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Microwave-assisted synthesis of fused heterocycles incorporating trifluoromethyl moiety

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ABSTRACT

4,4,4-Trifluoro-1-(thien-2-yl)butane-1,3-dione (**1**) reacts with 5-aminopyrazole, 1,2,4-aminotriazole and 2-aminobenzimidazole derivatives, in the presence of triethylorthoformate under pressurized microwave irradiation to afford the corresponding trifluoromethyl derivatives of pyrazolo[1,5-*a*]pyrimidine, 1,2,4-triazolo[1,5-*a*]pyrimidine, and pyrimido[1,2-*a*]benzimidazoles. Also, compound **1** couples readily with azole diazonium salts to give pyrazolo[5,1-*c*]triazine, benzimidazo[5,1-*c*]1,2,4-triazine, and triazolo[3,4-*c*]1,2,4-triazine derivatives incorporating trifluoromethyl group.

1. Introduction

Fluorine-containing heterocyclic compounds have attracted much interest because of their potent biological and pharmacological activities [1–3], in addition to their role in the development of new functional materials [4–10]. Pyrimidine and triazine ring systems fused with pyrazoles, triazoles and benzimidazoles have shown diverse biological activities [11–19]. Among these the important effects are analgesic and antinociceptive activities, many fluorinated analogues of biologically active molecules have exhibited dramatic enhancement in their properties. However, direct fluorination of heterocyclic compounds is not always straightforward. Recently, new methodologies of fluorination have been shown to be more elegant and applicable than conventional fluorination methods such as electrochemical fluorination [20–24] or using various fluorine-containing building blocks [25–27]. In this context, trifluoromethylated 1,3-dicarbonyl derivatives constitute important synthetic intermediates, incorporating multiple functionalities that can be involved either as nucleophilic or electrophilic species in a large variety of synthetic transformations [28–31]. Their versatility and effectiveness as potential multicomponent substrates have been proven to be building blocks for a wide variety of trifluoromethyl-substituted heterocyles. These include pyrazoles [32–34], pyridines [35], pyrimidines [36], isoxazoles [37], and thiazoles [38]. However, most of the thermal syntheses of such compounds consume a lot of time and/or lake of high selectivity. On the other hand, microwave irradiation has recently demonstrated its utility as an energy source to improve yields and/or save reaction conditions, especially in the field of heterocyclic synthesis [39–41]. The use of the pressurized microwave irradiation can be very advantageous to many chemistries where the solvent can be heated up to temperatures that are 2–4 times their respective boiling points and thus providing large rate enhancement. In addition, keeping the atmosphere from moisture that may affect the moisture sensitive reagents decreases the possibility of formation of the undesired byproducts. As a part of systematic study on the synthesis of new fused heterocyclic systems having potential unique properties [42,43], we report the synthesis of several pyrazolopyrimidine, triazolopyrimidine, and benzimidazolopyrimidines attached to trifluoromethyl moiety as well as fused triazine derivatives using microwaves.

2. Results and discussion

The behavior of 4,4,4-trifluoro-1-(thien-2-yl)butane-1,3-dione (**1**) towards some aminopyrazole derivatives as potential

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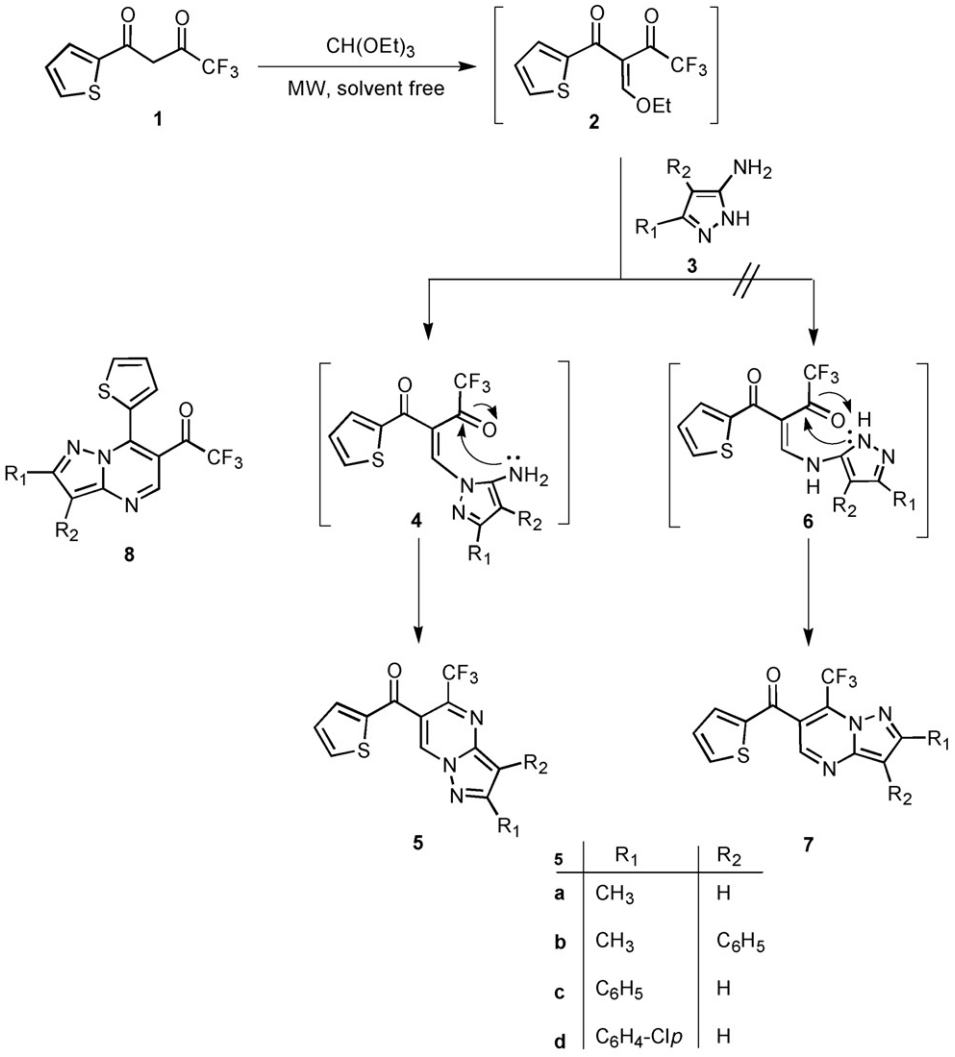


Scheme 1.

precursors for interesting biologically active pyrazolo[1,5-*a*]pyrimidine derivatives was investigated. Thus, when compound **1** was treated with 5-amino-1*H*-pyrazole derivatives **3a–d** in the presence of excess amount of triethylorthoformate under pressurized microwave irradiation, it afforded the corresponding 5-(trifluoromethyl)-pyrazolo[1,5-*a*]pyrimidine derivatives **5a–d** in almost quantitative yield (Scheme 1). The mass spectrum of compound **5a**, taken as an example of the prepared series, revealed a molecular ion peak at *m*/*z* 311. Its ^{1}H NMR spectrum revealed a singlet signal at δ 9.64 due to pyrimidine-CH and three doublets of doublet at δ 8.22 ($^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 4.0 Hz), 7.94 ($^3J_{HH}$ = 5.0 Hz, $^4J_{HH}$ = 1.0 Hz) and 7.29 ($^3J_{HH}$ = 4.0 Hz, $^4J_{HH}$ = 0.9 Hz) due to thiophene protons, respectively, in addition to a singlet signal at δ 6.94 due to pyrazole proton and a singlet at δ 2.51 due to methyl protons. The ^{19}F NMR chemical shift of the CF_3 group at δ −63.69 ppm confirms the presence of the cyclic structure **5a** rather than **8**. For the latter compound the fluorine chemical shift of the CF_3 group should be at higher field [44].

The formation of the products **5a–d** is assumed to take place *via* an initial addition of the more nucleophilic endocyclic nitrogen in the aminopyrazole derivatives **3a–d** to the α,β-unsaturated moiety in the ethoxymethylene derivative **2** to yield the corresponding acyclic non-isolable intermediates **4a–d** which undergo intramolecular cyclization and aromatization to give the final products **5a–d** (Scheme 1). This conclusion was further unequivocally confirmed by X-ray crystallography (Fig. 1), where single crystal X-ray diffraction of compound **5a** adds sharp evidence for the proposed structure **5a–d** rather than structure **7** or **8**.

Similarly, 4,4,4-trifluoro-1-(thien-2-yl)butane-1,3-dione (**1**) reacts with 3-amino-1,2,4-triazole (**9**) and triethylorthoformate to afford 6-thienoyl-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyrimidine (**10**) as shown in Scheme 2. The ^{1}H NMR spectrum of the latter product revealed a singlet at δ 10.13 due to pyrimidine-CH, a singlet at δ 9.03 due to the triazole proton and three doublets of doublet in the region of 7.31–8.29 due to thiophene protons. The IR spectrum of the same compound exhibited absorption band at 1695 cm^{-1} due to a carbonyl function.

Compound **1** reacts also with 2-amino-benzimidazole (**11**), under the same experimental conditions to afford only one isolable product (as examined by TLC). The reaction product was identified as 6-thienoyl-7-(trifluoromethyl) benzimidazo[1,2-*a*]pyrimidine (**12**) (Scheme 2).

Next, a new and convenient route to some heterocyclic fused triazines with bridgehead nitrogen atom was also investigated. Thus, 4,4,4-trifluoro-1-(thien-2-yl)butane-1,3-dione (**1**) couples smoothly with the diazonium salt of 1,2,4-aminotriazole **13**, in

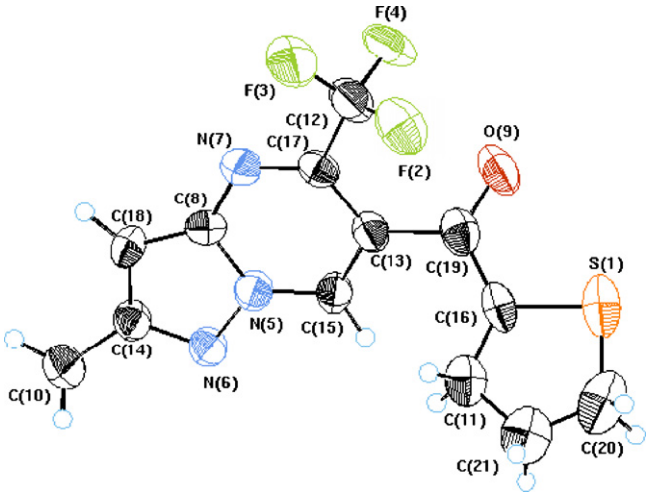
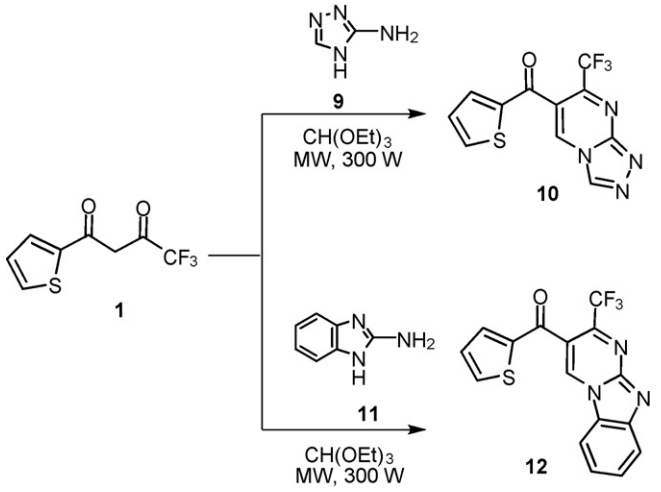


Fig. 1. X-ray structure of compound **5a**.

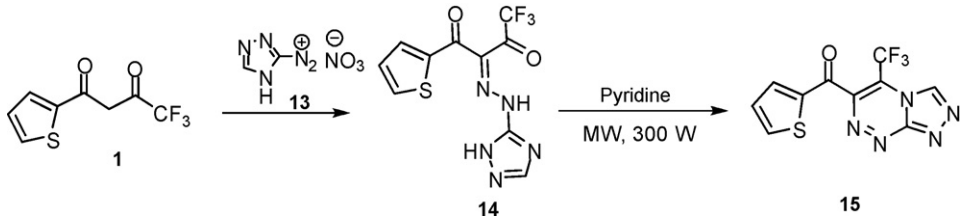


Scheme 2.

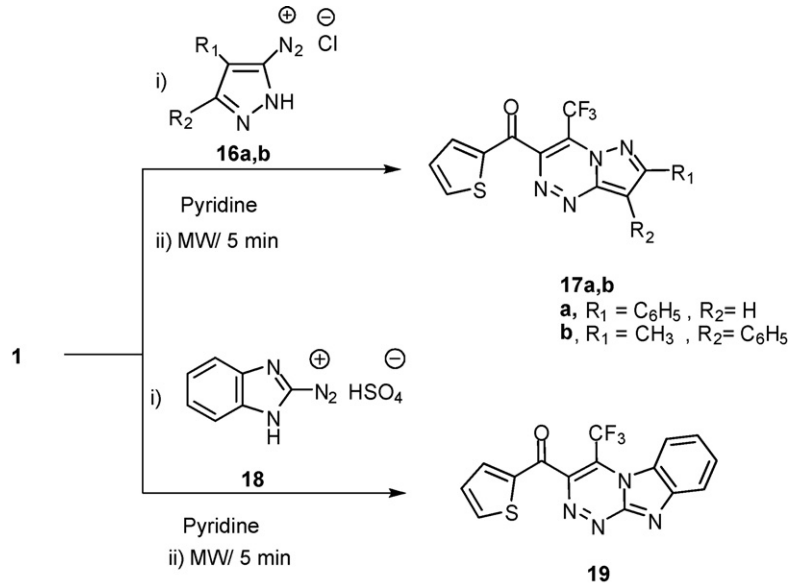
pyridine at 0 °C, to afford the corresponding hydrazone **14** which undergoes intramolecular cyclization in pyridine under microwave irradiation to afford the 6-thienoyl-5-(trifluoromethyl)-[1,2,4]triazolo[3,4-*c*][1,2,4]triazine (**15**) (Scheme 3). The IR spectrum of the isolated product **15** revealed the disappearance of band at 3419 cm^{-1} due to the NH function. The ^1H NMR spectrum of the latter product displayed a singlet signal at δ 9.31 of the triazole-CH and signals at δ 7.25–8.06 due to thiophene protons.

In a similar manner, compound **1** couples readily with the diazonium salt of 2-aminobenzimidazole and aminopyrazole derivatives **16a**,**b** and **18**, respectively, under the same experimental conditions, to afford, in each case, a single product according to TLC analysis (Scheme 4).

Based on the elemental analyses and spectral data, the structure of the isolated products were identified as 6-thienoyl-4-(trifluoromethyl)-pyrazolo[5,1-*c*][1,2,4]triazines **17a**,**b** and 3-thienoyl-4-



Scheme 3.



Scheme 4.

(trifluoromethyl)-benzimidazo[2,1-*c*][1,2,4]triazine (**19**), respectively (see Section 4).

3. Conclusions

This work shows that trifluoromethylated 1,3-dicarbonyl derivatives still constitute versatile substrates in fluorine chemistry and can be accommodated in many diverse synthetic pathways. The high synthetic potential of these very easily accessible reagents has found numerous applications, especially for the synthesis of fused heterocyclic compounds. Use of microwaves in new synthetic transformations making use of trifluoromethylated 1,3-dicarbonyls towards conventional methods should enlarge the scope of this field, allowing the facile and selective construction of highly functionalized fused heterocycles of high synthetic and biological value.

4. Experimental

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide disks on a pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in deuterated dimethyl sulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. ^{19}F NMR spectra were obtained using $CFCl_3$ as an internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. Microwave experiments were carried out using CEM Discover Labmate™ microwave apparatus (300 W with ChemDriver™ Software). 4,4,4-Trifluoro-1-(thien-2-yl)-butane-1,3-dione (**1**) was purchased from Fluka chemicals. Aminopyrazoles **3a–d** [45–47], heterocyclic diazonium salts **13**, **16a**,**b**, and **18** [48] were prepared according to procedures reported in the literature.

4.1. Reaction with heterocyclic amines

4.1.1. General procedure

To a mixture of 4,4,4-trifluoro-1-(thien-2-yl)-butane-1,3-dione (**1**) (2.22 g, 10 mmol) and the appropriate heterocyclic amine (aminopyrazoles **3a–d**, 3-amino-l,2,4-triazole (**9**) and 2-aminobenzimidazole (**11**)) (10 mmol) in triethylorthoformate (0.5 ml) was mixed in a process vial. The vial was capped properly and irradiated by microwaves using pressurized conditions (17.2 bar, 100 °C) for 5 min. The excess triethylorthoformate was evaporated *in vacuo* and the residual solid was taken in EtOH then collected by filtration, washed with ethanol, dried and finally recrystallized from EtOH/DMF to afford the corresponding pyrazolo[1,5-*a*]pyrimidine **5a–d**, 1,2,4-triazolo[4,3-*a*]pyrimidine **10**, and pyrimido[1,2-*a*]benzimidazole derivatives **12**, respectively. The physical and spectral data of the synthesized compounds **5a–d**, **10** and **12** are listed below.

*4.1.1.1. 3-Methyl-6-thienoyl-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine (**5a**).* Yield (89%); mp 170–171 °C; IR (KBr) υ 1655 (C=O), 1596 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.51 (3H, s), 6.94 (1H, s), 7.29 (1H, dd, $^3J_{HH}$ = 4.0 Hz, $^4J_{HH}$ = 0.9 Hz), 7.94 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^4J_{HH}$ = 1.0 Hz), 8.22 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 4.0 Hz), 9.64 (1H, s); ^{13}C NMR (DMSO-d_6): δ (14.37, CH_3), (98.51, 120.54, 137.89, 138.33, 143.05, 158.42: pyrazolo[1,5-*a*]pyrimidine), (116.32, CF_3), (122.88, 141.98, 142.40, 146.20: thiophene ring), (182.03, C=O); ^{19}F NMR (DMSO-d_6): δ −63.69 (s, CF_3); EIMS (probe) 70 eV, *m*/*z* (rel. int.): 311 [M]$^+$ (54). Anal. Calcd for $C_{13}H_8F_3N_3OS$: C, 50.16; H, 2.59; N, 13.50; S, 10.30. Found: C, 50.04; H, 2.53; N, 13.50; S, 10.20.

4.1.2. X-ray crystallography

A single crystal of compound **5a** was obtained by slow evaporation from benzene. The crystal structure was solved and refined using maxus (nonius, Deflt and MacScience, Japan) Mo-Kα radiation (λ = 0.71073 Å) and a graphite monochromator were used for data collection. The chemical formula and ring labeling system is shown in Fig. 1.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 693229. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union, Road, Cambridge CB2 1EZ, UK [fax: 44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

*4.1.2.1. 2-Methyl-3-phenyl-6-thienoyl-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine (**5b**).* Yield (86%); mp 184 °C; IR (KBr) υ 1658 (C=O), 1596 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.60 (3H, s), 7.24 (1H, dd, $^3J_{HH}$ = 4.0 Hz, $^4J_{HH}$ = 0.9 Hz), 7.25 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^4J_{HH}$ = 1.0 Hz), 7.53–7.82 (5H, m), 8.02 (1H, s) 8.22 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 4.0 Hz); ^{13}C NMR (DMSO-d_6): δ (12.76, CH_3), (98.51, 126.62, 135.98, 143.05, 146.80, 167.30: pyrazolo[1,5-*a*]pyrimidine), (104.60, CF_3), (125.32, 127.54, 129.64, 133.09: phenyl ring), (128.88, 133.33, 136.40, 157.82: thiophene ring), (182.83, C=O); ^{19}F NMR (DMSO-d_6): δ −63.48 (s, CF_3); EIMS (probe) 70 eV, *m*/*z* (rel. int.): 387 [M]$^+$ (43). Anal. Calcd for $C_{19}H_{12}F_3N_3OS$: C, 58.91; H, 3.12; N, 10.85; S, 8.28. Found: C, 58.88; H, 3.11; N, 10.78; S, 8.29.

*4.1.2.2. 2-Phenyl-6-thienoyl -5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine (**5c**).* Yield (82%); mp 202 °C; IR (KBr) υ 1660 (C=O), 1596 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 6.90 (1H, s), 7.26 (1H, dd, $^3J_{HH}$ = 4.0 Hz, $^4J_{HH}$ = 0.9 Hz), 7.27 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^4J_{HH}$ = 1.0 Hz), 7.54–7.80 (5H, m), 8.24 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 4.0 Hz), 9.73 (1H, s); ^{13}C NMR (DMSO-d_6): δ (98.53, 126.63, 133.33, 135.98, 145.80, 167.30: pyrazolo[1,5-*a*]pyrimidine), (118.60, CF_3), (125.32, 127.54, 129.63, 133.10: phenyl ring), (128.88, 136.40, 143.05, 157.82: thiophene ring), (182.84, C=O); ^{19}F NMR (DMSO-d_6): δ −63.01 (s, CF_3); EIMS (probe) 70 eV, *m*/*z* (rel. int.): 373 [M]$^+$ (50). Anal. Calcd for $C_{18}H_{10}F_3N_3OS$: C, 57.91; H, 2.70; N, 11.25; S, 8.59. Found: C, 57.87; H, 2.71; N, 11.35; S, 8.49.

*4.1.2.3. 2-(4-Chlorophenyl)-6-thienoyl-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine (**5d**).* Yield (75%); mp 214 °C; IR (KBr) υ 1654 (C=O), 1596 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 6.90 (1H, s), 7.26 (1H, dd, $^3J_{HH}$ = 4.0 Hz, $^4J_{HH}$ = 0.9 Hz), 7.27 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^4J_{HH}$ = 1.0 Hz), 7.74–8.10 (4H, m), 8.31 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 4.0 Hz), 8.79 (1H, s); ^{13}C NMR (DMSO-d_6): δ (98.54, 126.63, 133.09, 133.33, 146.80, 167.40: pyrazolo[1,5-*a*]pyrimidine), (119.91, CF_3), (125.32, 127.54, 129.65, 136.40: phenyl ring), (128.98, 135.98, 143.15, 157.82: thiophene ring), (182.83, C=O); ^{19}F NMR (DMSO-d_6): δ −62.19 (s, CF_3); EIMS (probe) 70 eV, *m*/*z* (rel. int.): 407 [M]$^+$ (38). Anal. Calcd for $C_{18}H_9ClF_3N_3OS$: C, 58.91; H, 3.12; N, 10.85; S, 8.28. Found: C, 58.88; H, 3.11; N, 10.78; S, 8.26.

*4.1.2.4. 6-Thienoyl-7-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyrimidine (**10**).* Yield (91%); mp > 300 °C; IR (KBr) υ 1695 (C=O) and 1596 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.31 (1H, dd, $^3J_{HH}$ = 4.5 Hz, $^4J_{HH}$ = 1.0 Hz), 7.93 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^4J_{HH}$ = 1.0 Hz), 8.29 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 4.5 Hz), 9.03 (1H, s), 10.13 (1H, s); ^{13}C NMR (DMSO-d_6): δ (119.32, CF_3), (123.88, 124.43, 135.88, 146.14, 151.28: triazolo[4,3-*a*]pyrimi-

dine), (128.73, 131.99, 136.58, 141.00: thiophene ring), (179.31, C=O); ^{19}F NMR (DMSO-d_6): δ −67.69 (s, CF_3); EIMS (probe) 70 eV, m/z (rel. int.): 298 $[M]^+$ (64). Anal. Calcd for $C_{11}H_5F_3N_4OS$: C, 44.30; H, 1.69; N, 18.79; S, 10.75. Found: C, 44.27; H, 1.71; N, 18.76; S, 10.78.

*4.1.2.5. 6-Thienoyl-7-(trifluoromethyl)benzimidazo[1,2-a]pyrimidine (**12**).* Yield (83%); mp 244 °C; IR (KBr) υ 1656 (C=O), 1596 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.15 (1H, d), 7.27 (1H, dd, $^3J_{HH}$ = 4.5 Hz, $^4J_{HH}$ = 1.0 Hz), 7.45 (1H, m), 7.93 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^4J_{HH}$ = 1.0 Hz), 7.45 (2H, m), 8.29 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 4.5 Hz), 9.02 (1H, s); ^{13}C NMR (DMSO-d_6): δ (102.37, 113.60, 116.32, 120.24, 120.58, 121.42, 133.44, 143.51, 146.20, 158.42: benzimidazo[1,2-*a*]pyrimidine), (117.62, CF_3), (122.90, 128.25, 130.77, 134.03: thiophene ring), (180.03, C=O); ^{19}F NMR (DMSO-d_6): δ −68.45 (s, CF_3); EIMS (probe) 70 eV, m/z (rel. int.): 347 $[M]^+$ (56). Anal. Calcd for $C_{16}H_8F_3N_3OS$: C, 55.33; H, 2.32; N, 12.10; S, 9.23. Found: C, 55.23; H, 2.42; N, 12.08; S, 9.13.

4.2. Coupling with azole diazonium salts

4.2.1. General procedure

To a cold solution of 4,4,4-trifluoro-1-(thien-2-yl)butane-1,3-dione (**1**) (2 mmol) in pyridine (25 ml) was added the appropriate heterocyclic diazonium salt **13**, **16a**,**b**, or **18** (2 mmol) portionwise over a period of 1/2 h. After stirring for further 3 h at 0–5 °C, the reaction mixture was left to stand in an ice-box for 12 h then diluted with water. The solid that precipitated was filtered off washed with water and dried. Crystallization from the proper solvent gave the corresponding coupling products. The coupling products were taken in pyridine and irradiated with microwaves in a vial for 5 min under the same experimental conditions in the pervious section. The excess pyridine was evaporated *in vacuo* and the residual solid was taken in EtOH then collected by filtration, washed with ethanol, dried and finally recrystallized from EtOH/DMF to afford the corresponding triazolo[3,4-*c*][1,2,4]triazine **15**, benzimidazo[2,1-*c*][1,2,4]triazine **19**, and pyrazolo[5,1-*c*][1,2,4]triazines **17a**,**b**. The physical and spectral data of the synthesized compounds **14**, **15**, **17a**,**b** and **19** are listed below.

*4.2.1.1. 2-(2-(1H-1,2,4-Triazol-5-yl)hydrazono)-4,4,4-trifluoro-1-(thien-2-yl)butane-1,3-dione (**14**).* Yield (91%); mp 254 °C; IR (KBr) υ 3419 (NH), 1705 (C=O), 1691 (C=O), 1596 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.25 (1H, dd, $^3J_{HH}$ = 4.5 Hz, $^4J_{HH}$ = 1.0 Hz), 7.89 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^4J_{HH}$ = 1.0 Hz), 8.06 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 4.5 Hz), 9.31 (1H, s), 13.49 (2H, broad, D_2O exchangable); ^{13}C NMR (DMSO-d_6): δ (122.32, CF_3), (123.98, 128.73, 132.99, 135.88: thiophene ring), (136.68, 141.00: triazole ring), (151.28 C=N hydrazone), (180.32, C=O), 189.32, $COCF_3$); ^{19}F NMR (DMSO-d_6): δ −77.08 (s, CF_3); EIMS (probe) 70 eV, m/z (rel. int.): 317 $[M]^+$ (34). Anal. Calcd for $C_{10}H_6F_3N_5O_2S$: C, 37.86; H, 1.91; N, 22.08; S, 10.11. Found: C, 37.82; H, 1.93; N, 22.12; S, 10.13.

*4.2.1.2. 6-Thienoyl-5-(trifluoromethyl)-[1,2,4]triazolo[3,4-c][1,2,4]triazine (**15**).* Yield (91%); mp 240 °C; IR (KBr) υ 1650 (C=O), 1596 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.25 (1H, dd, $^3J_{HH}$ = 4.5 Hz, $^4J_{HH}$ = 1.0 Hz), 7.89 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^4J_{HH}$ = 1.0 Hz), 8.06 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 4.5 Hz), 9.31 (1H, s); ^{13}C NMR (DMSO-d_6): δ (119.33, CF_3), (123.80, 135.88, 141.10, 151.38: triazolo[3,4-*c*][1,2,4]triazine), (128.76, 132.99, 136.58, 146.34: thiophene ring), (179.41, C=O); ^{19}F NMR (DMSO-d_6): δ −62.69 (s, CF_3); EIMS (probe) 70 eV, m/z (rel. int.): 299 $[M]^+$ (47). Anal. Calcd for $C_{10}H_4F_3N_5OS$: C, 40.14; H, 1.35; N, 23.40; S, 10.72. Found: C, 40.18; H, 1.33; N, 23.42; S, 10.75.

*4.2.1.3. 7-Phenyl-3-thienoyl-4-(trifluoromethyl)pyrazolo[5,1-c][1,2,4]triazine (**17a**).* Yield (82%); mp > 300 °C; IR (KBr) υ 1662 (C=O), 1596 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 6.90 (1H, s), 7.26 (1H, dd, $^3J_{HH}$ = 4.0 Hz, $^4J_{HH}$ = 0.9 Hz), 7.27 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^4J_{HH}$ = 1.0 Hz), 7.54–7.80 (5H, m), 8.24 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 4.0 Hz), 9.73 (1H, s); ^{13}C NMR (DMSO-d_6): δ (119.33, CF_3), (98.53, 125.52, 126.62, 135.97, 136.40, 143.15, 146.70, 157.82, 167.40: pyrazolo[5,1-*c*][1,2,4]triazine), (127.54, 128.78, 129.64, 133.19: thiophene ring), (182.83, C=O); ^{19}F NMR (DMSO-d_6): δ −65.45 (s, CF_3); EIMS (probe) 70 eV, m/z (rel. int.): 374 $[M]^+$ (65). Anal. Calcd for $C_{17}H_9F_3N_4OS$: C, 54.54; H, 2.42; N, 14.97; S, 8.57. Found: C, 54.57; H, 2.40; N, 14.95; S, 8.60.

*4.2.1.4. 7-Methyl-8-phenyl-3-thienoyl-4-(trifluoromethyl)pyrazolo[5,1-c][1,2,4]triazine (**17b**).* Yield (86%); mp 274 °C; IR (KBr) υ 1653 (C=O), 1596 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.60 (3H, s), 7.24 (1H, dd, $^3J_{HH}$ = 4.0 Hz, $^4J_{HH}$ = 0.9 Hz), 7.25 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^4J_{HH}$ = 1.0 Hz), 7.53–7.82 (5H, m), 8.02 (1H, s) 8.22 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 4.0 Hz); ^{13}C NMR (DMSO-d_6): δ (12.76, CH_3), (98.52, 127.64, 133.23, 146.82, 167.30: pyrazolo[5,1-*c*][1,2,4]triazine), (120.60, CF_3), (125.42, 126.72, 129.65, 143.15: phenyl ring), (128.88, 135.98, 136.42, 157.82: thiophene ring), (182.93, C=O); ^{19}F NMR (DMSO-d_6): δ −66.33 (s, CF_3); EIMS (probe) 70 eV, m/z (rel. int.): 388 $[M]^+$ (62). Anal. Calcd for $C_{18}H_{11}F_3N_4OS$: C, 55.67; H, 2.85; N, 14.43; S, 8.26. Found: C, 55.63; H, 2.83; N, 14.45; S, 8.22.

*4.2.1.5. 3-Thienoyl-4-(trifluoromethyl) benzimidazo[2,1-c][1,2,4]triazine (**19**).* Yield (83%); mp > 300 °C; IR (KBr) υ 1650 (C=O), 1596 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.15 (1H, d), 7.27 (1H, dd, $^3J_{HH}$ = 4.5 Hz, $^4J_{HH}$ = 1.0 Hz), 7.45 (1H, m), 7.93 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^4J_{HH}$ = 1.0 Hz), 7.45 (2H, m), 8.29 (1H, dd, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 4.5 Hz), 9.02 (1H, s); ^{13}C NMR (DMSO-d_6): δ (102.38, 113.61, 116.32, 120.25, 122.93, 130.77, 134.03, 158.43, 143.54,: benzimidazo[2,1-*c*][1,2,4]triazine), (117.63, CF_3), (121.42, 128.35, 133.44, 146.24: thiophene ring), (180.53, C=O); ^{19}F NMR (DMSO-d_6): δ −64.34 (s, CF_3); EIMS (probe) 70 eV, m/z (rel. int.): 348 $[M]^+$ (64). Anal. Calcd for $C_{15}H_7F_3N_4OS$: C, 51.73; H, 2.03; N, 16.09; S, 9.21. Found: C, 51.75; H, 2.05; N, 16.12; S, 9.24.

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