A FACILE ROUTE TO THE 6-HETARYL SUBSTITUTED PYRROLO[1,2-*a*]THIENO[3,2-*e*]PYRIMIDINE DERIVATIVES

Yulian M. VOLOVENKO, Elizaveta V. RESNYANSKA[1,*] and Anton V. TVERDOKHLEBOV

Kiev National Taras Shevchenko University, 01033, Volodimirska str., 62, Kiev, Ukraine; e-mail: [1] atver@mail.univ.kiev.ua

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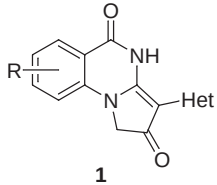
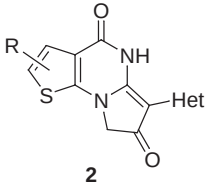
Hitherto unknown 6-hetaryl-4,5,7,8-tetrahydropyrrolo[1,2-*a*]thieno[3,2-*e*]pyrimidine-4,7-diones (**7a**–**7g**) were prepared by reaction of ethyl 2-aminothiophene-3-carboxylates **5** with 4-chloro-2-hetaryl-3-oxobutanonitriles **4** in DMF at 100 °C. When the same reagents were treated in the presence of triethylamine, a dependence of the reaction pathway on the nature of the hetaryl substituent in chloronitrile component was observed. This was explained in terms of steric factors.

Keywords: Nitrogen heterocycles; Pyrrolo[1,2-*a*]thieno[3,2-*e*]pyrimidines; Thiophenes; 2-Aminothiophene-3-carboxylates; 4-Chloro-2-hetaryl-3-oxobutanonitriles; Heterocyclization.

As a continuation of our research directed to the synthesis of hetaryl-substituted tricyclic heterocycles[1,2], the preparation of the 3-hetaryl-pyrrolo[1,2-*a*]quinazolines **1** has been worked out[3]. In order to extend our investigations in this field, it would be interesting to obtain corresponding thieno analogues **2**. Since certain pyrroloquinazolines like **1** were found to possess several types of biological activity[4], compounds **2** seem to be the attractive objects for screening. Moreover, some thienopyrimidines the moiety of which is included in the ring system of **2** were reported to exhibit promising biological properties[5].



1

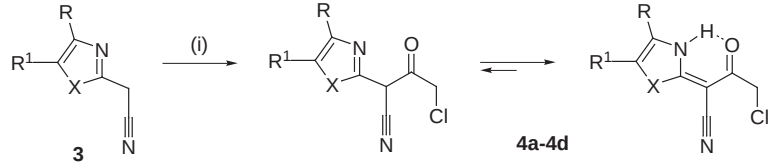


2

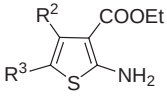
Some syntheses of pyrrolo[1,2-*a*]thieno[3,2-*e*]pyrimidine derivatives are reported in the literature[6–9]. All of them utilize 2-aminothiophene-3-carboxylates or carbonitriles as starting building blocks, probably because they are readily available *via* Gewald's procedure[10]. Some of these methods are step-by-step synthetic sequences including initial construction of the suitably functionalized pyrrole ring based on the amino group of starting aminothiophene followed by pyrimidine ring closure[6]. However, the overall yields of the desired tricycles using these reaction sequences are low and this fact makes them unsatisfactory for preparative purposes. Corresponding tandem synthetic procedures seem to be more convenient. Three approaches based on the tandem strategy have been published. The first one is based on reaction of 2-aminothiophene-3-carboxamides with 4-oxocarboxylic acids[7]. This is a good method; however, the number of available 4-oxo acids is quite limited. The second way includes conversion of 2-aminothiophenes into *N*-chloroacetyl derivatives, which undergo tandem double heterocyclization under treatment with active methylene nitriles in alkaline conditions[8]. Finally, the third approach allows to obtain pyrrolo-[1,2-*a*]thieno[3,2-*e*]pyrimidines directly from 2-aminothiophene derivatives by treatment with variously substituted 4-halobutanonitriles[9]. Nevertheless, none of the mentioned synthetic methods was applied for preparation of hitherto unknown hetaryl-substituted derivatives of the target moiety. The present paper reports our recent results in this field. It should be also noted that hetaryl-substituted derivatives of an isomeric system, namely pyrrolo-[1,2-*a*]thieno[2,3-e]pyrimidine, have been prepared[11].

Reaction of Gewald's thiophenes with 4-halobutanonitrile derivatives (3rd approach) was chosen for the synthesis of the title compounds because preparation of the required hetaryl-substituted 4-chlorobutanonitriles **4a**–**4d** *via* direct chloroacetylation of hetarylacetonitriles **3** (Scheme 1) was well elaborated in our laboratory[12]. However, chloronitriles **4** differ from the other 4-halobutanonitriles used in such syntheses previously[9] by the presence of the heterocyclic nitrogen possessing nucleophilic properties. Therefore, the intramolecular alkylation leading to compounds like **6** can take place as an alternative to the normal reaction pathway with aminothiophenes. Nevertheless, in spite of the well-known low basicity of the amino group of the Gewald's thiophenes and difficulty of its alkylation[13], chloronitriles **4a**–**4d** were found to react with compounds **5** in DMF at 100 °C to yield 6-hetaryl-4,5,7,8-terahydropyrrolo[1,2-*a*]thieno-[3,2-*e*]pyrimidine-4,7-diones **7a**–**7g**. The reaction probably occurs as a three-step tandem process. The initial step is an alkylation of amino group of compound **5** by chloronitrile **4**. Subsequent intramolecular addition of

the NH group to the nitrile triple bond leads to the intermediate amino-pyrrole derivative, which immediately undergoes intramolecular acylation of the newly formed amino group by the ester group to yield compound **7**. Under non-basic conditions, the mentioned intramolecular alkylation was not observed. Nonetheless, when the reaction of chloronitriles **4** with aminothiophenes **5** was carried out in the presence of triethylamine, the behavior of compounds **4a** and **4b** differed from that of **4c** and **4d**. When benzimidazolyl and benzothiazolyl derivatives **4a**, **4b** were used as starting

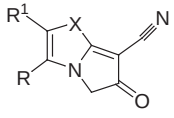


5	R^2	R^3
a	$-(CH_2)_4-$	
b	Ph	H



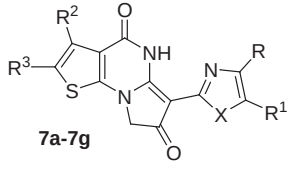
5a, 5b

4	R	R^1	X
a	benzo		NH
b	benzo		S
c	$4\text{-}BrC_6H_4$	H	S
d	$4\text{-}FC_6H_4$	H	S



6a, 6b

or **7e-7g**



7a-7g

6	R	R^1	X
a	benzo		NH
b	benzo		S

7	R	R^1	R^2	R^3	X
a	benzo		$-(CH_2)_4-$		NH
b	benzo		Ph	H	NH
c	benzo		$-(CH_2)_4-$		S
d	benzo		Ph	H	S
e	$4\text{-}BrC_6H_4$	H	$-(CH_2)_4-$		S
f	$4\text{-}FC_6H_4$	H	$-(CH_2)_4-$		S
g	$4\text{-}FC_6H_4$	H	Ph	H	S

(i) $ClCH_2COCl$, dioxane, 1 equivalent of pyridine

(ii) DMF, 2 equivalents of **5a, 5b**, 100 °C

(iii) dioxane, 1 equivalent of **5a, 5b**, 1 equivalent of Et_3N, reflux

SCHEME 1

materials, only tricyclic products of intramolecular alkylation **6a**, **6b** were isolated, whereas 4-arylthiazolyl derivatives **4c**, **4d** gave the expected pyrrolo[1,2-*a*]thieno[3,2-*e*]pyrimidines **7e**–**7g**. It should be noted that the transformation of chloronitriles **4a**, **4b** into compounds **6a**, **6b** on treatment with triethylamine or other bases has been reported previously[12,14]. Apparently, the different behavior of derivatives **4a**, **4b** and **4c**, **4d** under alkaline conditions is explained in terms of steric factors. In the case of compounds **4c**, **4d**, the substituent R shields heterocyclic nitrogen hindering intramolecular alkylation. Such hindrance is absent in compounds **4a**, **4b** and that facilitates their conversion into **6a**, **6b** in the presence of triethylamine.

An attempt to carry out the discussed reaction with ethyl 5-acetyl-2-amino-4-methylthiophene-3-carboxylate (**5c**, $R^2 = CH_3$, R^3 = Ac) failed. Only starting chloronitriles **4a**–**4d** were recovered after heating with compound **5c** in DMF for several hours. Perhaps the presence of an additional electron-withdrawing group, namely acetyl, decreases the nucleophilicity of the amino group making its alkylation impossible.

The structure of compounds **7a**–**7g** was confirmed by ^{1}H NMR, IR data and elemental analysis. ^{1}H NMR spectra of tricycles **7a**–**7g** recorded in DMSO-d_6 show a two-proton singlet at δ 4.5–4.8 ppm assigned to the methylene group. A D_2O-exchangable broad signal of the NH group is observed at δ 11.5–12.0 ppm. The proton signals of substituents R, R^1, R^2, R^3 appear at expected δ values. There are no signals of the ethoxy group in the ^{1}H NMR spectra of compounds **7**. Their IR spectra revealed the absence of nitrile absorption indicating clearly the ring closure with its participation. At the same time, strong absorption was observed in the 1 650–1 690 cm^{-1} region (two separate bands or occasionally one broad band). It was assigned to the two carbonyls. The absence of both absorption above 1 700 cm^{-1} in IR and ethoxy group signals in ^{1}H NMR confirms incorporation of the ester group into pyrimidine ring. Hence the spectral data and elemental analysis are in good agreement with the structure of 6-hetaryl-4,5,7,8-tetrahydropyrrolo[1,2-*a*]thieno[3,2-*e*]pyrimidine-4,7-diones **7a**–**7g**.

In conclusion, the present investigation has resulted in preparation of the first examples of hetaryl-substituted pyrrolo[1,2-*a*]thieno[3,2-*e*]pyrimidines. Scope and limitations of the method have been discussed. The chloronitriles **4** were shown to be suitable precursors for the synthesis of hetaryl-substituted heterocyclic systems and the study of their synthetic potential is being continued.

EXPERIMENTAL

General

Melting points were determined in open capillary tubes on Thiele's apparatus and are uncorrected. IR spectra were obtained on a Pay Unicam SP 3-300 spectrometer in KBr tablets. ^{1}H NMR spectra were recorded on Bruker WP-100 SY (100 MHz) and Varian VXR-300 (300 MHz) spectrometers in DMSO-d_6 solution (if not otherwise stated) using TMS as internal standard. ^{13}C NMR spectra were recorded on Mercury 400 spectrometer (100 MHz for ^{13}C) in CF_3CO_2D solution. Chemical shifts are given in δ-scale (ppm) downfield from TMS and coupling constants *J* in Hz. The purity of all compounds prepared was checked by TLC on Silufol UV-254 plates with chloroform–methanol (9 : 1) as eluent and confirmed by ^{1}H NMR spectroscopy.

Solvents and Reagents

Commercial dioxane was kept over sodium hydroxide overnight, then decanted, refluxed with sodium for one day and distilled. Commercial DMF was kept over P_2O_5 for 3–4 days and distilled under reduced pressure. Commercial triethylamine and pyridine were distilled over sodium hydroxide. Aminothiophenes **5a** and **5b** were prepared according to Gewald's method[10]. Chloronitriles **4a**–**4c** were obtained by previously described procedures[12]. 2-Bromo-1-(4-fluorophenyl)ethan-1-one was prepared as reported[15]. Cyanothioacetamide and chloroacetyl chloride are commercially available and were used without additional purification.

2-[4-(4-Fluorophenyl)thiazol-2-yl]acetonitrile (**3d**)

2-Bromo-1-(4-fluorophenyl)ethan-1-one (21.7 g, 0.1 mol) was added quickly to a warm solution of cyanothioacetamide (10 g, 0.1 mol) in ethanol (100 ml) and the resulting mixture was heated on a water bath for 2 h. After cooling, the precipitated crystals of **3d**·HBr were filtered off and suspended in concentrated aqueous ammonia for 1 h. The resulted crystals were separated by suction and dried to give analytical pure **3d** (7 g, 32%). The ethanolic mother liquor was evaporated to dryness *in vacuo* and the residue was thoroughly triturated with dilute aqueous ammonia. The solid obtained was filtered off and crystallized from ethanol to give an additional portion of **3d** (13 g, 60%). The overall yield is 92%. M.p. 64 °C. For $C_{11}H_7FN_2S$ (218.3) calculated: 60.54% C, 3.23% H, 12.84% N, 14.69% S; found: 60.49% C, 3.28% H, 12.92% N, 14.74% S. IR: 2 215 (CN), 1 590, 1 490, 1 210 (CF), 835, 740. ^{1}H NMR: 8.00 s, 1 H (S-CH=); 7.98 dd, 2 H, *J*(3′,2′) = 9.0, *J*(2′,F) = 3.3 (2′,6′-$H_{FC_6H_4}$); 7.21 t, 2 H, *J*(3′,2′) = *J*(3′,F) = 9.0 (3′,5′-$H_{FC_6H_4}$); 4.53 s, 2 H (CH_2).

4-Chloro-2-[4-(4-fluorophenyl)thiazol-2-yl]-3-oxobutanonitrile (**4d**)

Chloroacetyl chloride (2.4 ml, 0.03 mol) was added portionwise with caution to a warm (40–50 °C) solution of nitrile **3d** (6.5 g, 0.03 mol) and pyridine (2.5 ml, 0.0315 mol) in dioxane (15 ml). The resulting mixture was heated on a water bath for 1 h. After cooling, the precipitated solid was filtered off, thoroughly washed with water and dried to give **4d** (6.8 g, 77%). The substance obtained was sufficiently pure for further use. An analytical sample of **4d** was additionally purified by recrystallization from dioxane. M.p. 210 °C. For

$C_{13}H_8ClFN_2OS$ (294.7) calculated: 52.98% C, 2.74% H, 12.03% Cl, 9.50% N, 10.88% S; found: 53.04% C, 2.70% H, 12.10% Cl, 9.41% N, 10.79% S. IR: 3 280 (NH), 2 180 (CN), 1 600, 1 490, 1 220 (CF), 765. ^{1}H NMR: 12.02 br s, 1 H (NH); 7.80 dd, 2 H, *J*(3′,2′) = 8.7, *J*(2′,F) = 5.4 (2′,6′-$H_{FC_6H_4}$); 7.45 s, 1 H (S-CH=); 7.27 t, 2 H, *J*(3′,F) = *J*(3′,2′) = 8.7 (3′,5′-$H_{FC_6H_4}$); 4.24 s, 2 H (CH_2).

6-Hetaryl-4,5,7,8-tetrahydropyrrolo[1,2-*a*]thieno[3,2-*e*]pyrimidine-4,7-diones (**7a**–**7g**). General Procedure

Method A. Solution of chloronitrile **4a**–**4d** (0.003 mol) and aminothiophene **5a**, **5b** (0.006 mol) in DMF (3 ml) was boiled for several minutes to dissolve all starting materials and then heated on a water bath for 3–4 h. After cooling, the formed precipitate was filtered off, washed successively with water and methanol and dried at 100 °C under reduced pressure to give compounds **7a**–**7g**. In most cases the products were analytically pure but, if needed, they could be purified by recrystallization from DMF.

Method B. Solution of chloronitrile **4a**–**4d** (0.003 mol), aminothiophene **5a**, **5b** (0.003 mol) and triethylamine (0.4 ml, 0.003 mol) in dioxane (5 ml) was boiled for several minutes to dissolve all starting materials and then heated on a water bath for 3–4 h. After cooling the mixture was worked-up as in method *A*. When compounds **4c**, **4d** were used as starting materials, pyrrolo[1,2-*a*]thieno[3,2-*e*]pyrimidines **7e**–**7g** were isolated. Starting from chloronitriles **4a** or **4b**, 6-oxo-5,6-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole-7-carbonitrile (**6a**) and 6-oxo-5,6-dihydrobenzo[*d*]pyrrolo[2,1-*b*]thiazole-7-carbonitrile (**6b**), respectively, were obtained irrespective of the aminothiophene **5** used. The identity of compounds **6a**, **6b** with previously described ones[12,14] was proven by comparison with authentic samples (IR spectra and mixed melting points).

3-(2-Benzoimidazolyl)-1,2,4,5,6,7,8,9-octahydrobenzo[4,5]thieno[3,2-e]pyrrolo[1,2-a]pyrimidine-2,5-dione (**7a**). Yield 67% (method *A*). M.p. > 300 °C. For $C_{20}H_{16}N_4O_2S$ (376.4) calculated: 63.81% C, 4.28% H, 14.88% N, 8.52% S; found: 63.78% C, 4.21% H, 14.92% N, 8.59% S. IR: 3 200 (NH), 2 920, 1 665, 1 615, 1 570, 1 540, 1 455, 1 020, 960, 745. ^{1}H NMR: 11.84 br s, 1 H (NH); 7.66 m, 2 H ($H_{R,R1}$); 7.25 m, 2 H ($H_{R,R1}$); 4.49 s, 2 H (1-H); 2.90 t, 2 H, *J*(6,7) = 6.5 (6-H); 2.72 t, 2 H, *J*(9,8) = 7.0 (9-H); 1.79 m, 4 H (7,8-H). ^{13}C NMR: 24.18 (7-C), 25.31 (8-C), 27.50 (9-C), 28.10 (6-C), 58.40 (1-C), 89.19 (3-C), 117.97 (5b-C), 119.67 (9a-C), 130.56 (5a-C), 132.51 (10a-C), 136.80 (5,6-C_{Het}), 137.25 (4,7-C_{Het}), 144.43 (3a,7a-C_{Het}), 154.86 (3a-C), 160.04 (2-C_{Het}), 163.08 (5-C), 192.99 (2-C).

6-(Benzoimidazol-2-yl)-3-phenyl-4,5,7,8-tetrahydropyrrolo[1,2-a]thieno[3,2-e]pyrimidine-4,7-dione (**7b**). Yield 58% (method *A*). M.p. > 300 °C. For $C_{22}H_{14}N_4O_2S$ (398.5) calculated: 66.32% C, 3.54% H, 14.06% N, 8.05% S; found: 66.29% C, 3.55% H, 14.11% N, 7.98% S. IR: 3 200 (NH), 1 655 (CO), 1 620 (CO), 1 560, 1 540, 1 475, 1 440, 1 330, 1 170, 720. ^{1}H NMR: 11.63 br s, 1 H (NH); 7.73 m, 2 H ($H_{R,R1}$); 7.42 m, 7 H (H_{R2}, $H_{R,R1}$); 7.25 s, 1 H (H_{R3}); 4.74 s, 2 H (8-H).

3-(Benzothiazol-2-yl)-1,2,4,5,6,7,8,9-octahydro[1]benzothieno[3,2-e]pyrrolo[1,2-a]pyrimidine-2,5-dione (**7c**). Yield 57% (method *A*). M.p. > 300 °C. For $C_{20}H_{15}N_3O_2S_2$ (393.5) calculated: 61.05% C, 3.84% H, 10.68% N, 16.30% S; found: 61.12% C, 3.82% H, 10.62% N, 16.28% S. IR: 2 930 (CH), 1 685 (CO), 1 665 (CO), 1 590, 1 540, 1 510, 1 185, 1 110, 950, 750. ^{1}H NMR: 11.72 br s, 1 H (NH); 8.05 d, *J*(4′,5′) = 8.1, 1 H (4′-$H_{R,R1}$); 7.97 d, 1 H, *J*(7′,6′) = 8.1 (7′-$H_{R,R1}$); 7.49 t, 1 H, *J*(6′,5′) = *J*(6′,7′) = 8.1 (6′-$H_{R,R1}$); 7.35 t, 1 H, *J*(5′,6′) = *J*(5′,4′) = 8.1 (5′-$H_{R,R1}$); 4.61 s, 2 H (1-H); 2.91 m, 2 H (6-H); 2.75 m, 2 H (9-H); 1.82 m, 4 H (7,8-H).

^{13}C NMR: 28.35 (7-C), 29.35 (8-C), 31.78 (9-C), 32.20 (6-C), 63.01 (1-C), 101.01 (3-C), 122.98 (5b-C), 123.22 (9a-C), 123.45 (5a-C), 129.82 (10a-C), 133.81 (6-C_{Het}), 134.80 (5-C_{Het}), 136.98 (7-C_{Het}), 139.74 (4-C_{Het}), 142.03 (7a-C_{Het}), 144.99 (3a-C_{Het}), 160.63 (3a-C), 165.89 (2-C_{Het}), 170.25 (5-C), 195.85 (2-C).

6-(Benzothiazol-2-yl)-3-phenyl-4,5,7,8-tetrahydropyrrolo[1,2-a]thieno[3,2-e]pyrimidine-4,7-dione (**7d**). Yield 49% (method *A*). M.p. > 300 °C. For $C_{22}H_{13}N_3O_2S_2$ (415.5) calculated: 63.60% C, 3.15% H, 10.11% N, 15.43% S; found: 63.64% C, 3.09% H, 10.16% N, 15.48% S. IR: 3 215 (NH), 1 690 (CO), 1 670 (CO), 1 600, 1 545, 1 510, 1 080, 955, 750, 715. ^{1}H NMR: 11.52 br s, 1 H (NH); 7.96 m, 2 H ($H_{R,R1}$); 7.45 m, 7 H (H_{R2}, $H_{R,R1}$); 7.21 s, 1 H (H_{R3}); 4.63 s, 2 H (8-H).

3-[4-(4-Bromophenyl)thiazol-2-yl]-1,2,4,5,6,7,8,9-octahydro[1]benzothieno[3,2-e]pyrrolo-[1,2-a]pyrimidine-2,5-dione (**7e**). Yields 52% (method *A*) and 56% (method *B*). M.p. > 300 °C. For $C_{22}H_{16}BrN_3O_2S_2$ (498.4) calculated: 53.02% C, 3.24% H, 16.03% Br, 8.43% N, 12.87% S; found: 53.08% C, 3.19% H, 16.11% Br, 8.38% N, 12.95% S. IR: 3 200 (NH), 2 920 (CH), 1 665 (CO), 1 595, 1 560, 1 505, 1 175, 1 120, 1 060, 1 000, 950, 825, 775. ^{1}H NMR: 11.95 br s, 1 H (NH); 7.89 d, 2 H, J(3′,2′) = 9.0 (3′,5′-H_R); 7.85 s, 1 H (H_{R1}); 7.65 d, 2 H, J(3′,2′) = 9.0 (2′,6′-H_R); 4.51 s, 2 H (1-H); 2.80 m, 4 H (6,9-H); 1.79 m, 4 H (7,8-H).

3-[4-(4-Fluorophenyl)thiazol-2-yl]-1,2,4,5,6,7,8,9-octahydro[1]benzothieno[3,2-e]pyrrolo-[1,2-a]pyrimidine-2,5-dione (**7f**). Yields 45% (method *A*) and 50% (method *B*). M.p. > 300 °C. For $C_{22}H_{16}FN_3O_2S_2$ (437.5) calculated: 60.40% C, 3.69% H, 9.60% N, 14.66% S; found: 60.47% C, 3.74% H, 9.57% N, 14.71% S. IR: 3 200 (NH), 2 920 (CH), 1 670 (CO), 1 660 (CO), 1 580, 1 200 (CF), 920, 835, 740. ^{1}H NMR (CF_3CO_2D): 7.75 dd, 2 H, J(2′3′) = 8.4, J(2′,F) = 3.7 (2′,6′-H_R); 7.58 s, 1 H (H_{R1}); 7.31 t, 2 H, J(3′,2′) = J(3′,F) = 8.4 (3′,5′-H_R); 5.05 s, 2 H (1-H); 3.09 m, 2 H (6-H); 2.91 m, 2 H (9-H); 2.02 m, 4 H (7,8-H). ^{13}C NMR: 23.46 (7-C), 24.48 (8-C), 26.79 (9-C), 27.35 (6-C), 57.68 (1-C), 95.61 (3-C), 112.02 (1′-C_R), 118.59 (5b-C), 119.18 (9a-C), 119,95 (5a-C), 125.16 (10a-C), 130.81 (3′,5′-C_R), 135.06 (2′,6′-C_R), 136.77 (5-C_{Het}), 145.66 (4-C_{Het}), 155.34 (2-C_{Het}), 160.56 (3a-C), 165.36 d, J_{CF} = 145 (4′-C_R,), 168.58 (5-C), 190.59 (2-C).

6-[4-(4-Fluorophenyl)thiazol-2-yl]-3-phenyl-4,5,7,8-tetrahydropyrrolo[1,2-a]thieno[3,2-e]pyrimidine-4,7-dione (**7g**). Yields 42% (method *A*) and 46% (method *B*). M.p. 259 °C. For $C_{24}H_{14}FN_3O_2S_2$ (459.5) calculated: 62.73% C, 3.07% H, 9.14% N, 13.96% S; found: 62.68% C, 3.15% H, 9.10% N, 14.01% S. IR: 3 215 (NH), 1 680 (CO), 1 660 (CO), 1 606, 1 210 (CF), 865, 740. ^{1}H NMR (CF_3CO_2D): 8.00 dd, 2 H, J(3′,2′) = 9.2, J(2′,F) = 3.3 (2′,6′-H_R); 7.75 s, 1 H (R1); 7.38 m, 5 H (H_{R2}); 7.24 t, 2 H, J(3′,2′) = J(3′,F) = 9.2 (3′,5′-H_R); 7.20 s, 1 H (R3); 4.58 s, 2 H (8-H).

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