	7.40
5d	192–4	$C_{20}H_{19}N_4ClO_3S$ (430.92)	55.75	4.44	13.00	7.44
	(56)		55.40	4.60	13.30	7.70
6b	204–6	$C_{23}H_{18}N_4OS$ (398.49)	69.33	4.55	14.06	8.05
	(70)		69.50	4.60	14.20	8.20
6d	197–9	$C_{24}H_{20}N_4O_2S$ (428.52)	67.27	4.70	13.07	7.48
	(68)		67.40	4.90	13.20	7.60
7a	109–11	$C_{13}H_{14}N_4O_2S$ (290.35)	53.78	4.86	19.30	11.04
	(65)		53.80	5.00	19.60	11.20
7b	108–10	$C_{19}H_{18}N_4O_2S$ (366.45)	62.28	4.95	15.29	8.75
	(76)		62.40	5.10	15.40	9.00
8	174–6	$C_{17}H_{14}N_4OS$ (322.39)	63.34	4.38	17.38	9.95
	(68)		63.00	4.50	17.60	10.20
10	144–6	$C_{16}H_{14}N_4S$ (294.38)	65.28	4.79	19.03	10.89
	(70)		65.10	4.80	19.30	11.00

[a]Compounds **2c–d**, **3a–d** were crystallized from acetic acid, **4b–c**, **5b**, **5d**, **7a**, **8** from an ethanol/water mixture, and **5a**, **6d** from ethyl acetate. **2c**: ^{1}H NMR ($CDCl_3$) δ 4.2 (s, 2H, $\underline{CH_2}Ph$), 7.3–7.82 (m, 10H, ArH's), 10.35 (s, 1H, CH=N). **6b**: ^{13}C NMR δ 41.5 (SCH), 58.8 (NCH), 127.3, 127.8, 128.5, 128.7, 128.9, 129.2, 130.0, 134.6 (ArCH's), 126.2, 134.4, 136.0 (ArC's), 142.6, 152.8 (triazole-C's), 195.4 (C=O). **7b**: ^{13}C NMR δ 14.2 (CH_3), 35.0 ($S\underline{C}H_2C{=}O$), 62.0 (OCH_2), 128.3, 128.8, 129.2, 130.1, 135.3 (ArCH's), 126.5, 131.6 (ArC's), 146.7, 152.1 (triazole-C's), 165.9 (CH=N), 168.4 (C=O). **7a**: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, CH_3), 4.15 (s, 2H, SCH_2CO), 4.21 (q, 2H, OCH_2), 7.4–7.85 (m, 5H, ArH's), 8.56, 8.69 (2s, 2H, CH=N, triazole-H). **8**: ^{1}H NMR ($CDCl_3$) δ 5.0 (s, 2H, SCH_2), 7.46–8.02 (m, 10H, ArH's), 8.54, 8.65 (2s, 2H, CH=N, triazole-H).



a, R = H; b, R = Ph; c, R = $PhCH_2$; d, R = p-$MeOC_6H_4$

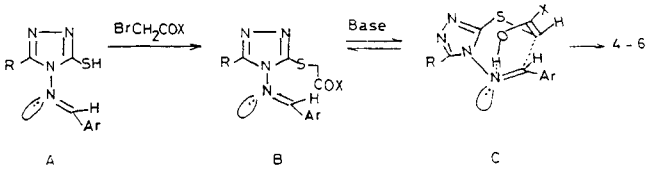
2a-d, 4b-d Ar = Ph; 3a-d, 5a-d Ar = p-ClC_6H_4



X = OEt, Ph

Fig. A

Fig. B



EXPERIMENTAL

All melting points are uncorrected. NMR spectra were measured on a Varian GEMINI 200 instrument (200 MHz, ^1H NMR, and 50 MHz, ^{13}C NMR). All ^{13}C NMR spectra were recorded using the APT pulse sequence. The starting compounds **1a** [12], **1b, d** [1], **1c** [13], **2a** [12], **2b** [14] were prepared as reported in the literature.

Preparation of 4-Arylideneamino-3-mercapto-1,2,4-triazoles **2c–d, 3a–d**

A mixture of the appropriate compound **1a–d** (10 mmol) and benzaldehyde and/or *p*-chlorobenzaldehyde (10 mmol) in acetic acid (10 mL) was heated under reflux for 1 hour. After cooling, the product was collected as pure crystals of the corresponding **2c–d** or **3a–d** in 85–90% yield (Table 2). These compounds may be recrystallized from acetic acid.

Reaction of **2a–d, 3a–d** *with ethyl bromoacetate or phenacyl bromide in DMF and TEA*

A solution of each **2a–d, 3a–d** (5 mmol) and ethyl bromoacetate or phenacyl bromide (5 mmol) in DMF (5 mL) and TEA (1.5 mL) was heated under reflux for 10 minutes. After cooling and dilution with water, the precipitates that had formed were collected and crystallized from the proper solvent to give **4b–d, 5a–d, 6b,d, 7a, 8** (Table 2).

4-Benylideneamino-3-ethoxycarbonylmethylthio-5-phenyl-1,2,4-triazole **7b**

To a suspension of **1a** (0.5 g) in aqueous sodium carbonate solution (4%, 5 mL) was added ethyl bromoacetate (0.22 mL), and the mixture was stirred for 10 minutes at 50–60°C and then left at room temperature for 2 hours. The precipitates that had formed were collected and crystallized from ethanol to give colorless crystals of **7b** (Table 2).

Synthesis of **4b** *from* **7b**

A solution of **7b** (0.2 g) in DMF (3 mL) and TEA (0.5 mL) was heated under reflux for 2 minutes and then cooled and diluted with water. The precipitate that had formed was collected and recrystallized from ethanol to give colorless crystals of **4b** (0.2 g, 100%), mp 207°C (identical with **4b** prepared from **1a**, mixed mp, and ^1H NMR).

3,6-Diphenyl-6,7-dihydro-5H-1,2,4-triazolo-[3,4-b][1,3,4]Thiadizine **1**

A solution of **9** [1] (0.5 g) and $NaBH_4$ (0.1 g) in absolute methanol (10 mL) was heated under reflux for 1 hour. After cooling and dilution with water, the precipitate that had formed was collected and recrystallized from ethanol to give 0.35 g of colorless crystals of **10** (Table 1).

REFERENCES

[1] E. Hoggarth, *J. Chem. Soc.*, 1952, 4811.

[2] T. George, R. Tahilramani, O. A. Dabholkar, *Ind. J. Chem.*, *7*, 1969, 959.

[3] S. Bala, P. Gupta, M. L. Sachdeva, A. Singh, H. K. Pujari, *Ind. J. Chem.*, *16B*, 1978, 481.

[4] G. S. Dhindsa, R. K. Vaid, *Ind. J. Chem.*, *25B*, 1986, 283.

[5] J. Mohan, G. S. R. Anjanayulu, K. V. S. Yamini, *J. Ind. Chem. Soc.*, *68*, 1991, 474.

[6] P. C. Gorgoi, J. C. S. Kataky, *Ind. J. Heterocycl. Chem., 1*, 1991, 61.
[7] P. G. Gorgoi, M. M. Dutta, J. C. S. Kataky, *Heterocycles, 32*, 1991 1897.
[8] J. C. Pascal, H. Pinhas, *Ger. Offen., 2*, 1978, 818, 395; *Chem. Abstr., 90*, 1979, 152246.
[9] P. Molina, M. Alajarin, M. J. P. Vega, R. M. Claramunt, J. Elguero, *J. Chem. Soc., Perkin Trans I*, 1978, 1853.
[10] H. M. R. Hoffmann, *Angew. Chem. Int. Edn., 8*, 1969, 556.
[11] R. C. Seccombe, C. H. L. Kennard, *J. Chem. Soc., Perkin II*, 1973, 9.
[12] H. Beyer, C. F. Kroeger, G. Busse, *Liebigs Ann., 637*, 1966, 135.
[13] K. T. Potis, R. M. Huseby, *J. Org. Chem., 31*, 1966, 3528.
[14] F. Kruzer, M. Wilkinson, *J. Chem. Soc. C*, 1969, 1218.