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Intramolecular Diels-Alder reactions of 1,2,4-triazines. Synthesis of 3-alkylpyridines via Raney nickel desulfurization of thieno[2,3-*b*]pyridines

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ABSTRACT

2-Aryl-2,3-dihydrothieno[2,3-b]pyridines have been prepared via intramolecular Diels-Alder reactions of suitably 3-substituted 1,2,4-triazine intermediates, followed by their reductive desulfurization with Raney Nickel to form 3-substituted pyridines. A one-pot synthesis of 2-aryl-2,3-dihydrothieno[2,3-b]-pyridines from thiosemicarbazide is described as well.

1. Introduction

The versatility displayed with 1,2,4-triazines possessing suitable dienophilic appendages in their 3- or 6-position for obtaining various fused heterocycles via intramolecular Diels-Alder reactions has been previously demonstrated [1–16]. The mode of cycloaddition in these reactions involves addition across C3 and C6 of the 1,2,4-triazine nucleus with subsequent aromatization of the intermediate cycloadduct by extrusion of molecular nitrogen, affording fused heterocyclic species, often under extremely mild conditions [1–15]. The usual need for an electron-rich dienophile is overcome due to the intramolecular process. We have now extended this methodology to form 2-aryl-2,3-dihydrothieno[2,3-*b*]pyridines through 3-appropriately substituted 1,2,4-triazines. These, in turn, can undergo reductive desulfurization with Raney Nickel to give 3-substituted pyridines. Such functionalized pyridines are of interest, since they may serve as potential intermediates for ultimately obtaining various analogues of tetrahydrofolic acid.

2. Results and discussion

The first approach attempted for obtaining 2-aryl-2,3-dihydrothieno[2,3-*b*]pyridines **7**, was via the 3-(arylmethylenothio)-1,2,4-triazines **3**, which by alkylation on the active benzylic position with propargyl bromide could give the desired triazines **5** followed by an intramolecular Diels-Alder reaction to give the 2-aryl-2,3-dihydrothieno[2,3-*b*]pyridines **7** (Scheme 1).

Unfortunately this attempted alkylation proved fruitless, even in the case of the sulfoxide **4**, in which the benzylic position is even more active. No significant influence in the reactivity of the benzylic position could be achieved by varying the electron withdrawing substituents Y in the *para*-position of the phenyl group of **3**. We therefore decided that preparation of the requisite cycloaddition precursors **5** might be achieved by incorporating the dienophilic sidechain into the active methylene group of compound **2** prior to the condensation reaction with the 1,2-dicarbonyl compounds **1.** For this purpose, S-(1-aryl-3-butynyl-) thiosemicarbazide hydrogen bromides or iodides **13** were synthesized through bromides [17] **11** or iodides [17] **12** (Scheme 2).

During the alkylation of thiosemicarbazide to give **13**, an elimination process was observed to occur as well, leading to the 4-aryl-3-buten-1-yne **14.** The elimination process was expected to some extent since heating was required during the alkylation, but it was substantial when substituent Y was a strong electron withdrawing

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[2] This manuscript is dedicated to the memory of Professor EC Taylor.

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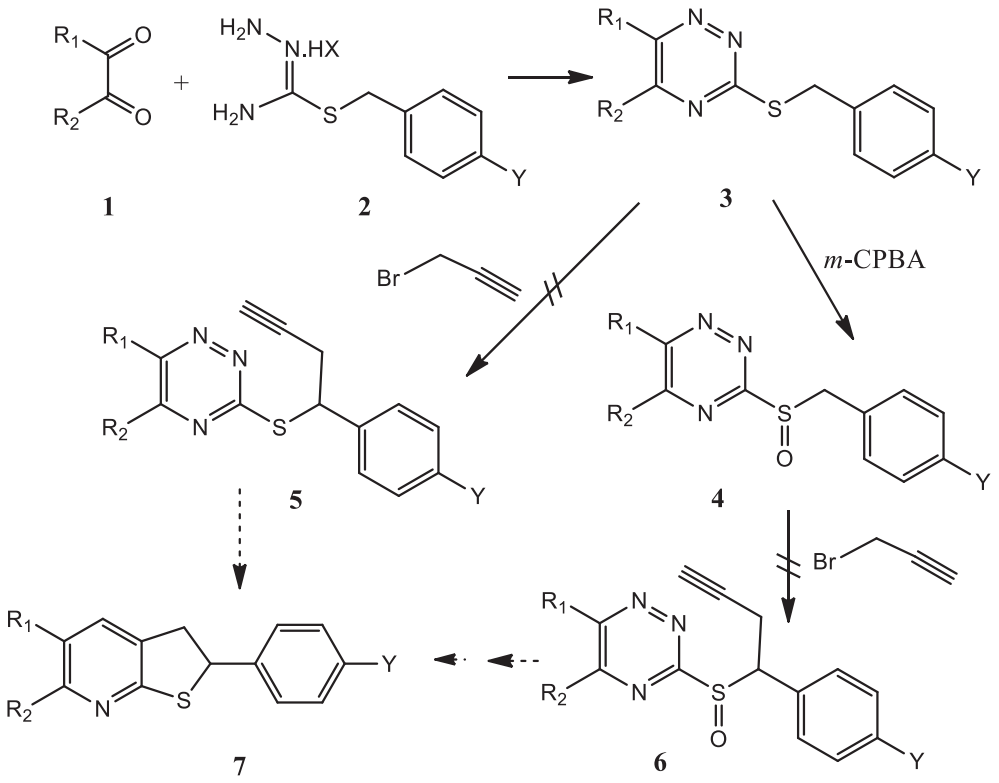
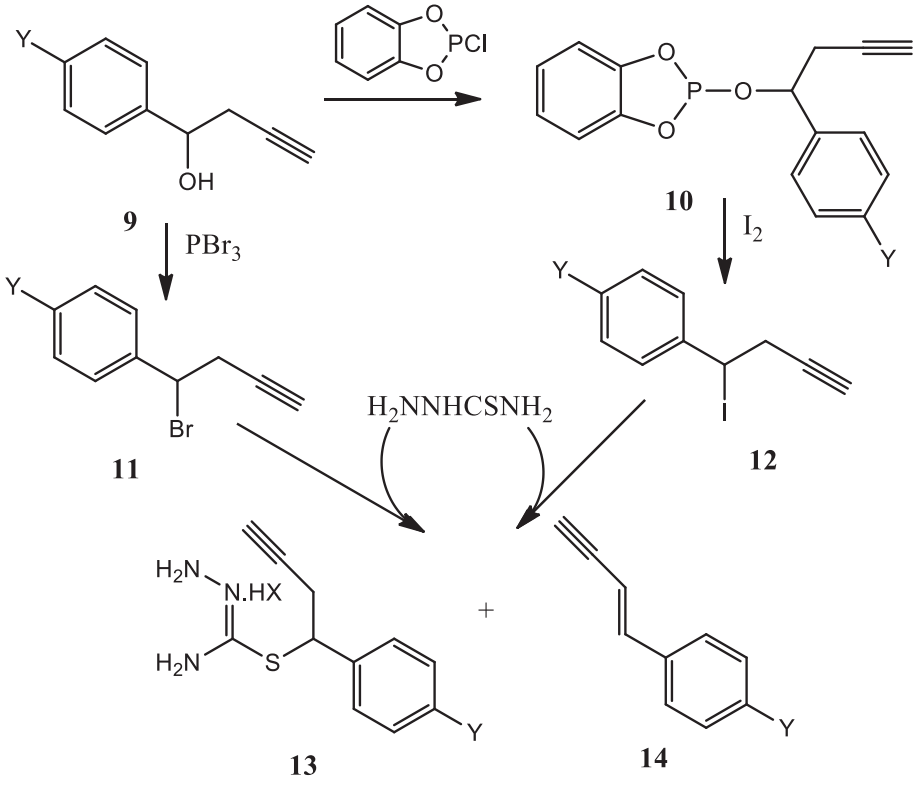


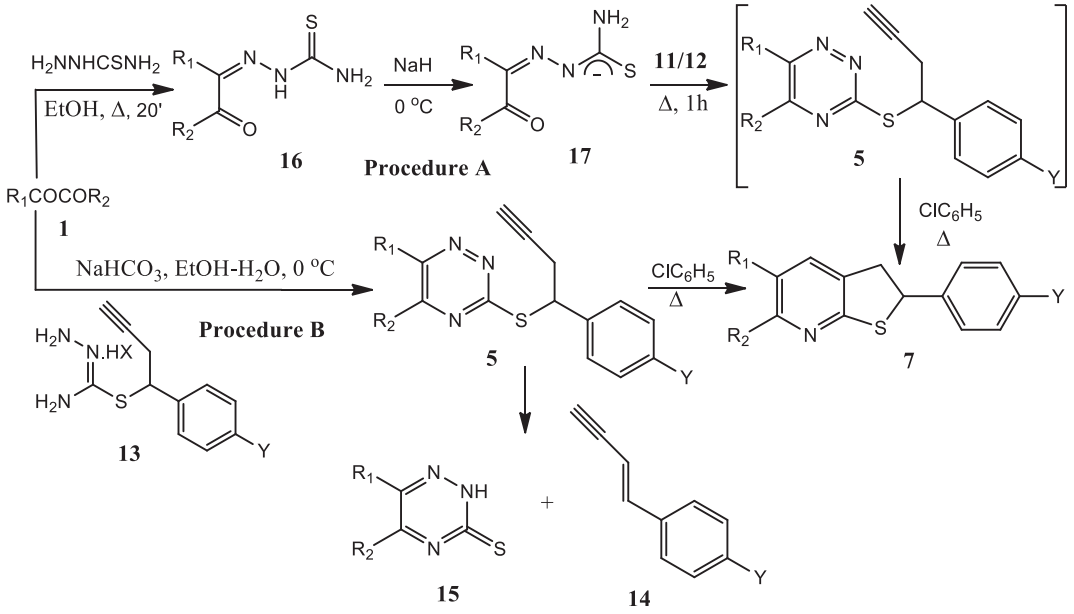
Scheme 1. Procedures attempted for the synthesis of compounds **7**



Scheme 2. Synthetic procedures for compounds **13**

group (e.g., carbomethoxy-group), limiting therefore the yield of **13**. A similar type of elimination reaction takes place also during the heating required for the condensation reaction of **13** with 1,2-dicarbonyl compounds **1**, diminishing thus the yield of **5** (Procedure B, Scheme 3).

yield and temperature. This buttressing effect [7] of the α-substituent in the tethered chain is presumably a consequence of "entropic assistance" provided by the aryl group, which facilitates orientation of the side chain into a preferred conformation for cycloaddition (Thorpe-Ingold effect).



Scheme 3. Successful synthetic procedures for compounds **7a-g**

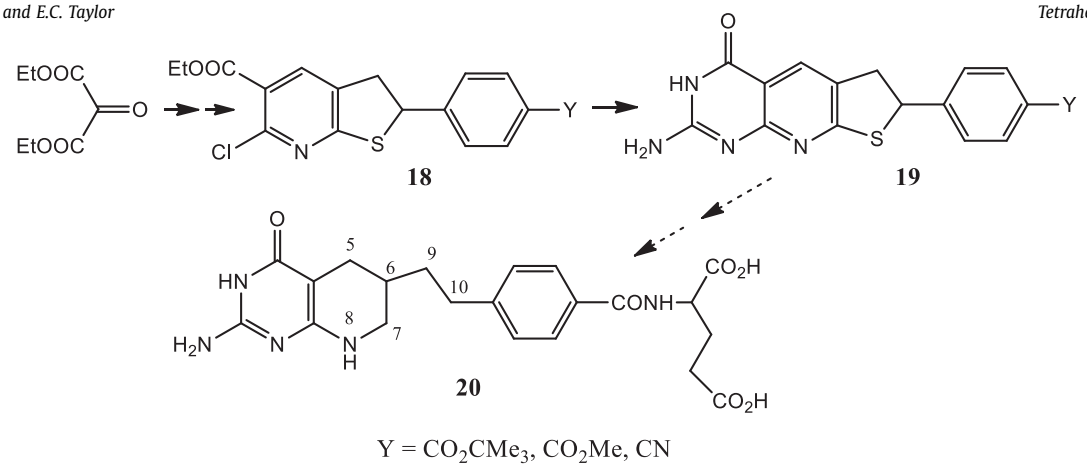
To overcome this problem, Procedure A was used (Scheme 3). This strategy, which has been successfully applied before in similar reactions [7], explored the one-pot synthesis of 2-aryl-2,3-dihydrothieno[2,3-*b*]pyridines **7**, starting from the condensation of 1,2-dicarbonyl compounds **1** with thiosemicarbazide to provide the hydrazones **16**. Deprotonation of **16** with one equivalent of NaH gave the delocalized anion **17**. This upon alkylation with 4-aryl-4-bromo (or iodo-)-1-butyne **11**/(**12**), led directly to the triazines **5**, which was not isolated, avoiding thus its further conversion to the elimination products **14** and **15**. Changing the solvent at this point to chlorobenzene, followed by refluxing for 6 h, resulted in the formation of 2-aryl-2,3-dihydrothieno[2,3-*b*]pyridines **7**. The yields of **7** shown in Table 1 are based on the 1,2-dicarbonyl compounds **1** and therefore are relatively low (except for **7a** in which the yield is based on the corresponding triazine **5a**, where Procedure B was followed). On the other hand, the competitive elimination reaction giving 1,2,4-triazin-3-thione **15** and 4-aryl-3-buten-1-yne **14** (Scheme 3) could not be avoided, due to heating during the Diels-Alder reaction, thus decreasing the yields of **7** to a significant degree. This competitive reaction did not occur when the substituent Y was hydrogen. Since the duration of the Diels-Alder reaction was kept constant (6 h), we cannot compare the effect of the substituents R_1 and R_2 of the triazines **5** on the rate of the condensation reaction. However, the substituent in the α-position of the tethered chain seems to facilitate the Diels-Alder reaction, in terms of time,

We modified the previous methodology to obtain the fused pyridine **18**, derived from diethylketomalonate, which permits the continuation towards the 6,7-annulated-5-deazapterine [18] **19**, a precursor of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid, DDATHF **20** (Scheme 4). 2-Amino-5-deaza-pterines **19** can be obtained by reacting compounds **18** with guanidine hydrochloride in *N*-methyl-2-pyrrolidinone. In fact, we have successfully synthesized such a compound (Y = CN), in 40% yield (data not included). Compounds **19** can then be hydrolyzed to their carboxylic acids and coupled with diethyl L-glutamate. Desulfurization, hydrolysis of the ethyl esters and reduction of the pyridinic ring could lead to the desired compound **20**.

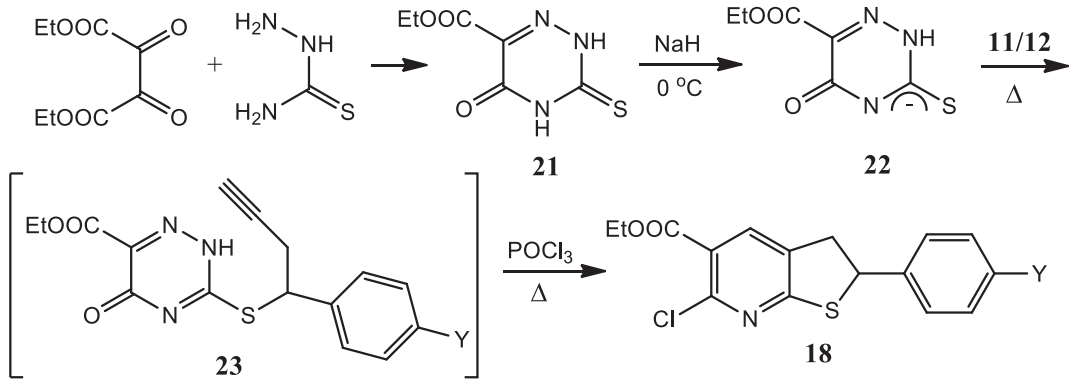
The modification of the procedure consisted of the formation of

Table 1

R_1	R_2	X	Y	7	Yield %	Procedure
H	Ph	Br	H	a	78	B
H	Ph	I	CN	b	29	A
H	Ph	Br	CO_2Me	c	trace	B
H	4-ClC_6H_4	Br	CN	d	30	A
$(CH_2)_4$<		Br	CN	e	15	A
Me	Me	Br	CN	f	30	A
H	4-$MeOC_6H_4$	Br	CN	g	23	A



Scheme 4. Potential synthetic scheme for 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF) **20**



Scheme 5. Synthetic procedure for compounds **18a-c**

the thione [19] **21**, which upon treatment with NaH gave the anion **22**. Alkylation of **22** with **11**/**12** provided the intermediate triazinone **23,** which was refluxed in $POCl_3$ to give directly the 2-aryl-5-carboethoxy-6-chloro-2,3-dihydrothieno[2,3-*b*]pyridine **18** (Scheme 5) and Table 2.

Table 2

Y	23	18	Yield %	mp °C
H	a	a	48	88–89
CN	b[a]	b	15	144–145
CO_2Me	c[a]	c	35	132–134

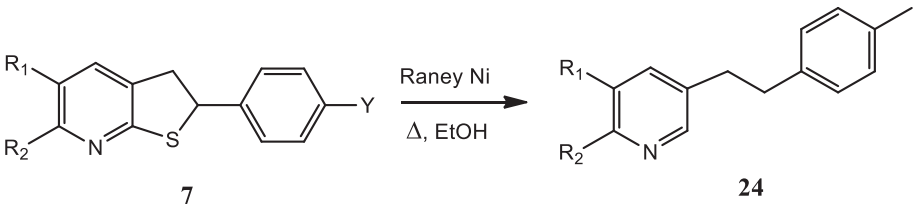
[a] **23b,c** were not isolated to avoid decomposition via elimination.

Finally, reductive desulfurization of **7** was undertaken, to form their corresponding 3-substituted pyridines. This desulfurization with Raney Nickel worked sufficiently well as depicted in Scheme 6, and

Table 3

Y	R_1	R_2	7	24	Yield %	Reflux time (h)
H	H	Ph	**a**	a[a]	86	5
CN	H	Ph	**b**	b[b]	96	5
CN	H	*p*-ClC_6H_4	**d**	b[b]	91	5
CN	$(CH_2)_4$<		**e**	**c**	98	5
CN	Me	Me	**f**	**d**	95	5
CN	H	*p*-$MeOC_6H_4$	**g**	**e**	93	48RT + 2[c]

[a] **24a** is a phenyl-ethyl pyridine, since Y = H in **7a**.
[b] During desulfurization of **7d**, chlorine was cleaved. Therefore, the desulfurization product of **7d** is identical with the desulfurization product of **7b**, characterized as **24b**.
[c] 48RT + 2: 24 h strirring under room temperature and 2 h refluxing in chlorobenzene (132 °C).



Scheme 6. Desulfurization of compounds **7** to obtain compounds **24a-e**

Table 3, but with some restrictions regarding substituents.

It is remarkable that the cyano-group was converted all the way to the methyl-group, presumably via the formation of a primary benzylic amine [20]. Thus, in the case that we need to retain a functional group for its eventual conversion to a carboxyl group, instead of a cyano group, we should use a carboalkoxy group which is not affected [21] by Raney Nickel, or we should attempt the hydrolysis of the nitrile group before the desulfurization. We also observed that the chloro-substituent in **7d** was cleaved during desulfurization [22]. We are not sure if the chlorine in the 6-position of **18** would behave in the same way during desulfurization. In this case, the condensation with guanidine should precede the desulfurization of **18**.

3. Conclusions

Using two alternative routes, we have synthesized a series of 2-aryl-2,3-dihydrothieno[2,3-b]pyridines (**7a-g** and **18a-c**) via intramolecular Diels-Alder reactions of suitably 3-substituted 1,2,4-triazine intermediates. Reaction conditions (e.g. solvent, temperature, reaction time, substitution) could be optimized for improving the yields of these compounds in the future. The reductive desulfurization of **7a-g** with Raney nickel led to the formation of 3-substituted pyridines (**24a-e**) in good yields. Compounds such as **18a-c** can serve as precursors of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF **20**) analogues, known to exhibit anticancer therapeutic properties [23].

4. Experimental section

Melting points were determined on a Thomas-Hoover open capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a PerkinElmer 1320 Infrared Spectrophotometer, and NMR spectra were determined on a Nicolet QE300 (300 MHz) spectrometer. Mass spectra were determined on a AEI MS-9 instrument, and elemental analyses were carried out by Eli Lilly & Co., Indianapolis, Indiana. Commercial reagents were utilized without further purification.

4.1. Formation of 2-aryl-2,3-Dihydrothieno[2,3-b]pyridines (7). Procedure A

A mixture of the 1,2-dicarbonyl compound (10 mmol) and thiosemicarbazide (10.0 mmol) in 30 mL of absolute ethanol was heated at reflux for 20 min. The resulting solution was then cooled in an ice bath, and sodium hydride (80% in mineral oil, 10 mmol) was cautiously added to the mixture, which was then stirred at room temperature with exclusion of water for 15 min. This was followed by the dropwise addition of 4-aryl-4-bromo-(or iodo-) butyne (10.0 mmol), and the resulting reaction mixture was heated at reflux with exclusion of water for 1 h. Ethanol was removed from the reaction mixture by evaporation under reduced pressure, and the residual oily solid was redissolved in chlorobenzene (10 mL). This mixture was refluxed (132 °C) with exclusion of moisture for 6 h. A saturated solution of sodium bicarbonate (20 mL) was added to the resultant reaction solution, and this aqueous mixture was extracted with methylene chloride (3 × 20 mL). The methylene chloride extracts were combined, dried (anhy. Na_2SO_4), and evaporated under reduced pressure to yield an oil which was chromatographed over silica gel (~60 g); elution with methylene chloride-ether (90:10) yielded the desired 2-aryl-2,3-dihydrothieno[2,3-*b*] pyridines (**7**) plus a variable amount of the 5,6-substituted-1,2,4-triazine-3-thiones (**15**) and the corresponding *trans* 4-aryl -3-buten-1-ynes (**14**) [elimination products].

4.2. Procedure B

To a stirred mixture of the phenyl glyoxal hydrate (10.0 mmol) and sodium bicarbonate (10.0 mmol) in ethanol (10 mL) at 0 °C was added dropwise a solution of S-(1-aryl-3-butynyl)thiosemicarbazide (10.0 mmol) in water (10 mL). After the addition the reaction mixture was stirred at room temperature for 4 h. Ethanol was removed from the resulting reaction mixture by evaporation under reduced pressure, and the residual aqueous mixture was extracted with methylene chloride (3 × 20 mL). The methylene chloride extracts were combined, dried (anhy. Na_2SO_4), and evaporated under reduced pressure. The residual oil was purified by silica gel (~50 g) column chromatography with methylene chloride as eluting solvent. The 5-phenyl-S-(1-aryl-3-butynylthio)-1,2,4-triazine **5** was isolated as an oil and was refluxed in chlorobenzene for 6 h, giving the corresponding fused pyridine **7**.

4.3. 2,6-Diphenyl-2,3-dihydrothieno[2,3-b]pyridine (7a)

Following Procedure B with 3-(1-phenyl-3-butynylthio)-5-phenyl-triazine (**5a**). Yield: 78%. Obtained as a white solid, mp 130–132 °C; following recrystallization from 50 : 50 ether/petroleum ether. ^{1}H NMR ($CDCl_3$) δ 3.46 (dd, $J_1 = 15$ Hz, $J_2 = 6$ Hz, 1H); 3.68 (dd, $J_1 = 15$ Hz, $J_2 = 9$ Hz, 1H); 5.13 (t, $J = 7.5$ Hz, 1H); 7.27–7.49 (m, 10H); 7.98 (d, $J = 6$ Hz, 2H). HRMS: Calcd for $C_{19}H_{15}NS$: *m/z* 289.0925. Found *m/z* 289.0919. Anal. Calcd for $C_{19}H_{15}NS$: C, 78.86; H, 5.22; N, 4.87. Found: C, 77.43; H, 5.07; N, 5.37.

4.4. 2-(p-Cyanophenyl)-6-phenyl-2,3-dihydrothieno[2,3-b]pyridine (7b)

Following Procedure A with phenyl glyoxal monohydrate. Yield: 29%. Obtained as a white solid, mp 137–138 °C. ^{1}H NMR ($CDCl_3$) δ 3.40 (dd, $J_1 = 15$ Hz, $J_2 = 6$ Hz, 1H); 3.75 (dd, $J_1 = 18$ Hz, $J_2 = 9$ Hz, 1H); 5.09 (t, $J = 7.5$ Hz, 1H); 7.40–7.57 (m, 5H); 7.62 (dd, $J_1 = 6$ Hz, $J_2 = 3$ Hz, 4H); 7.98 (dd, $J_1 = 3$ Hz, $J_2 = 1.5$ Hz, 2H). HRMS: Calcd for $C_{20}H_{14}N_2S$: *m/z* 314.0878. Found *m/z* 314.0868. Anal. Calcd for $C_{20}H_{14}N_2S$: C, 76.40; H, 4.49; N, 8.91; S, 10.20. Found: C, 76.14; H, 4.70; N, 8.74; S, 10.05.

4.5. 2-(p-Carbomethoxyphenyl)-6-phenyl-2,3-dihydrothieno[2,3-b] pyridine (7c)

Following Procedure B with the corresponding triazine **5c**. Isolated by preparative TLC in trace quantity. ^{1}H NMR ($CDCl_3$) δ 3.40 (dd, $J_1 = 15$ Hz, $J_2 = 6$ Hz, 1H); 3.75 (dd, $J_1 = 18$ Hz, $J_2 = 9$ Hz, 1H); 3.92 (s, 3H); 5.15 (t, $J = 9$ Hz, 1H); 7.40–8.06 (m, 11H). HRMS: Calcd for $C_{21}H_{17}NO_2S$: *m/z* 347.0990. Found *m/z* 347.0980.

4.6. 2-(p-Cyanophenyl)-6-(p-chlorophenyl)-2,3-dihydrothieno[2,3-b]pyridine (7d)

Following Procedure A with *p*-chlorophenyl glyoxal monohydrate. Yield = 30%. Obtained as a white solid, mp 158–160 °C. ^{1}H NMR ($CDCl_3$) δ 3.40 (dd, $J_1 = 15$ Hz, $J_2 = 6$ Hz, 1H); 3.75 (dd, $J_1 = 15$ Hz, $J_2 = 6$ Hz, 1H); 5.09 (t, $J = 6$ Hz, 1H); 7.39–7.63 (m, 8H); 7.92 (d, $J = 9$ Hz, 2H). HRMS: Calcd for $C_{20}H_{13}N_2SCl$: *m/z* 348.0488. Found *m/z* 348.0472. Anal. Calcd for $C_{20}H_{13}N_2SCl$: C, 68.86; H, 3.76; N, 8.03; S, 9.19; Cl, 10.16. Found: C, 68.64; H, 3.69; N, 7.93; S, 8.96; Cl, 9.90.

4.7. 2-(p-Cyanophenyl)-2,3,5,6,7,8-hexahydrothieno[2,3-b] quinoline (7e)

Following Procedure A with 1,2-cyclohexanedione. Yield: 15%.

Obtained as a white solid, mp 134–135 °C; following recrystallization from 50 : 50 ether/petroleum ether. ^{1}H NMR ($CDCl_3$) δ 1.76–1.90 (m, 4H); 2.68 (t, J = 6 Hz, 2H); 2.83 (t, J = 6 Hz, 2H); 3.30 (dd, J_1 = 18 Hz, J_2 = 9 Hz, 1H); 3.65 (dd, J_1 = 15 Hz, J_2 = 6 Hz, 1H); 5.01 (t, J = 6 Hz, 1H); 7.09 (s, 1H); 7.51 (d, J = 6 Hz, 2H); 7.58 (d, J_2 = 6 Hz, 2H). HRMS: Calcd for $C_{18}H_{16}N_2S$: *m/z* 292.1034. Found *m/z* 292.1023. Anal. Calcd for $C_{18}H_{16}N_2S$: C, 73.94; H, 5.52; N, 9.58; S, 10.96. Found: C, 73.66; H, 5.45; N, 9.72; S, 11.11.

4.8. 2-(p-Cyanophenyl)-5,6-dimethyl-2,3-dihydrothieno[2,3-b] pyridine (7f)

Following Procedure A with 2,3-butanedione. Yield: 30%. Obtained as a white solid, mp 115–117 °C; following recrystallization from 50 : 50 ether/petroleum ether. ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3H); 2.43 (s, 3H); 3.30 (dd, J_1 = 15.9 Hz, J_2 = 6.8 Hz, 1H); 3.65 (dd, J_1 = 15.9 Hz, J_2 = 8.4 Hz, 1H); 5.02 (t, J = 7.7 Hz, 1H); 7.15 (s, 1H); 7.52 (d, J = 6 Hz, 2H); 7.60 (d, J = 6 Hz, 2H). HRMS: Calcd for $C_{16}H_{14}N_2S$: *m/z* 266.0878. Found *m/z* 266.0866. Anal. Calcd for $C_{16}H_{14}N_2S$: C, 72.15; H, 5.30; N, 10.52; S, 12.04. Found: C, 71.94; H, 5.33; N, 10.31; S, 11.97.

4.9. 2-(p-Cyanophenyl)-6-(p-methoxyphenyl)-2,3-dihydrothieno [2,3-b]pyridine (7g)

Following Procedure A with *p*-methoxyphenyl glyoxal monohydrate. Yield: 23%. Obtained as a white solid, mp 143–145 °C; following recrystallization from 50 : 50 methylene chloride/petroleum ether. ^{1}H NMR ($CDCl_3$) δ 3.38 (dd, J_1 = 16.1 Hz, J_2 = 6.9 Hz, 1H); 3.73 (dd, J_1 = 16.2 Hz, J_2 = 8.5 Hz, 1H); 3.86 (s, 3H); 5.08 (t, J = 8.1 Hz, 1H); 6.97 (d, J = 9 Hz, 2H); 7.35 (d, J = 6 Hz, 1H); 7.43 (d, J = 6 Hz, 1H); 7.55 (d, J = 9 Hz, 2H); 7.62 (J = 6 Hz, 2H); 7.93 (d, J = 9 Hz, 2H). HRMS: Calcd for $C_{21}H_{16}N_2OS$: *m/z* 344.0983. Found *m/z* 344.0972. Anal. Calcd for $C_{21}H_{16}N_2OS$: C, 73.23; H, 4.68; N, 8.13; S, 9.31. Found: C, 72.98; H, 4.56; N, 7.98; S, 9.12.

4.10. 2-Phenyl-5-carboethoxy-6-chloro-2,3-dihydrothieno[2,3-b] pyridine (18a)

A suspension of 3-(1-phenyl-3-butynylthio)-6-carboethoxy-1,2,4-triazine-5(2H)-one (**23a**) (0.13 g, 0.395 mmol) in 2.63 mL of phosphorous oxychloride was heated at reflux for 10 h. After this period, the volatiles of the reaction mixture were evaporated under reduced pressure and the residual black gum was taken up in methylene chloride and filtered through a silica gel pad, eluting with 1:1 hexane/ethyl acetate. The filtrate was evaporated under reduced pressure to yield 0.06 g (48%) of a white solid, mp 88–89 °C. ^{1}H NMR ($CDCl_3$) δ 1.39 (t, J = 7.5 Hz, 3H); 3.44 (dd, J_1 = 18 Hz, J_2 = 9 Hz, 1H); 3.68 (dd, J_1 = 18 Hz, J_2 = 9 Hz, 1H); 4.39 (q, J = 7.5 Hz, 2H); 5.17 (t, J = 7.5 Hz, 1H); 7.30–7.42 (m, 5H); 7.92 (s, 1H). HRMS: Calcd for $C_{16}H_{14}NO_2SCl$: *m/z* 319.0434. Found *m/z* 319.0430. Anal. Calcd for $C_{16}H_{14}NO_2SCl$: C, 60.09; H, 4.41; N, 4.38. Found: C, 59.88; H, 4.40; N, 4.36.

4.11. 2-(p-Cyanophenyl)-5-carboethoxy-6-chloro-2,3-dihydrothieno[2,3-b]pyridine (18b)

To a mixture of 6-carboethoxy-4,5-dihydro-5-oxo-1,2,4-triazine-3-thione (**21**) (1.0 g, 4.98 mmol) and sodium hydride (0.15 g, 5.0 mmol, 80% dispersion in mineral oil) in 7.0 mL of absolute ethanol cooled to 0 °C, a solution of 4-(*p*-cyanophenyl)-4-bromo-1-butyne **11** (1.16 g, 4.96 mmol) in 6.0 mL of ethanol was added dropwise. After the addition, the mixture was stirred at 0 °C for 15 min and then heated at reflux for 1 h. To the cooled solution was added 14.0 mL of saturated ammonium chloride solution. The mixture was extracted with methylene chloride (3 × 15 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was heated with 20.0 mL of phosphorus oxychloride at reflux for 6 h. The excess of phosphorus oxychloride was evaporated under reduced pressure and the residue was dissolved in a small amount of methylene chloride and filtered through a silica gel pad with 50:50 hexane/ethyl acetate as eluant. Evaporation under reduced pressure gave 0.26 g (15%) of a white solid, mp 144–145 °C. ^{1}H NMR ($CDCl_3$) δ 1.39 (t, J = 7.5 Hz, 3H); 3.40 (dd, J_1 = 15 Hz, J_2 = 6 Hz, 1H); 3.75 (dd, J_1 = 18 Hz, J_2 = 9 Hz, 1H); 4.38 (q, J = 7.5 Hz, 2H); 5.16 (t, J = 7.5 Hz, 1H); 7.51 (d, J = 9 Hz, 2H); 7.63 (d, J = 9 Hz, 2H); 7.88 (s, 1H). HRMS: Calcd for $C_{17}H_{13}N_2O_2SCl$: *m/z* 344.0386. Found *m/z* 344.0393. Anal. Calcd for $C_{17}H_{13}ClN_2O_2S$: C, 59.21; H, 3.80; N, 8.12; S, 9.30; Cl, 10.28. Found: C, 58.96; H, 3.74; N, 7.89; S, 9.09; Cl, 10.46.

4.12. 2-(4-Carbomethoxyphenyl)-5-carboethoxy-6-chloro-2,3-dihydrothieno[2,3-b] pyridine (18c)

6-Carboethoxy-4,5-dihydro-5-oxo-1,2,4-triazine-3-thione (**21**) (1.35 g, 6.72 mmol) was stirred for 10 min at 0 °C in *N*-methyl-2-pyrrolidinone (12 mL) and NaH (0.16 g, 6.67 mmol) was added carefully. After a while the suspension became a deep red solution and the stirring was continued for another 15 min at 0 °C. 4-Bromo-4-(4-carbomethoxyphenyl)-1-butyne (1.27 g, 4.76 mmol) in *N*-methyl-2-pyrrolidinone (4 mL) was added dropwise and the stirring at 0 °C was continued for an additional 15 min before heating for 2 h at 78–80 °C in an oil bath. The reaction mixture was then cooled, sat. NH_4Cl solution (24 mL) was added, followed by extraction with CH_2Cl_2 (3 × 24 mL). The organic layer was dried with Na_2SO_4, filtered and evaporated under reduced pressure. *N*-methyl-2-pyrrolidinone was removed by distillation, using an oil pump. Phosphorous oxychloride (20 mL) was added to the residue followed by refluxing for 3 h under a nitrogen atmosphere. The excess of phosphorus oxychloride was evaporated under reduced pressure and the residue was dissolved in a small amount of methylene chloride and filtered through a silica gel pad with 60:40 hexane/ethyl acetate as eluant. Evaporation under reduced pressure provided pale yellow crystals which were further purified by trituration with ether (0.63 g, 35%, based on the bromide). mp 132–134 °C. ^{1}H NMR ($CDCl_3$) δ 1.39 (t, J = 7.5 Hz, 3H); 3.43 (dd, J_1 = 15 Hz, J_2 = 6 Hz, 1H); 3.72 (dd, J_1 = 18 Hz, J_2 = 9 Hz, 1H); 3.91 (s, 3H); 4.38 (q, J = 7.5 Hz, 2H); 5.18 (t, J = 7.5 Hz, 1H); 7.47 (d, J = 6 Hz, 2H); 7.87 (s, 1H); 8.00 (d, J = 6 Hz, 2H). HRMS: Calcd for $C_{18}H_{16}ClNO_4S$: *m/z* 377.0488. Found *m/z* 377.0478.

4.13. 3-(1-Phenyl-3-butynylthio)-5-phenyl-1,2,4-triazine (5a)

Following Procedure B: Yield: 62%. Obtained as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 1H); 3.07–3.14 (m, 2H); 5.31 (t, J = 6 Hz, 1H); 7.27–8.12 (m, 10H); 9.35 (s, 1H). HRMS: Calcd for $C_{19}H_{15}N_3S$: *m/z* 317.0987. Found *m/z* 317.0987.

4.14. 3-[1-(p-Carbomethoxyphenyl)-3-butynylthio]-5-phenyl-1,2,4-triazine (5c)

Following Procedure B: Obtained in trace quantity as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.05 (d, J = 2.5 Hz, 1H); 3.05–3.12 (m, 2H); 3.90 (s, 3H); 5.34 (t, J = 6 Hz, 1H); 7.53–8.17 (m, 9H); 9.37 (s, 1H). HRMS: Calcd for $C_{21}H_{17}N_3O_2S$: *m/z* 375.1041. Found *m/z* 375.1034.

4.15. 3-(1-Phenyl-3-butynylthio)-6-carboethoxy-1,2,4-triazin-5(2H)-one (23a)

A solution of S-(1-phenyl-3-butynyl)isothiosemicarbazide

hydrobromide (**13a**) (0.42 g, 1.4 mmol), diethylketomalonate (0.25 g, 1.4 mmol) and sodium bicarbonate (0.12 g, 1.4 mmol) in 3 mL of ethanol was heated at reflux for 6 h and stirred at room temperature overnight. The white precipitate was collected by filtration and washed with water and ether. Recrystallization from ethanol/water gave 0.33 g (70%) of a white solid, mp 188–190 °C. ^{1}H NMR ($CDCl_3$) δ 1.44 (t, J = 7.5 Hz, 3H); 2.03 (d, J = 2.5 Hz, 1H); 3.03 (m, 2H); 4.48 (q, J = 6 Hz, 2H); 5.27 (t, J = 6 Hz, 1H); 7.31–7.48 (m, 5H). HRMS: Calcd for $C_{16}H_{15}N_3O_3S$: *m/z* 329.0834. Found *m/z* 329.0829.

4.16. S-(1-phenyl-3-butynyl)isothiosemicarbazide hydrobromide (13a)

A mixture of 4-bromo-4-phenyl-1-butyne (2.0 g, 9.5 mmol) and thiosemicarbazide (0.87 g, 9.5 mmol) in 20 mL of ethanol was heated at reflux for 2 h. The solution was evaporated under reduced pressure and the residue filtered through a silica gel pad. The silica gel pad was eluted first with methylene chloride to remove the unreacted starting materials and then eluted with ethanol. Evaporation of the ethanol gave 0.97 g (34%) of a white solid, mp 137–138 °C. ^{1}H NMR (DMSO-d_6) δ 2.41–2.55 (m, 1H); 2.80–2.99 (m, 2H); 3.29–3.42 (m, 2H); 5.16 (t, J = 7.5 Hz, 1H); 7.14–7.48 (m, 5H); 9.30 (bs, 1H). HRMS: Calcd for $C_{11}H_{13}N_3S$: *m/z* 219.0830. Found *m/z* 219.0835.

4.17. S-[1-(p-carbomethoxyphenyl)-3-butynyl]isothiosemicarbizide hydrobromide (13c)

Following the procedure described for **13a:** Yield: 21%. Obtained as a pale yellow solid, mp 169–170 °C. ^{1}H NMR (DMSO-d_6) δ 2.07 (s, 2H); 2.13 (s, 2H); 2.29 (s, 1H); 2.91–2.97 (m, 2H); 3.91 (s, 3H); 5.38 (t, J = 7.5 Hz, 1H); 7.70–8.05 (dd, J_1 = 9 Hz, J_2 = 9 Hz, 4H); 9.52 (bs, 1H). HRMS: Calcd for $C_{13}H_{15}N_3O_2S$: *m/z* 277.0885. Found *m/z* 277.0880.

4.18. Reductive desulfurization of 7a-b and 7d-g with Raney Nickel. General Procedure [24]

A mixture of **7** (90 mg) and Raney Nickel (ca. 1.0 g, Aldrich, washed with water, then ethanol) in 20 mL ethanol was refluxed for 5 h (except of the case of **7g**, see Table 3). The mixture was filtered through Celite, which was washed well with ethanol. Evaporation of the ethanol gave compounds **24a-e** which were recrystallized from 50:50 methylene chloride/hexanes.

4.19. 2-Phenyl-5-(2-phenylethyl)pyridine (24a)

Yield: 86%. Obtained as a white solid, mp 80–82 °C. ^{1}H NMR ($CDCl_3$) δ 2.98 (s, 4H); 7.17–7.67 (m, 10H); 7.99 (dd, J_1 = 9 Hz, J_2 = 6 Hz, 2H), 8.52 (s, 1H). HRMS: Calcd for $C_{19}H_{17}N$: *m/z* 259.1361. Found *m/z* 259.1366.

4.20. 2-Phenyl-5-[2-(p-tolyl)ethyl]pyridine (24b)

Yield: 96%. Obtained as a white solid, mp 70–72 °C. ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H); 2.95 (s, 4H); 7.10–7.11 (m, 4H); 7.44–7.67 (m, 5H); 8.01 (dd, J_1 = 9 Hz, J_2 = 6 Hz, 2H); 8.52 (s, 1H). HRMS: Calcd for $C_{20}H_{19}N$: *m/z* 273.1517. Found *m/z* 273.1514. Anal. Calcd for $C_{20}H_{19}N$: C, 87.87; H, 7.01; N, 5.12. Found: C, 87.61; H, 7.28; N, 5.06.

4.21. 3-[2-(p-Tolyl)ethyl]-5,6,7,8-tetrahydro-quinoline (24c)

Yield: 98%. Obtained as a white solid, mp 42–43 °C. ^{1}H NMR ($CDCl_3$) δ 1.79–1.89 (m, 4H); 2.32 (s, 3H); 2.73 (t, J = 6 Hz, 2H); 2.83 (s, 4H); 2.89 (t, J = 6 Hz, 2H); 7.09 (m, 4H); 7.15 (s, 1H); 8.17 (s, 1H). HRMS: Calcd for $C_{18}H_{21}N$: *m/z* 251.1674. Found *m/z* 251.1685.

4.22. 2,3-Dimethyl-5-[2-(p-tolyl)ethyl]pyridine (24d)

Yield: 95%. Obtained as a white solid, mp 30–32 °C. ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H); 2.33 (s, 3H); 2.47 (s, 3H); 2.84 (s, 4H); 7.08 (m, 4H); 7.20 (s, 1H); 8.14 (s, 1H). HRMS: Calcd for $C_{16}H_{19}N$: *m/z* 225.1517. Found *m/z* 225.1518.

4.23. 2-(p-Methoxyphenyl)-5-[2-(p-tolyl)ethyl]pyridine (24e)

Yield: 93%. Obtained as a white solid, mp 106–108 °C. ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H); 2.92 (s, 4H); 3.86 (s, 3H); 7.04 (d, J = 23 Hz, 2H); 7.10 (m, 4H); 7.54 (dd, J_1 = 21, J_2 = 9 Hz, 2H); 7.93 (d, J = 6 Hz, 2H); 8.45 (s, 1H). HRMS: Calcd for $C_{21}H_{21}NO$: *m/z* 303.1623. Found *m/z* 303.1623. Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.11; H, 6.95; N, 4.84.

4.24. Preparation of bromides 11, iodides 12 and carbinols 9

Bromides **11** or iodides **12** were prepared from their corresponding carbinols **9**, with pyridine and phosphorus tribromide or with *o*-phenylene phosphorochloridite, pyridine and iodine respectively, as previously described [17], and purified by distillation or column chromatography. Carbinols **9** were obtained by a modified Reformatsky reaction [17,25,26], in which the catalyst was zinc-copper couple instead of zinc, from the corresponding *p*-substituted benzaldehydes and propargyl bromide. Their purification was achieved by column chromatography (silica gel, CH_2Cl_2–Et_2O, 90/10).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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This work was performed about 30 years ago, while M.V. Papadopoulou was doing postdoctoral research under the supervision of Professor E.C. Taylor (to whom this paper is dedicated) at Princeton University.

Appendix A. Supplementary data

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