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SYNTHESIS OF FUNCTIONALIZED 1*H*-PYRAZOLO[4,3-*e*]-[1,2,4]TRIAZINES AND THEIR FUSED DERIVATIVES VIA *IPSO*-SUBSTITUTION OF METHYLSULFONYL GROUP WITH *O*-, *N*-, *S*- AND *C*-NUCLEOPHILES[1]

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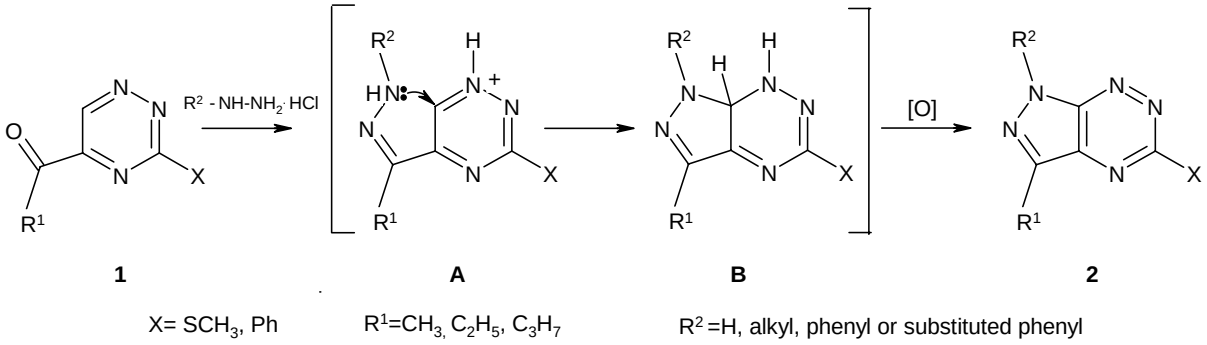
Abstract–*Ipso*-substitution reaction of 3-methyl-5-methylsulfonyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (**4**) with a range of *C*-, *N*-, *O*- and *S*-nucleophiles afforded the corresponding substitution products (**5a-m**) in high yields. The reaction of 5-hydrazino compound (**5m**) with carboxylic acids furnished 1*H*-pyrazolo[4,3-*e*]-1,2,4-triazolo[4,3-*b*][1,2,4]triazines (**8a**) and (**8b**).

A variety of naturally occurring bicyclic heteroaromatic compounds are well known for their wide range of biological activity.[2] It has been reported that *O*- and *N*-alkyl derivatives of 1*H*-pyrazolo[4,3-*e*][1,2,4]triazine such as *pseudoiodinine* and *nostocine* A, isolated from the cultural fluids of *Pseudomonas fluorescent* and *Nostoc spongiaeforme*, exhibit an interesting combination of biological activity.[3-5] In addition to cytostatic effects they inhibit the growth of Gram-positive and Gram-negative bacteria with a somewhat weaker action against fungi.[5] Despite the potential usefulness of such compounds, simple methods for the introduction of a range substituents into this heterocyclic ring system have not been developed and for this reason new advances in this subject continue to be of interest.

Previous published synthetic approaches toward making 3,5-disubstituted 1*H*-pyrazolo[4,3-*e*][1,2,4]triazine have utilized the condensation of either 5-arylidene- or 5-benzoyl-3-phenyl-1,2,4-triazin-6-ones with hydrazine or phenylhydrazines.[6,7] The methods have been effectively applied only in the synthesis of phenyl and substituted phenyl derivatives and are inefficient for generation of analogues with varying C-5 substituents. Recently, we have reported a new approach to 1*H*-pyrazolo[4,3-*e*][1,2,4]triazines (**2**) by one-pot reaction between 5-acyl-1,2,4-triazines (**1**) and various hydrazine derivatives under acidic conditions.[8,9] The reaction most probably proceeds *via* the corresponding

hydrazone (**A**), followed by acid-promoted ring closure, involving the bicyclic intermediate (**B**), that by an air oxidation gives **2** (see Scheme 1).

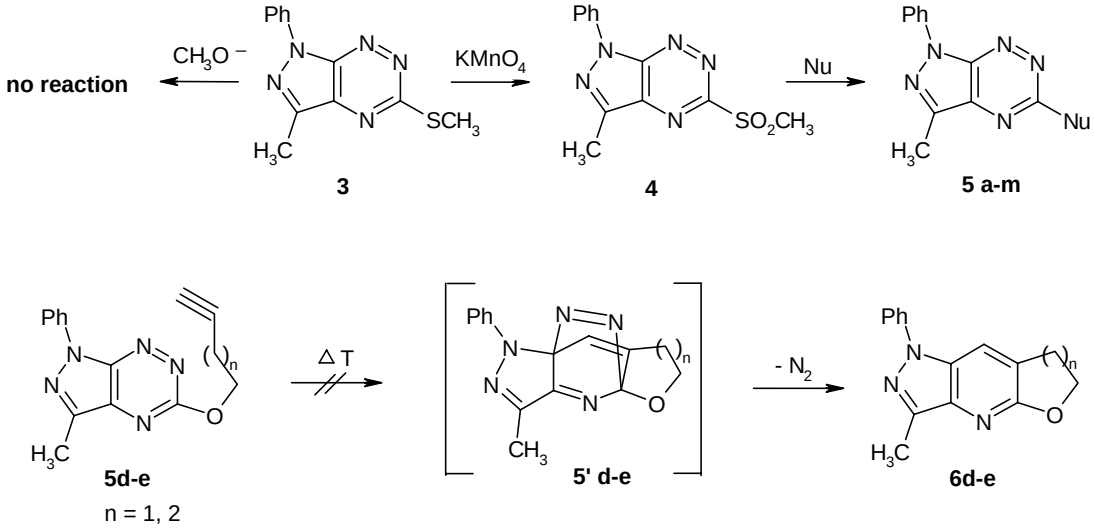


Scheme 1

This method seems to be general and allows to introduce the substituents into pyrazole and triazine rings in the first step. Moreover, the presence of good leaving group at C-5 in **2** should provide a rapid derivatization of this heterocyclic core *via* nucleophilic displacement. Since alkylsulfanyl substituents bound to the 1,2,4-triazine ring are very reactive and readily exchangeable by a number of heteroatom nucleophiles[10] we have applied this route to the synthesis of C-5 functionalized 1*H*-pyrazolo[4,3-*e*][1,2,4]triazine derivatives.

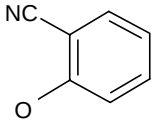
The common intermediate, 3-methyl-5-methylsulfanyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (**3**) has been readily prepared using literature procedure[8] from easily available 5-acetyl-3-methylsulfanyl-1,2,4-triazine[11] and phenylhydrazine hydrochloride. In the initial experiment **3** has been subjected to reaction with sodium methoxide in boiling methyl alcohol. Contrary to expectation compound (**3**) appeared to be unreactive and attempts to perform nucleophilic substitution of methylsulfanyl group afforded only unreactive starting material. In searching for more effective nucleofugal group, we have explored the substitution reaction between sodium methoxide and 3-methyl-5-methylsulfonyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (**4**), easily available by oxidation of **3** with potassium manganate(VII) under phase transfer catalytic conditions. When instead of **3**, compound (**4**) is used, and the same reaction conditions were applied as mentioned above, 3-methoxy derivative (**5b**) is formed in 90% yield within 30 min (Scheme 2, Table 1). Sodium hydroxide and sodium ethoxide react efficiently with **4** giving directly 5-substituted products (**5a**) and (**5c**). A similar behavior was observed with alkoxides bearing an acetylene unit at the terminal position. These nucleophiles give functionalized pyrazolotriazines (**5d**) and (**5e**) with dienophilic side chain tethered to C-5 (Table 1, Entries 4 and 5). Also nucleophilic substitution of methylsulphinate by phenoxy group leading to **5f** occurs readily in reaction of **4** with sodium *o*-cyanophenoxide in DMF (Table 1, Entry 6). When 1,2,4-triazines bearing side chain containing an alkyne or a cyano functionality are employed thermal cycloadditions, the

bicyclic or polycyclic pyridines are formed after expulsion of nitrogen.[2] Application of this intramolecular Diels-Alder reaction for compounds (**5d-e**) should provide a direct route to furo[2,3-*b*]pyrazolo[3,4-*e*]pyridine (**6d**) and pirano[2,3-*b*]pyrazolo[3,4-*e*]pyridine (**6e**), which could otherwise hardly be prepared by other methods. However, all attempts to transform compounds (**5d-e**) into **6d-e** fail because of low reactivity of the fused 1,2,4-triazine unit in 1*H*-pyrazolo[4,3-*e*][1,2,4]triazine ring system.

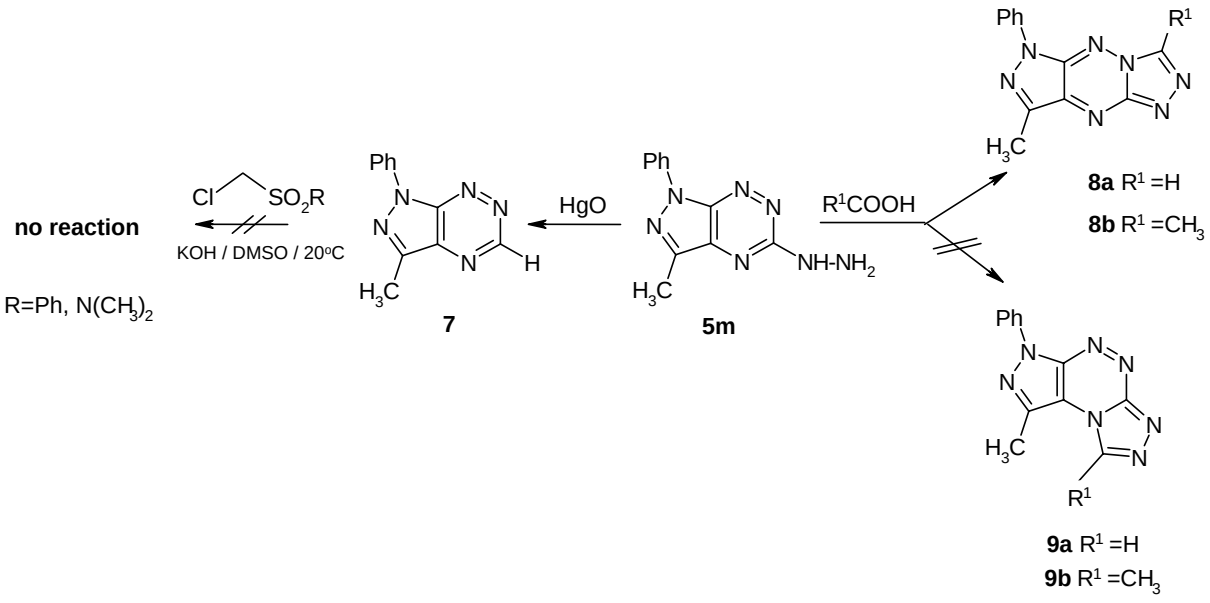


Scheme 2

Table 1. Yields and reaction times of compounds (**5a-m)**.

Entry	5	Nu	Reaction times	Yield [%]
1	**a**	OH	10 min	90
2	**b**	OCH_3	30 min	90
3	**c**	OC_2H_5	1 h	88
4	**d**	$OCH_2CH_2C{\equiv}CH$	2 h	74
5	**e**	$OCH_2CH_2CH_2C{\equiv}CH$	2 h	75
6	**f**		3 h	84
7	**g**	S-Ph	10 min	97
8	**h**	$CH(COOC_2H_5)_2$	3 h	90
9	**i**	NH_2	1 h	83
10	**j**	NH-Ph	17 h	73
11	**k**	$NH\text{-}CH_2\text{-}Ph$	4.5 h	89
12	**l**	$NH\text{-}CH_2CH_2CH_2CH_3$	1 h	99
13	**m**	$H_2N\text{-}NH_2$	3 h	76

The ability of the 5-methylsulfonyl group in compound (**4**) to undergo the displacement reactions mentioned above, has been successfully employed for the synthesis of sulfur, carbon and nitrogen analogues of 1*H*-pyrazolo[4,3-*e*][1,2,4]triazine. Reactions of **4** with sodium thiophenoxide and ethyl malonate carbanion in THF afford the corresponding substitution products (**5g**) and (**5h**) in good yield. The reaction of **4** with liquid ammonia at –33 ^{o}C gives desired 5-amino-3-methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (**5i**) quantitatively. Interesting, treatment of **4** with ethanolic ammonia at -18 ^{o}C afforded **5i** in low yield , whereas 5-ethoxy derivative (**5c**) was obtained as a main product. Primary aliphatic and aromatic amines are also excellent reagents for this nucleophilic substitution reaction giving good yields of products, regardless of the kind of the amine used (Scheme 2, Table 1, Entries 9-11). Similarly, the treatment of **4** with anhydrous hydrazine in teterahydrofuran provides 5-hydrazino-3-methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (**5m**) exclusively. Oxidation of the latter with yellow mercury(II) oxide results in replacement of 5-hydrazino group by hydrogen, giving 3-methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (**7**), respectively. Bearing in mind that functionalization of monocyclic 1,2,4-triazines can be achieved in a more direct way by nucleophilic substitution of hydrogen we have attempted to apply this methodology to the synthesis of C-5 substituted pyrazolotriazines. Among many variants of this process, the most general appears to be vicarious nucleophilic substitution of hydrogen when carbanions with a good leaving group attached to the carbanionic center are employed as nucleophiles.[12,13,14] This reaction enables the preparation of a wide variety of the C-3 and C-5 substituted 1,2,4-triazines.[15] However, pyrazolotriazine derivative (**7**) is resistant to nucleophilic substitution of hydrogen, when reacting with chloromethyl phenylsulfone or *N*,*N*-dimethyl(chloromethane)sulfonamide in dry DMSO in the presence of powdered potassium hydroxide (Scheme 3).



Scheme 3

The potential of 5-hydrazino compound (**5m**) for synthesis of more elaborate ring systems is illustrated by reaction of **5m** with carboxylic acids (see Scheme 3). Thus treatment of hydrazino compound (**5m**) with formic or acetic acid furnished 1*H*-pyrazolo[4,3-*e*]-1,2,4-triazolo[4,3-*b*][1,2,4]triazines (**8a**) and (**8b**) respectively, the derivatives of a new heteroaromatic ring system (Scheme 3). Theoretically, another direction of ring closure toward the N-4 atom may be assume in which case the angularly arranged 1*H*-pyrazolo[4,3-*e*]-1,2,4-triazolo[3,4-*c*][1,2,4]triazines (**9a**) and (**9b**) would form. NOE difference spectroscopy provides an unambiguous assignment for linear structure for **8b**. It was found that irradiation of the protons of the methyl group in pyrazole ring in **8b** (2.65 ppm) did not lead to Nuclear Overhauser Enhancement for the signal of protons of the methyl group in 1,2,4-triazole ring (2.17 ppm). Lack of such interactions confirms the linear structure for compounds (**8a**) and (**8b**).

In summary, we have prepared several functionalised 1*H*-pyrazolo[4,3-*e*][1,2,4]triazines (**5a-m**) by nucleophilic substitution of 4 bearing sulfonyl group at C-5 with *O*-, *N*-, *S*- and *C*-nucleophiles. The ease and efficiency of this one-pot approach makes it attractive for the preparation of other 1*H*-pyrazolo[4,3-*e*][1,2,4]triazine analogues and their condensed derivatives.

EXPERIMENTAL

Melting points were determined on Boetius melting point apparatus and are uncorrected. IR spectra were measured with a Magna IR-760 spectrophotometer. The ^{1}H-NMR spectra were recorded in deuteriochloroform ($CDCl_3$) on a Varian Gemini 200 MHz spectrometer. Chemical shifts are expressed in ppm with reference to TMS as an internal standard. Coupling constants are given in hertz (Hz). MS spectra were measured on AMD 604 spectrometer [electron impact (EI)] and API 350 [electrospray ionization (ESI)]. Elemental analyses were recorded on Perkin-Elmer 2400-CHN analyser and the results for the indicated elements were within 0.3 % of the calculated values.

3-Methyl-5-methylsulfonyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (4)

To a solution of **3** (257 mg, 1 mmol) in 20 mL of benzene were added water (30 mL), potassium manganate(VII) (474 mg, 3 mmol), catalytic amounts of tetrabutylammonium bromide (65 mg, 0.2 mmol) and 1,5 mL of acetic acid. The reaction mixture was stirred at rt for 1 h. A saturated solution of $Na_2S_2O_5$ in water was added to the mixture until the purple color disappeared. The organic layer was separated and water phase was extracted with benzene (3x10 mL). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel and chloroform as eluent) and recrystallized from ethanol to give 257 mg (89%) of **4**.

mp 141 ^{o}C; ^{1}H-NMR ($CDCl_3$) δ: 2.87 (s, 3H), 3.60 (s, 3H), 7.40-7.49 (m, 1H), 7.56-7.67 (m, 2H), 8.33-

8.39 (m, 2H); IR (KBr) cm^{-1}: 1600, 1350, 1120, 820, 780, 700; MS (*m*/*z*, %): 289 (22) [M^+], 141 (50), 104 (40), 77 (100); Anal. Calcd for $C_{12}H_{11}N_5O_2S$: C, 49.82; H, 3.80; N, 24.22. Found: C, 49.86; H, 3.82; N, 24.14.

5-Hydroxy-3-methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (5a)

A solution of sulfone (**4**) (145 mg, 0.5 mmol) and KOH (31 mg, 0.55 mmol) in ethanol-water 4:1 (20 mL) was refluxed for 10 min. After that time the mixture was acidified with acetic acid. The red precipitate that formed was filtered off to give 102 mg (90%) of **5a**. mp 235-237 ^oC; ^1H-NMR (CD_3COOD) δ: 2.58 (s, 3H), 7.26-7.34 (m, 1H), 7.48-7.52 (m, 2H), 8.01-8.06 (m, 2H); HRMS (ESI, *m*/z) 228.0881, Calcd for $C_{11}H_{10}N_5O$ (M^+H) 228.0880.

The hygroscopic nature of the compound led to variability in the microanalytical data.

5-Methoxy-3-methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (5b) and 5-ethoxy-3-methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (5c)

Compound (**4**) (289 mg, 1 mmol) was added to a solution of metal sodium (26 mg, 1.1 mmol) in dry appropriate alcohol-methanol or ethanol (20 mL). The mixture was heated at reflux (for the reaction time see Table 1). The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel and eluted with chloroform. Evaporation of the solvent afforded **5b** or **5c**.

5b mp121-122 ^oC (recrystallized from ethanol); ^1H-NMR ($CDCl_3$) δ: 2.70 (s,3H), 4,27 (s, 3H), 7.29-7.38 (m, 1H), 7.50-7.60 (m, 2H), 8.31-8.38 (m, 2H); IR (KBr) cm^{-1}: 1600, 1510, 1120, 1030,780;

MS (m/z, %): 241 (45) [M^+], 213 (14), 129 (48), 104 (25), 95 (25), 77 (100); Anal. Calcd for $C_{12}H_{11}N_5O$: C, 59.75; H, 4.56; N, 29.04. Found: C, 59.59; H, 4.55; N, 28.96.

5c mp 104-105 ^oC (recrystallized from ethanol); ^1H-NMR ($CDCl_3$) δ: 1.57 (t, 3H, J=7.0 Hz), 2.69 (s, 3H), 4.70 (q, 2H, J=7 Hz), 7.29-7.38 (m, 1H), 7.50-7.60 (m, 2H), 8.30-8.37 (m, 2H); IR (KBr) cm^{-1}: 1600, 1130, 1070, 780; MS (EI, *m*/z, %): 255 (45) [M^+], 227 (13), 199 (18), 129 (16), 104 (36), 77 (100); Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.09; N, 27.45. Found: C, 61.28; H, 5.06; N, 27.25.

5-(3-Butynyloxy)-3methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (5d) and 5-(4-petynyloxy)-3-methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (5e)

To a suspension of sodium hydride (45 mg, 1.1 mmol, 60 % suspension in paraffin oil) in dry tetrahydrofuran (20 mL) was added appropriate unsaturated alcohol (1.1 mmol) and then 289 mg (1 mmol) of **4** at once. The mixture was heated at reflux for 2 h. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography packing with silica gel and using chloroform as eluent.

5d mp 134-135°C (recrystallized from ethanol); ^{1}H-NMR ($CDCl_3$) δ: 2.07 (t, 1H, J=2.6 Hz), 2.70 (s, 3H), 2.83-2.91 (m, 2H, J=2.7 Hz, J=7.0 Hz), 4.75 (t, 2H, J=7.0 Hz), 7.30-7.39 (m, 1H), 7.50-7.61 (m, 2H), 8.30-8.37 (m, 2H); IR (KBr) cm^{-1}: 3280 (C≡C), 2936, 1600, 1130, 1100, 780; MS (*m*/*z*, %): 279 (1) [M^+]; 251 (100), 223 (4), 209 (7), 181 (14), 154 (5), 77 (50); Anal. Calcd for $C_{15}H_{13}N_5O$: C, 64.51; H, 4.65; N, 25.08. Found: C, 64.29; H, 4.78; N, 24.96.

5e mp 99-100 °C (recrystallized from ethanol); ^{1}H-NMR ($CDCl_3$) δ: 1.99 (t, 1H, J=2.6 Hz), 2.11-2.25 (m, 2H), 2.48-2.56 (td, 2H, J=2.6 Hz, J=6.6 Hz), 4.74 (t, 2H, J=6.1 Hz), 7.31-7.39 (m, 1H), 7.52-7.60 (m, 2H), 8.32-8.37 (m, 2H); IR (KBr) cm^{-1}: 3250 (C≡C), 2930, 1600, 1330, 1130, 1070, 700; MS (*m*/*z*, %): 293 (5) [M^+], 265 (38), 236 (6), 188 (10), 130 (16), 77 (100); Anal. Calcd for $C_{16}H_{15}N_5O$: C, 65.52; H, 5.12; N, 23.89. Found: C, 65.32; H, 5.32; N, 23.99.

5-(2-Cyanophenoxy)-3-methyl-1-phenyl-1*H*-pirazolo[4,3-*e*][1,2,4]triazine (5f)

To a solution of sulfone (**4**) (289 mg, 1 mmol) in dry DMF (10 mL) sodium 2-cyanophenolate (155 mg, 1.1 mmol) was added. The resulting solution was stirred at 120 °C for 1.5 h, then was poured into ice/water (100 mL). The precipitate solid of **5f** was collected by filtration and washed with water. The crude product was purified on column chromatography (silica gel, chloroform) to yield 259 mg (79%) of yellow solid. mp 183 °C (recrystallized from ethanol); ^{1}H-NMR ($CDCl_3$) δ: 2.71 (s, 3H), 7.31-7.46 (m, 3H), 7.50-7.60 (m, 2H), 7.68-7.81 (m, 2H), 8.29-8.36 (m, 2H); IR (KBr) cm^{-1}: 2980, 2230 (C≡N), 1600, 1300, 1150, 750; MS (m/z, %): 328 (37) [M^+]; 299 (11), 259 (6), 223 (7), 196 (11), 77 (100); Anal. Calcd for $C_{18}H_{12}N_6O$: C, 65.85; H, 3.65; N, 25.60. Found: C, 65.57; H, 3.83; N, 25.68.

3-Methyl-1-phenyl-5-phenylosulfanyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (5g).

To the solution of **4** (145 mg, 0.5 mmol) in dry THF (5 mL) cooled to 0-5 °C was added thiophenol (0.1 mL) and sodium hydride (24 mg, 0.55 mmol, 60 %). The resulting mixture was stirred at 0-5 °C for 10 min. After that time the solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (silica gel, chloroform) and recrystallized from ethanol to give 144 mg (90%) of **5g**.

mp 142 °C (recrystallized from ethanol); ^{1}H-NMR ($CDCl_3$) δ: 2.65 (s, 3H), 7.33-7.37 (m, 1H), 7.46-7.57 (m, 5H), 7.71-7.76 (m, 2H), 8.29-8.34 (m, 2H); IR (KBr) cm^{-1}: 1600, 1500, 1290, 1120, 780, 700; MS (*m*/*z*, %): 319 (44) [M^+], 290 (69), 214 (28), 188 (16), 121 (100), 77 (86); Anal. Calcd for $C_{17}H_{13}N_5S$: C, 63.94; H, 4.07; N, 21.94. Found: C, 63.85; H, 4.21; N, 22.04.

2-(3-Methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazin-5-yl)malonic acid diethyl ester (5h)

To a solution of sulfone **4** (145 mg, 0.5 mmol) in dry THF (10 mL) was added malonic diethyl ester (0.3 mL, 2 mmol) and sodium hydride (80 mg, 2 mmol, 60 %). The reaction mixture was refluxed for 3 h and

then the solvent was evaporated under reduced pressure. The resulting precipitate was chromatographed (silica gel, chloroform) and recrystallized from ethanol to give 140 mg (76 %) of **5h**. mp 140 °C; ^{1}H-NMR ($CDCl_3$) δ: 1.32 (t, 6H, J=7 Hz), 2.77 (s, 3H), 4.34 (q, 4H, J=7 Hz), 5.54 (s, 1H), 7.33-7.41 (m, 1H), 7.53-7.61 (m, 2H), 8.35-8.41 (m, 2H); HRMS (ESI) *m*/*z*, 392.1343, Calcd for $C_{18}H_{19}N_5O_4Na$ [M^+Na] 392.1329. This compound undergoes partial hydrolysis during recrystallization from ethanol what led to variability in the microanalytical data.

5-Amino-3-methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (5i)

Compound (**4**) (289 mg, 1 mmol) was dissolved in 15 mL of dry liquid ammonia with exclusion of moistuire. The mixture was stirred for 1 h at –33 °C and after that time ammonia was evaporated. Crude solid was recrystallized from ethanol to give 219 mg (97 %) of **5i** as yellow solid. mp 241 °C; ^{1}H-NMR ($CDCl_3$) δ: 2.70 (s, 3H), 7.27-7.50 (m, 3H, $1H_{Ar,}$ NH_2), 7.50-7.62 (m, 2H), 8.05-8.14 (m, 2H); IR (KBr) cm^{-1}: 3350, 2990, 1600, 760, 700; MS (*m*/z, %): 226 (65) [M^+]; 198 (23), 156 (5), 121 (9), 104 (65), 95 (27), 77 (100); Anal. Calcd for $C_{11}H_{10}N_6$: C, 58.40; H, 4.42; N, 37.16. Found: C, 58.25; H, 4.51; N, 36.99.

General procedure for the reaction of the sulfone (4) with amines

The sulfone (**4**) (289 mg, 1 mmol) was dissolved in 5 mL of anhydrous and fresh distilled amine. The resulting solution was refluxed until the starting materials disappeared (TLC). The solvent was evaporated to dryness and the residue was purified on silica gel and eluted with chloroform. Evaporation of the solvent gave products (**5j-5l**).

3-Methyl-1-phenyl-5-phenylamino-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (5j)

mp 264 °C (recrystallized from ethanol); ^{1}H-NMR ($CDCl_3$) δ: 2.72 (s, 3H), 6.65 (s, 1H, NH), 7.18-7.25 (m, 1H), 7.34-7.49 (m, 3H), 7.50-7.61 (m, 2H), 7.68-7.81 (m, 2H), 8,12-8.25 (m, 2H); IR (KBr) cm^{-1}: 3280, 2980, 1610, 1500, 1130, 770, 690; MS (*m*/z, %): 302 (46) [M^+], 273 (23), 232 (9), 197 (18), 104 (48), 77 (100); Anal. Calcd for $C_{17}H_{14}N_6$: C, 67.54; H, 4.63; N, 27.81. Found: C, 67.55; H, 4.71; N, 27.78.

5-Benzylamino-3-methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (5k)

mp 173 °C (recrystallized from ethanol); ^{1}H-NMR ($CDCl_3$) δ: 2.67 (s, 3H), 4.83 (s, 2H), 7.26-7.32 (m, 1H), 7.32-7.40 (m, 3H), 7.40-7.48 (m, 2H), 7.41-7.48 (m, 2H), 8.03-8.12 (m, 2H); IR (KBr) cm^{-1}: 3250, 1580, 750, 700; MS (*m*/z, %): 316 (67) [M^+], 287 (41), 211 (23), 142 (14), 91 (100), 77 (83); Anal. Calcd for $C_{18}H_{16}N_6$: C, 68.35; H, 5.06; N, 26.58. Found: C, 68.05; H, 5.22; N, 26.62.

5-Butylamino-3-methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (5l)

mp 151 °C (recrystallized from ethanol); ^{1}H-NMR ($CDCl_3$) δ: 0.99 (t, 3H, J=7.3 Hz), 1.44-1.53 (m, 2H), 1.70-1.78 (m, 2H), 2.69 (s, 3H), 3.64 (t, 2H, J=7.1 Hz), 7.34-7.38 (m, 1H), 7.51-7.56 (m, 2H), 8.04-8.07 (m, 2H); IR (KBr) cm^{-1}: 3250, 2970, 1580, 760,700; MS (*m*/*z*, %): 282 (78) [M^+]; 253 (11), 211 (51), 184 (16), 104 (37), 77 (100); Anal. Calcd for $C_{15}H_{18}N_6$: C, 63.82; H, 6.38; N, 29.78. Found: C, 63.76; H, 6.36; N, 29.74.

5-Hydrazino-3-methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (5m)

To the solution of **4** (289 mg, 1 mmol) in dry THF (10 mL) cooled to 0-5 °C was added 0.1 mL (3 mmol) anhydrous hydrazine. The reaction was stirred at 0-5 °C for 30 min and additional 3 h at rt. After that time the solvent was evaporated *in vacuo* and the crude product was recrystallized from ethanol to give 215 mg (89%) of the orange solid. mp 190 °C; ^{1}H-NMR ($CDCl_3$) δ: 2.66 (s, 3H), 4.09 (s, 2H, NH_2), 6.91 (s, 1H, NH), 7.31-7.35 (m, 1H), 7.49-7.57 (m, 2H), 8.28-8.33 (m, 2H); IR (KBr) cm^{-1}: 3300, 1600, 750; MS (EI, *m*/*z*, %): 241 (30) [M^+], 226 (12), 198 (10), 129 (20), 104 (34), 77 (100); HRMS (ESI) *m*/*z* 242.1133, Calcd for $C_{11}H_{12}N_7$ (M^+H) 242.1149.

The hygroscopic nature of this compound led to variability in the microanalytical data.

3-Methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine (7)

To the solution of compound (**5m**) (241 mg, 1 mmol) in dry ethanol (20 mL) yellow mercury oxide(II) (1.08 g, 5 mmol) was added and the mixture was heated at reflux for 1 h. After that time the reaction mixture was filtered off and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, chloroform) to give 129 mg (61%) of **7**. mp 95 °C (recrystallized from ethanol); ^{1}H-NMR ($CDCl_3$) δ: 2.80 (s, 3H), 7.33-7.41 (m, 1H), 7.54-7.62 (m, 2H), 8.36-8.41 (m, 2H), 9.82 (s, 1H); IR (KBr) cm^{-1}: 1600, 760, 700; MS (*m*/*z*, %): 211 (42) [M^+], 183 (18), 142 (100), 115 (46), 77 (64), 51 (90); Anal. Calcd for $C_{11}H_9N_5 \cdot 0.25\ H_2O$: C, 61.25; H, 4.40; N, 32.48. Found: C, 61.52; H, 4.39; N, 32.70.

7-Methyl-1-phenyl-1*H*-pyrazolo[4,3-*e*]-1,2,4-triazolo[4,3-*b*][1,2,4]triazine (8a) and 3,7-dimethyl-5-phenyl-1*H*-pyrazolo[4,3-*e*]-1,2,4-triazolo[4,3-*b*][1,2,4]triazine (8b)

Compound (**5m**) (120 mg, 0.5 mmol) was treated with appropriate carboxylic acid (2 mL) and heated at 100 °C for 1 h. The reaction mixture was poured into ice/water (50 mL) and the precipitated solids (**8a**) or (**8b**) were collected by filtration and washed with water. The crude products were purified by column chromatography using chloroform-ethanol mixture 30:1 as eluent.

8a Yield 92 %. mp 180 °C (recrystallized from ethanol); ^{1}H-NMR ($CDCl_3$) δ: 2.80 (s, 3H), 7.31-7.39 (m, 1H), 7.52-7.60 (m, 2H), 8.09-8.14 (m, 2H), 9.35 (s, 1H); MS (*m*/*z*, %): 251 (100) [M^+], 155 (12, 103 (72),

77(44); Anal. Calcd for $C_{12}H_9N_7$: C, 57.37; H, 3.58; N, 39.04. Found: C, 57.30; H, 3.60; N, 39.05.

8b Yield 89 %. mp 205 ^oC (recrystallized from ethanol); ^1H-NMR ($CDCl_3$) δ: 2.17 (s, 3H), 2.65 (s, 3H), 7.32-7.36 (m, 1H), 7.49-7.57 (m, 2H), 8.27-8.31 (2H); MS (*m*/*z*, %): 265 (4) [M^+], 241 (41), 226 (11), 197 (12), 129 (18), 104 (25), 94 (12), 77 (100); Anal. Calcd for $C_{13}H_{11}N_7 \cdot H_2O$: C, 55.12; H, 4.59; N, 34.62. Found: C, 55.13; H, 4.62; N, 34.45.

REFERENCES

1. Part 25 in a series "1,2,4-Triazines in Organic Synthesis". For Part 24, see D. Branowska, *Tetrahedron*, 2004, in print.
2. H. Neunhoeffer, in *Comprehensive Heterocyclic Chemistry*, Vol. 6, ed. by A. R. Katritzky and C. V. Ress, Pergamon Press, Oxford, 1996, pp. 507-573.
3. H. J. Linder and G. Schaden, *Chem. Ber*., 1972, **105**, 1949.
4. K. Hirata, H. Nakagami, J. Takashina, T. Mahmud, M. Kobayashi, Y. In, T. Ishida, and K. Miyamoto, *Heterocycles*, 1996, **43**, 1513.
5. V. V. Smirnov, E. A. Kiprianowa, A. D. Garagulya, S. E. Esipov, and S. A. Dovjenko, *FEMS Microbiology Lett*., 1997, **153**, 357.
6. K. Nalepa and J. Slouka, *Pharmazie*, 1984, **39**, 504.
7. M. Z. A. Badr, M. M. Aly, Z. H. Khalil, and A. A. Attalla, *Ind. J. Chem*., 1982, **21B**, 115.
8. A. Rykowski, M. Mariusz, and Z. Karczmarzyk, *Heterocycles*, 2000, **53**, 2175.
9. M. Mojzych and A. Rykowski, *Polish J. Chem*., 2003, **77**, 1797.
10. V. N. Charushin, S. G. Alexeev, O. N. Chupakhin, and H. C. van der Plas, *Adv. Heterocycl. Chem*., 1989, **46**, 73.
11. A. Rykowski and T. Lipińska, *Synt. Comm*., 1996, **26,** 4409.
12. V. N. Charushin, O. N. Chupakhin, and H. C. van der Plas "*Nucleophilic Substitution of Hydrogen*", Academic Press, 1994.
13. M. Mąkosza and K. Wojciechowski, *Heterocycles*, 2001, **54**, 445.
14. M. Mąkosza and K. Wojciechowski, *Chem. Rev*., 2004, **104**, 2631.
15. A. Rykowski and M. Mąkosza, *Liebigs Ann. Chem.*, 1988, 627.