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Multi-component solvent-free versus stepwise solvent mediated reactions: Regiospecific formation of 6-trifluoromethyl and 4-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridines

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ABSTRACT

A simple and efficient regiospecific synthesis of 6-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridines has been achieved in excellent yields *via* a three-component reaction between 2-hydrazinobenzothiazoles, α-cyanoacetophenones and trifluoromethyl-β-diketones under solvent-free conditions. This method was found to be more convenient than the classical stepwise solvent mediated process, which furnished not only the opposite regioisomer *i.e.* 4-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridines (50–60%) but also an undesired amide, 5-acetylamino-1-(benzothiazol-2′-yl)-3-phenyl-1*H*-pyrazole as a side product. The structure of the two regioisomers was established with certainty on the basis of rigorous analysis of ^{1}H, ^{13}C, ^{19}F-NMR spectral data and (^{1}H–^{13}C) gs-HMQC, (^{1}H–^{13}C) gs-HMBC experiments.

1. Introduction

Multicomponent reactions (MCRs) are special type of synthetically useful organic reactions, in which three or more simple reactants are consumed in a single chemical step to produce a product that incorporates substantial portions of all the reactants. Generally multicomponent reactions, being one-pot process, afford good yields. They are fundamentally different from two component stepwise reactions in several ways such as: the simplicity of one-pot procedure, possible structural variation, complicated synthesis and large number of accessible compounds. Organic reactions under solvent-free conditions have gained much attention due to several advantages over the conventional methods in terms of enhanced selectivity, cleaner reaction profile, ease of manipulation and relatively benign conditions [1–6].

Among the condensed heterocyclic systems, pyrazolo[3,4-*b*]pyridines are an important class of heterocyclic systems being part of therapeutically interesting compounds that display significant activity such as antimicrobial [7], antiviral [8], anti-inflammatory [9], antitumor agents [10] and as potent PDE4B inhibitors [11]. In addition, pyrazolo[3,4-*b*]pyridines with a trifluoromethyl group are known to possess multidrug function with antimalarial activity [12]. The foregoing observations prompted us to undertake the preparation of trifluoromethyl substituted pyrazolo[3,4-*b*]pyridines. Generally, the synthesis of such heterocycles is accomplished by two distinct routes. The first one (Route A, Fig. 1) involves formation of a pyrazole ring on a 3-acetyl/cyanopyridine bearing a good leaving group in 2-position, but this method lacks versatility in terms of substitution, as only pyridines containing, methyl, aryl, hydroxyl and amino groups at position-3 can be attained.

The second route uses the condensation reaction of 5-amino-1*H*-pyrazoles with bifunctional electrophiles to form the pyridine moiety (Route B, Fig. 1), and offers a great diversity and flexibility in terms of substitution at pyrazole and pyridine rings. Nevertheless, this method is disadvantageous due to multiple step synthesis, large reaction times and low/moderate yields. Moreover, formation of different regioisomers has been reported in the literature *i.e.* in the reaction of 5-amino-1*H*-pyrazoles with trifluoromethyl-*β*-diketones under similar reaction conditions [13,14].

In view of these observations and our ongoing interest to develop greener protocols for the synthesis of heterocyclic compounds [15–18], we report here a mild and efficient MCR providing a regiospecific synthesis of 6-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridines under solvent-free conditions. At the same time, and in order to compare the results obtained by MCR with those using a multistep solvent mediated process, regioisomeric 4-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridines will also be described.

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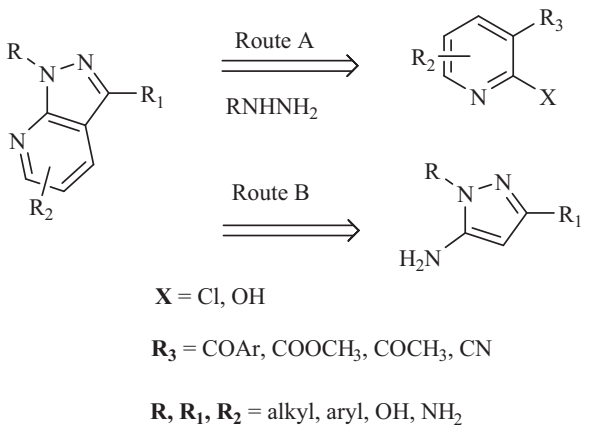


Fig. 1. Synthetic routes of pyrazolo[3,4-*b*]pyridines.

2. Results and discussion

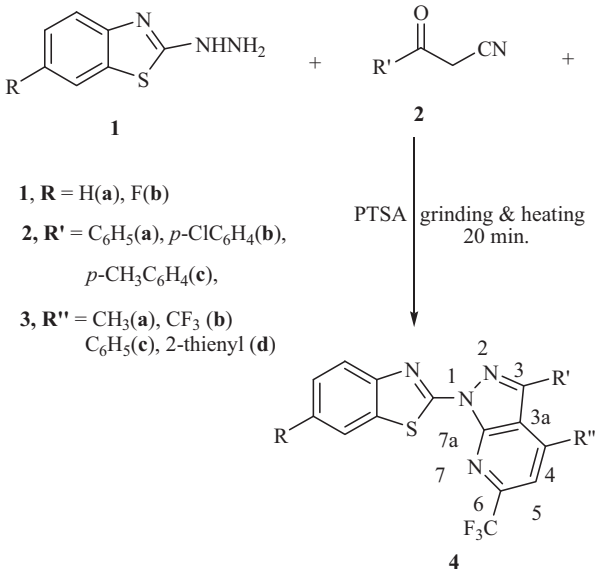
Scheme 1 outlines the general method, we have used to prepare the title compounds: reaction between 2-hydrazinobenzothiazole **1a**, α-cyanoacetophenone **2a** and 4,4,4-trifluoro-1-phenylbutane-1,3-dione **3a** for 20 min, in the presence of *p*-toluenesulphonic acid (PTSA) as a catalyst, resulted in the formation of pyrazolo[3,4-*b*]pyridine **4a** in 79% yield. Theoretically, this reaction may lead to two isomeric products having the CF_3 group located either at position 4 or 6 of the pyrazolo[3,4-*b*]pyridine ring, but only a single product was isolated which was characterized to be 1-(benzothiazol-2′-yl)-3-phenyl-4-methyl-6-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridine **4a**, by the combined use of multinuclear NMR spectroscopy. The ^{1}H NMR spectrum of compound **4a** displayed two sharp singlets at δ 2.56 ppm (3H) and at δ 7.51 ppm (1H) corresponding to methyl and H-5 protons of the pyrazolo[3,4-*b*]pyridine system. The ^{13}C NMR spectrum of **4a** exhibited a quartet due to CF_3 group at δ 147.62 ppm with a coupling constant $^2J_{C\text{-}F}$ = 35.2 Hz indicating the presence of the CF_3 group at C-6. Further support to the presence of the CF_3 group at position 6 was obtained from the ^{19}F NMR spectrum of **4a** which exhibited a signal at δ −66.75 ppm. It has been reported in the literature that trifluoromethyl groups at positions 2 and 4, adjacent to the pyridine nitrogen, displayed fluorine signals at about δ −68 and −62 ppm, respectively [19].

To examine the scope of this new MCR, a series of different symmetrical and unsymmetrical β-diketones **3b-d** were selected, and our results prove that this protocol can be applied to aliphatic, aryl and heteroaryltrifluoromethyl-β-diketones (Scheme 1).

In order to compare the efficiency, synthetic utility, regioselectivity/regiospecificity and scope of the MCR over the classical approach, the synthesis of pyrazolo[3,4-*b*]pyridines was also attempted in a stepwise manner in solvents *i.e.* ethanol and acetic acid (Scheme 2). Initially, the key intermediate, 3-aryl-1-(benzothiazol-2′-yl)-5-amino-1*H*-pyrazole **5a** was prepared by cyclocondensation of **1a** with α-cyanoacetophenone **2a**, in refluxing ethanol in the presence of a few drops of acetic acid for 5–6 h. Subsequently, the reaction of **5a** with trifluoromethyl-β-diketone **3a** was accomplished by refluxing in acetic acid for 10 h. TLC of the crude reaction mixture indicated the formation of two products, none of which matching the previously obtained under solvent-free conditions, **4a**. Finally, both the products were separated by column chromatography and identified as 1-(benzothiazol-2′-yl)-3-phenyl-6-methyl-4-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridine **6a** and 5-acetylamino-1-(benzothiazol-2′-yl)-3-phenyl-1*H*-pyrazole **7** (see Section 4).

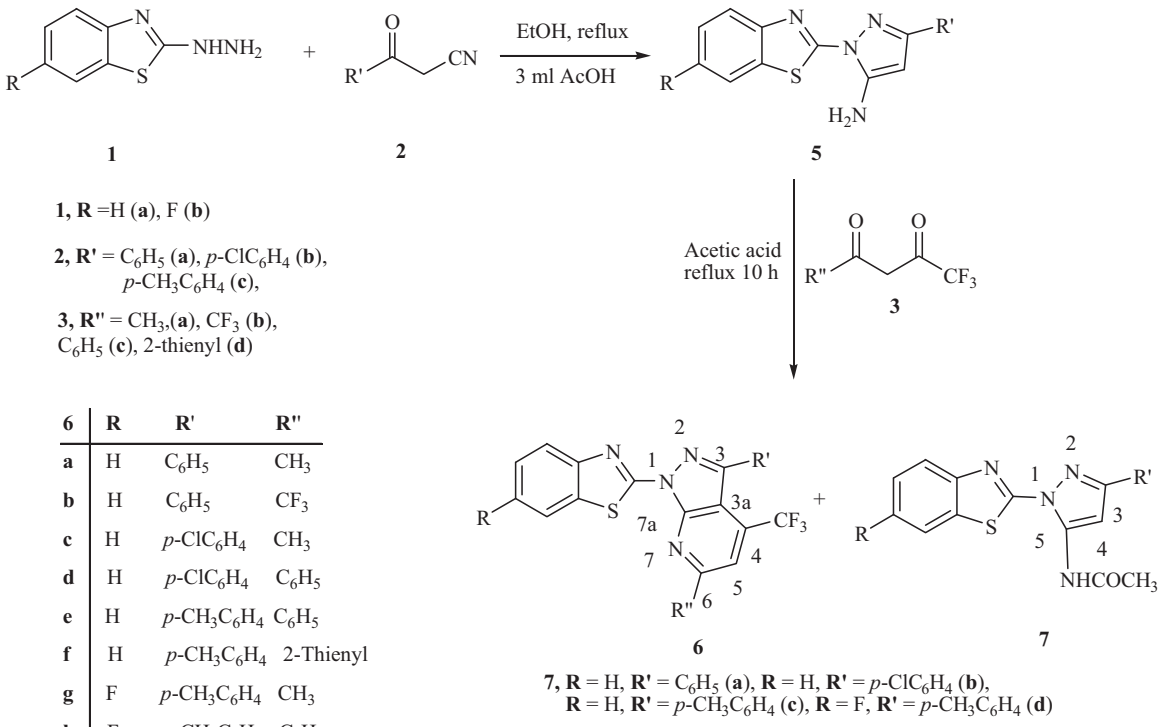
The synthesis of regioisomers **6b-h** was also achieved in a similar manner by applying different β-ketonitriles **2b-c** and various β-diketones **3b-d** (Scheme 2). Comparison of the conditions and results between the MCR and the stepwise solvent mediated synthesis are given in Table 1.

Again, unambiguous assignment of the structure to compound **6a** was based on multinuclear NMR data. ^{1}H NMR spectrum of **6a** showed, the lack of the signal at δ 5.82 ppm due to the NH_2 of 5-aminopyrazole, and the presence of a singlet at δ 7.50 ppm corresponding to the H-5 proton of the pyrazolo[3,4-*b*]pyridine system in **6a**. Also, **6a** displayed a singlet at δ 2.93 ppm for the CH_3 group, a downfield value compared to that observed at δ 2.56 ppm in **4a**, in agreement with the deshielding effect of the (–N=C–) fragment. The ^{13}C NMR spectrum of **6a** exhibited a characteristic quartet at δ 132.86 ppm ($^2J_{C\text{-}F}$ = 35.1 Hz) due to the CF_3 group at carbon C-4 [14]. If the trifluoromethyl group was located at position 6 the signal would appear at about 147 ppm due to the deshielding effect of the (–N=C–) fragment. The ^{19}F NMR spectrum of compound **6a** showed a signal at δ −60.04 ppm typical of a 4-CF_3



4	R	R'	R''
a	H	C_6H_5	CH_3
b	H	C_6H_5	CF_3
c	H	*p*-ClC_6H_4	CH_3
d	H	*p*-ClC_6H_4	C_6H_5
e	H	*p*-$CH_3C_6H_4$	C_6H_5
f	H	*p*-$CH_3C_6H_4$	2-thienyl
g	F	*p*-$CH_3C_6H_4$	CH_3
h	F	*p*-$CH_3C_6H_4$	C_6H_5

Scheme 1. Multicomponent solvent-free synthesis of 6-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridines (**4**).



6	R	R'	R''
a	H	C_6H_5	CH_3
b	H	C_6H_5	CF_3
c	H	*p*-ClC_6H_4	CH_3
d	H	*p*-ClC_6H_4	C_6H_5
e	H	*p*-$CH_3C_6H_4$	C_6H_5
f	H	*p*-$CH_3C_6H_4$	2-Thienyl
g	F	*p*-$CH_3C_6H_4$	CH_3
h	F	*p*-$CH_3C_6H_4$	C_6H_5

Scheme 2. Stepwise solvent mediated synthesis of 4-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridines (**6**).

Table 1
Reaction times and yields of the MCR preparation of **4a-h** and the stepwise solvent mediated synthesis of **6a-h**.

Compounds	Overall yield in the MCR process (20 min)	Compounds	Overall yield in the stepwise solvent mediated process (5 h + 10 h)
4a	79	**6a**	52
4b	80	**6b**	61
4c	86	**6c**	43
4d	82	**6d**	22
4e	76	**6e**	45
4f	74	**6f**	50
4g	88	**6g**	47
4h	84	**6h**	45

[19]. Detailed ^{19}F NMR data of **4a-h** and **6a-h** are gathered in Table 2.

Concluding evidence of the structures of compounds **4** and **6** were obtained by recording the 2D NMR (^1H–^1H) gs-COSY, (^1H–^{13}C) gs-HMQC and (^1H–^{13}C) gs-HMBC experiments (see Supplementary material). All results of the correlations are presented for compound **4a** in Table 3 and for **6a** in Table 4.

The (^1H–^{13}C) gs-HMBC of compound **4a** shows cross peaks of the methyl protons (δ 2.56) with C-5 (δ 117.26) and with C-3a (δ 118.10) (see Fig. 2a), thus confirming that the CH_3 is at position 4 of the pyrazolo[3,4-*b*]pyridine system. Furthermore, the low fluorine coupling ($^3J_{CF}$ = 2.0 Hz) of the CF_3 group with C-5 of pyrazolopyridine ring indicates no connectivity of the 6-CF_3 with C-5.

The (^1H–^{13}C) gs-HMBC spectrum of compound **6a** presents cross peaks of the methyl protons (δ 2.93) with C-5 (δ 116.68) and C-6 (161.22), but none cross peak was observed with C-3a (110.0) (see Fig. 2b), showing that such CH_3 group is not adjacent to C-3a, so being at position 6. In this compound, the fluorine coupling ($^3J_{CF}$ = 5.2 Hz) of the CF_3 group with C-5 of pyrazolopyridine is in agreement with the better connectivity of the 4-CF_3 with C-5.

Compounds **7** were identified on the basis of IR, ^1H NMR and their physical data as reported in literature [20]. The IR spectra presents sharp bands at 3200 cm^{-1} due to NH stretch in addition to a strong band at about 1700 cm^{-1} due to >C=O stretch. The ^1H NMR spectra of compounds **7** show a singlet of three proton intensity at δ 2.3 ppm due to –$COCH_3$ group, and all other protons in the aromatic region including the singlet corresponding to H-5 of the pyrazole ring.

As the chemistry for the formation of the 4-trifluoromethyl-pyrazolo[3,4-b]pyridines (**6**) is similar to that described in

Table 2
^{19}F NMR data for **4a–h** and **6a-h**.

Compounds	CF_3 position	δ	Compounds	CF_3 position	δ
4a	6	−66.75	**6a**	4	−60.04
4b = 6b	6	−66.74	**4b = 6b**	4	−59.81
4c	6	−66.79	**6c**	4	−59.77
4d	6	−66.64	**6d**	4	−59.88
4e	6	−66.59	**6e**	4	−59.81
4f	6	−66.67	**6f**	4	−60.01
4g	6	−66.78	**6g**	4	−59.99
4h	6	−66.66	**6h**	4	−60.03

Table 3
NMR data in $CDCl_3$, chemical shifts (δ, ppm) and coupling constants (J, Hz), for compound **4a**.

Nuclei	δ	J	gs-HMQC correlation	gs-HMBC correlation
4-CH_3	2.56 (s, 3H)		20.05	
6′-H	7.39 (t, 1H)		124.83	
5′-H			126.47	
5-H	7.48–7.55 (m, 5H)		117.26	
H*m* + H*p*			128.41	
			129.69	
H*o*	7.72 (m, 2H)		129.94	
7′-H	7.92 (td, 1H),	^3J = 7.9, ^4J = ^5J = 0.6	121.26	
4′-H	8.11 (dd, 1H)	^3J = 8.1	123.06	
4-CH_3	20.05	^1J = 128.8, ^3J = 4.6	2.56	7.50
5-CH	117.26	^1J = 163. 8, $^3J_{CF}$ = 2.0	7.51	2.56
3a-C	118.10	–	–	2.56, 7.51
7′-CH	121.26	^1J = 164.1, ^3J = 7.7	7.92	7.50
6-CF_3	121.43	$^1J_{CF}$ = 275.0	–	–
4′-CH	123.06	^1J = 164.1, ^3J = 7.7	8.11	7.39
6′-CH	124.83	^1J = 162.6, ^3J = 7.7	7.39	8.11
5′-CH	126.47	^1J = 163.1, ^3J = 7.7	7.50	7.92
m-CH	128.41	^1J = 159.9	7.53	7.53
p-CH	129.69	^1J = 161.0, ^3J = ^3J = 7.2	7.53	7.72
o-CH	129.94	^1J = 156.4	7.72	7.72, 7.53
i-C	131.66	^3J = ^3J = 7.8	–	7.53
7a′-C	133.36	^3J = 6.1; ^3J = 9.2	–	7.39, 8.11
4-C	146.86	$^2J_{CH3}$ = 6.1	–	2.56
6-C	147.62	$^2J_{CF}$ = 35.2	–	7.50
7a-C	149.79	–	–	–
3a′-C	149.82	–	–	7.92, 7.50
3-C	149.92	–	–	7.72
2′-C	155.79	–	–	–

Table 4
NMR data in $CDCl_3$. chemical shifts (δ, ppm) and coupling constants (J, Hz), for compound **6a**.

Nuclei	δ	J	gs-HMQC correlation	gs-HMBC correlation
6-CH_3	2.93(s, 3H)		25.15	
6′-H	7.39(t, 1H)		124.87	
5′-H			126.45	
5-H	7.48–7.50(m, 5H)		116.68	
H*m*, H*p*			127.89	
			129.33	
H*o*	7.62(m, 2H)		129.76	
7′-H	7.89(td, 1H,)	J = 8.0; J = J = 0.5	121.12	
4′-H	8.11 (td, 1H,	J = 8.2; J = J = 0.4	123.21	
6-CH_3	25.15	^1J = 129.3	2.93	7.50
3a-C	110.0	^3J = 7.6		7.50
5-CH	116.68	^1J = 167.2	7.50	2.93
		$^3J_{CH3}$ = 4.6		
		$^3J_{CF}$ = 5.2		
7′-CH	121.12	^1J = 164.1	7.89	7.50
		^3J = 9.2		
CF_3	122.0	$^1J_{CF}$ = 273.9	–	–
		^3J = 4.6		
4′-CH	123.21	^1J = 164.1	8.11	7.39
		^3J = 7.7		
6′-CH	124.87	^1J = 161.8	7.39	8.11
		^3J = 8.4		
5′-CH	126.45	^1J = 158.0	7.50	7.89
		^3J = 7.7		
m-CH	127.89	^1J = 162.0	7.50	7.50
		^3J = 7.2		
p-CH	129.33	^1J = 161.0	7.50	7.62
		^3J = ^3J = 7.7		
o-CH	129.76	^1J = 161.0	7.62	7.62, 7.50
		^3J = ^3J = 6.2		
i-C	131.68	^3J = ^3J = 6.9	–	7.50
4-C	132.86	$^2J_{CF}$ = 35.1	–	
7a′-C	133.17	^3J = 10.0	–	8.11, 7.39
		^3J = 7.0		
3-C	148.46	–	–	7.62
3a′-C	150.15	–	–	7.89,7.50
7a-C	151.40	–	–	–
2′-C	156.47	–	–	–
6-C	161.22	–	–	2.93, 7.50

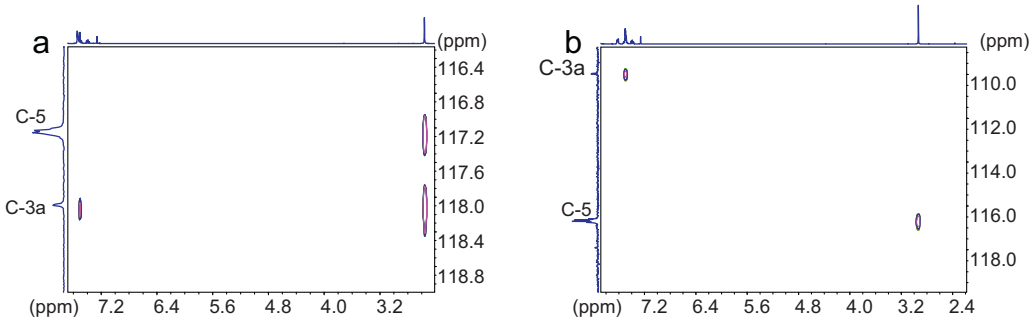


Fig. 2. $^{1}H-^{13}C$ gs-HMBC of 1-(benzothiazol-2-yl)-4-methyl-3-phenyl-6-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**4a**) in $CDCl_3$(a) and 1-(benzothiazol-2-yl)-6-methyl-3-phenyl-4-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**6a**) in $CDCl_3$(b).

previous works [14,21], the regiospecificity reversal exhibited in solvent-free reactions suggests an alternative mechanism without the intermediacy of the 5-aminopyrazole derivatives **5**, most probably a tandem reaction in which the cyclization of two rings take place simultaneously giving rise to the regioisomeric 6-trifluoromethylpyrazolo[3,4-b]pyridines (**4**). This proposal, based on the observation that the multi-component solvent-free reaction (MCR) generates regioisomers **4** in short reaction times (10 min) meanwhile in the stepwise solvent mediated synthesis the corresponding 5-aminopyrazoles **5** were obtained after 15 min, will be further investigated extending the MCR reaction to other substrates.

3. Conclusion

In a nutshell, a one-step three-component reaction of structurally diverse fluorinated-β-diketones with 2-hydrazinobenzothiazoles and α-cyanoacetophenones resulted in the formation of 6-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridines. This methodology is not only advantageous in terms of high yield, considerably reduction in reaction time and cleaner work up, but also induces regiospecificity. In solvent mediated synthesis, there was formation of 4-trifluoromethyl isomers along with undesired amides as side products.

4. Experimental

Melting points were determined in open capillaries in electrical apparatus and are uncorrected. IR spectra were recorded on a Buck scientific IRM-500 spectrophotometer in KBr pellet (ν_{max} in cm^{-1}). ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker instrument at 300 MHz and 75 Hz respectively. ^{19}F-NMR spectra were performed on DRX-300 and DPX-400 at 282 and 376 MHz respectively, at SAIF Lucknow, India.

2D ($^{1}H-^{1}H$) gs-COSY and inverse proton detected heteronuclear shift correlation spectra, ($^{1}H-^{13}C$) gs-HMQC, ($^{1}H-^{13}C$) and gs-HMBC, of compounds **4a** and **6a**, were acquired on a Bruker DRX 400 (9.4 Tesla, 400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C) spectrometer with a 5-mm inverse-detection H–X probe equipped with a z-gradient coil, at 300 K and processed using standard Bruker NMR software and in non-phase-sensitive mode. Gradient selection was achieved through a 5% sine truncated shaped pulse gradient of 1 ms.

Selected parameters for ($^{1}H-^{1}H$) gs-COSY were spectral width 3600 and 600 Hz, the acquisition data size was 1024 points and one transient was accumulated per increment, with a 1 s relaxation delay, for a total of 256 experiments, data processing using zero filling in the *F*1 domain and shifted sine-bell apodization of factor 0 in both dimensions.

Selected parameters for($^{1}H-^{13}C$)gs-HMQC and gs-HMBC spectra were spectral width 3500 Hz for ^{1}H and 20.5 kHz for ^{13}C, 1024 × 256 data set, number of scans 2 (gs-HMQC) or 4 (gs-HMBC) and relaxation delay 1 s. The FIDs were processed using zero filling in the *F*1 domain and a sine-bell window function in both dimensions was applied prior to Fourier transformation. In the gs-HMQC experiments GARP modulation of ^{13}C was used for decoupling.

Trifluoromethylβ-diketones (**4a-b**) are available commercially. Diketones (**4c-d**) [22], α-cyanoacetophenones [23] and 2-hydrazino-6-substitutedbenzothiazoles [24] were prepared according to the literature procedure.

4.1. General procedure for three-component solvent-free synthesis of 1-(benzothiazol-2′-yl)-3-aryl-4-substituted-6-trifluoromethyl-1H-pyrazolo[3,4-b]pyridines 4a-h

Equimolar amounts of appropriate 2-hydrazinobenzothiazole **1a-b**, α-cyanoacetophenone **2a-c**, and PTSA were mixed thoroughly in pestle mortar and heated on water bath for 4–5 min and then equimolar amount of appropriate trifluoromethyl β-diketones **3a-d** was added to it and mixed thoroughly. The reaction mixture was again heated 80–90 °C for 15 min on water bath. The solid was obtained by addition of aq. ethanol, filtered and crystallized from the mixture of ethanol and chloroform to give pure **4**.

1-(Benzothiazol-2′-yl)-4-methyl-3-phenyl-6-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine **4a**: Yield 79%; Mp 236 °C; IR (KBr, cm^{-1}): 1528, 3078 (–C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.56 (s, 3H, 4-CH_3), 7.39 (t, 1H, 6′-H), 7.48–7.55 (m, 5H, 5′-H, 5-H, H*m*, H*p*), 7.72 (m, 2H, H*o*), 7.92 (td, 1H, 7′-H, *J* = 7.9, 0.6 Hz), 8.11 (dd, 1H, 4′-H, *J* = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.05 (4-CH_3), 117.26 (q, $^{3}J_{C-F}$ = 2.0 Hz), 118.10, 121.26, 121.43 (q, $^{1}J_{C-F}$ = 275 Hz), 123.06, 124.83, 126.47, 128.41, 129.69, 129.94, 131.66, 133.36, 146.86, 147.62 (q, $^{2}J_{C-F}$ = 35.2 Hz), 149.79, 149.82, 149.92, 155.79; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −66.75 (6-CF_3); MS (EI) *m*/*z*: 411 $[M+1]^+$; Elemental analysis calcd. for $C_{21}H_{13}F_3N_4S$: C, 61.46; H, 3.19; N, 13.65. Found: C, 61.38; H, 3.16; N, 13.62.

1-(Benzothiazol-2-yl)-3-phenyl-4,6-bistrifluoromethyl-1H-pyrazolo[3,4-b]pyridine **4b**: Yield 80%; Mp 247 °C; IR (KBr, cm^{-1}): 1528, 3078(–C=N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.41–7.65 (m, 7H, C_6H_5, 5′, 6′-H), 7.97 (d, 1H, 7′-H, *J* = 8.1 Hz), 8.01 (s, 1H, 5-H), 8.16 (d, 1H, 4′-H, *J* = 8.7 Hz,); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 111.60, 112.85, 119.71 (q, $^{1}J_{C-F}$ = 274 Hz), 120.00 (q, $^{1}J_{C-F}$ = 273 Hz), 120.33, 122.39, 124.37, 125.76, 127.08, 128.78, 128.82, 129.60, 132.31, 134.48(q, $^{2}J_{C-F}$ = 36 Hz), 147.32 (q, $^{2}J_{C-F}$ = 37 Hz), 147.54, 147.62, 149.11, 154.08; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −59.81 (4-CF_3), −66.74 (6-CF_3); MS (EI) *m*/*z*: 465 $[M+1]^+$; Elemental analysis calcd. for $C_{21}H_{10}F_6N_4S$: C, 54.31; H, 2.17; N, 12.06. Found: C, 54.28; H, 2.15; N, 12.02.

1-(Benzothiazol-2′-yl)-3-(p-chlorophenyl)-4-methyl-6-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine **4c**: Mp 198 °C; IR (KBr, cm^{-1}): 1528, 3063 (–C=N); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.60 (s, 3H, 4-CH_3), 7.43 (t, 1H, 6′-H), 7.59 (m, 4H, C_6H_4, 5′, 5-H), 7.69 (d, 2H, C_6H_4, *J* = 7.2 Hz), 7.95 (d, 1H, 7′-H, *J* = 8.1 Hz) 8.15 (d, 1H, 4′-H, *J* = 7.8 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.18 (4-CH_3), 117.39, 117.65, 121.29, 121.36 (q, $^1J_{C\text{-}F}$ = 273 Hz),123.07, 124.96, 126.56, 128.78, 130.12, 131.28, 133.35, 136.05,146.68, 147.74 (q, $^2J_{C\text{-}F}$ = 35 Hz), 148.71, 149.65, 149.73, 155.58; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −66.79 (6-CF_3); MS (EI) *m/z*: 445/447 (3:1) $[M+1]^+/[M+1+2]^+$; Elemental analysis calcd. for $C_{21}H_{12}ClF_3N_4S$: C, 56.70; H, 2.72; N, 12.59. Found: C, 56.67; H, 2.70; N, 12.56.

1-(Benzothiazol-2′-yl)-3-(p-chlorophenyl)-4-phenyl-6-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine **4d**: Mp 228 °C; IR (KBr, cm^{-1}): 1512, 3024 (–C═N); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.13–7.58 (m, 11H, C_6H_4, Ph, 5′, 6′-H), 7.76 (s, 1H, 5-H), 7.97 (d, 1H, 7′-H, *J* = 8.1 Hz,), 8.18 (d, 1H, 4′-H, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 116.84, 117.03, 121.51(q, $^1J_{C\text{-}F}$ = 273 Hz), 122.39, 122.88, 125.66, 126.66, 126.87, 127.99, 128.63, 129.17, 129.33, 129.66, 129.97, 135.17, 136.45, 147.44 (q, $^2J_{C\text{-}F}$ = 35 Hz), 146.83, 148.69, 150.45, 150.55, 156.28; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −66.64 (6-CF_3); MS (EI) *m/z*: 507/509 (3:1) $[M+1]^+/[M+1+2]^+$; Elemental analysis calcd. for $C_{26}H_{14}ClF_3N_4S$: C, 61.60; H, 2.78; N, 11.05. Found: C, 61.58; H, 2.75; N, 11.02.

1-(Benzothiazol-2′-yl)-4-phenyl-3-(p-tolyl)-6-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine **4e**: Mp 200 °C; IR (KBr, cm^{-1}): 1528, 3063(–C═N); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.33 (s, 3H, 4″-CH_3), 6.95 (d, 2H, C_6H_4, *J* = 7.8 Hz), 7.18 (d, 2H, C_6H_4, *J* = 8.1 Hz), 7.24–7.59 (m, 7H, Ph, 5′, 6′-H), 7.75 (s, 1H, 5-H), 7.97 (d, 1H, 7′-H, *J* = 7.8 Hz), 8.21 (d, 1H, 4′-H, *J* = 8.1 Hz,); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.36 (4″-CH_3), 115.80, 116.77, 121.41 (q, $^1J_{C\text{-}F}$ = 273 Hz), 122.67, 125.20, 126.22, 126.54, 126.90, 128.35, 128.46, 128.73, 129.43, 129.65, 132.60, 139.17, 135.20, 147.46 (q, $^2J_{C\text{-}F}$ = 35 Hz), 148.43, 149.59, 150.37, 150.53, 156.18; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −66.59 (6-CF_3); MS (EI) *m/z*: 487 $[M+1]^+$; Elemental analysis calcd. for $C_{27}H_{17}F_3N_4S$: C, 66.66; H, 3.52; N, 11.52. Found: C, 66.62; H, 3.48; N, 11.48.

1-(Benzothiazol-2′-yl)-4-(2‴-thienyl)-3-(p-tolyl)-6-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine **4f**: Mp 210 °C; IR (KBr, cm^{-1}): 1528, 3063 (–C═N); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.48 (s, 3H, 4″-CH_3), 6.82 (m, 1H, C_4H_3S), 7.11 (m, 1H, C_4H_3S), 7.32–7.65 (m, 7H, C_6H_4, C_4H_3S, 5′, 6′-H), 7.77 (s, 1H, 5-H), 7.96 (d, 1H, 7′-H, *J* = 7.8), 8.18 (d, 1H, 4′-H, *J* = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.34 (4″-CH_3), 115.75, 117.14, 121.24, 121.34 (q, $^1J_{C\text{-}F}$ = 273 Hz), 122.37, 125.57, 126.43, 127.54, 128.56, 128.73, 129.02, 129.22, 129.43, 132.22, 135.39, 135.80, 147.52 (q, $^2J_{C\text{-}F}$ = 35 Hz), 147.76, 148.14, 150.13, 150.44, 156.24; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −66.67 (6-CF_3); MS (EI) *m/z*: 493 $[M+1]^+$; Elemental analysis calcd. for $C_{25}H_{15}F_3N_4S_2$: C, 60.96; H, 3.07; N, 11.38. Found: C, 60.92; H, 3.02; N, 11.34.

1-(6′-Fluorobenzothiazol-2′-yl)-4-methyl-3-(p-tolyl)-6-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine **4g**: Mp 236 °C; IR (KBr, cm^{-1}): 1535, 3063 (–C═N); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.49 (s, 3H, 4″-CH_3), 2.60 (s. 3H, 4-CH_3), 7.34–7.37 (m, 3H, C_6H_4, 5′-H), 7.53 (s, 1H, 5-H), 7.60–7.63 (m, 3H, C_6H_4,7′-H), 8.05–8.10 (m, 1H, 4′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.16 (4-CH_3), 21.36 (4″-CH_3), 115.60, 116.40, 118.76 (q, $^1J_{C\text{-}F}$ = 273 Hz), 122.10, 123.14, 126.55 (d, $^2J_{C\text{-}F}$ = 24 Hz), 128.16, 129.06, 129.87, 132.63, 135.34, 147.56 (q, $^2J_{C\text{-}F}$ = 35 Hz), 147.92, 148.39, 150.21, 150.31, 155.99, 157.16; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −66.78 (6-CF_3), −116.16 (6′-F); MS (EI) *m/z*: 443 $[M+1]^+$; Elemental analysis calcd. for $C_{22}H_{14}F_4N_4S$: C, 59.72; H, 3.19; N, 12.66. Found: C, 59.68; H, 3.15; N, 12.64.

1-(6′-Fluorobenzothiazol-2-yl)-4-phenyl-3-(p-tolyl)-6-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine **4h**: Mp 218 °C; IR (KBr, cm^{-1}): 1528, 3078 (–C═N); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.33 (s, 3H, 4″-CH_3), 6.95 (d, 2H, C_6H_4*J* = 7.8 Hz), 7.16 (d, 2H, C_6H_4, *J* = 7.8 Hz), 7.24–7.40 (m, 6H, Ph, 5′-H), 7.63 (d, 1H, 7′-H, *J* = 8.1 Hz), 7.74 (s, 1H, 5-H), 8.01–8.12 (m, 1H, 4′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.35 (4″-CH_3), 115.74, 116.72, 121.42 (q, $^1J_{C\text{-}F}$ = 273 Hz), 122.57, 123.16, 126.18 (d, $^2J_{C\text{-}F}$ = 24 Hz), 126.56, 126.98, 128.13,128.76, 129.56, 129.86, 129.88, 132.77, 135.16, 147.68 (q, $^2J_{C\text{-}F}$ = 35 Hz), 147.82, 148.34, 150.34, 150.47, 156.11, 157.28; ^{19}F-NMR (282 MHz, $CDCl_3$) δ: −66.66 (6-CF_3), −116.03 (6′-F); MS (EI) *m/z*: 505 $[M+1]^+$; Elemental analysis calcd. for $C_{27}H_{16}F_4N_4S$: C, 64.28; H, 3.20; N, 11.11. Found: C, 64.24; H, 3.16; N, 11.06.

4.2. General procedure for the synthesis of 3-phenyl-1-(benzothiazol-2′-yl)-5-aminopyrazole **5a**

A mixture of 2-hydrazinobenzothiazole **1a** (0.825 g, 5 mmol) and α-cyanoacetophenone **2a** (0.73 g, 5 mmol) was refluxed in ethanol containing acetic acid (3ml) for 5–6 h. Excess solvent was removed by distillation. The crude product so obtained was recrystallized from ethanol to give **5a** (1.09 g, 75%), Mp 201 °C (lit. [20], 202 °C). Other compounds (**5b-d**) of this type were prepared similarly.

5-amino-1-(benzothiazol-2′-yl)-3-phenyl-1-H-pyrazole **5a**: Mp 200 °C (lit. [20] 202 °C).

5-amino-1-(benzothiazol-2′-yl)-3-(p-chlorophenyl)-1-H-pyrazole **5b**: Mp 226 °C (lit. [20] 227 °C).

5-amino-1-(benzothiazol-2′-yl)-3-(p-tolyl)-1-H-pyrazole **5c**: Mp 227°C (lit. [20] 228 °C).

5-amino-1-(6′-fluorobenzothiazol-2′-yl)-3-(p-tolyl)-1-H-pyrazole **5d**: Mp 213 °C; IR (KBr, cm^{-1}): 3201, 3317 (NH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.42 (3H, s, 4″-CH_3), 7.24–7.84 (m, 8H, C_6H_4, 4′, 5′, 7′, 4-H); MS (EI) *m/z*: 325 $[M+1]^+$; Elemental analysis calcd. for $C_{17}H_{13}FN_4S$: C, 62.95; H, 4.04; N, 17.27. Found: C, 62.91; H, 4.01; N, 17.24.

4.3. General procedure for synthesis of 1-(benzothiazole-2′-yl)-3-aryl-6-substituted-4-trifluoromethyl-1H-pyrazolo[3,4-b]pyridines **6a-h** *and 5-acetylamino-1-(benzothiazol-2′-yl)-3-substituted-1-H-pyrazoles* **7a-d**

3-aryl-1-(benzothiazol-2′-yl)-5-aminopyrazole **5** (5 mmol) was dissolved in acetic acid (20 ml) and equimolar amount of appropriate trifluoromethyl-β-diketones **3** was added to it. The reaction mixture was heated to reflux at about 10 h. After completion of reaction, the reaction mixture was poured in excess of water and filtered. The crude products thus obtained were separated by column chromatography using silica gel (100–200 mesh) with petroleum ether/ethyl acetate (99.5/0.5) as an eluent afforded **6** and further elution of column with petroleum ether/ethyl acetate (99: 1) furnished **7**.

1-(Benzothiazol-2′-yl)-6-methyl-3-phenyl-4-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine **6a**: Mp 256 °C; IR (KBr, cm^{-1}): 1528, 3078 (–C═N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.93 (s, 3H, 6-CH_3), 7.39 (t, 1H, 6′-H) 7.42–7.50 (m, 5H, H*m*, H*p*, 5′, 5-H), 7.62 (m, 2H, H*o*), 7.89 (dd, 1H, 7′-H, *J* = 8.0, 0.5 Hz), 8.11 (td, 1H, 4′-H, *J* = 8.2, 0.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.15 (6-CH_3), 110.0, 116.68 (q, $^3J_{C\text{-}F}$ = 5.2 Hz), 121.12, 122.0 (q, $^1J_{C\text{-}F}$ = 273.9 Hz), 123.21, 124.87, 126.45, 127.89, 129.33, 129.76, 131.68, 132.86 (q, $^2J_{C\text{-}F}$ = 35.1 Hz), 133.17, 148.46, 150.15, 151.40, 156.47, 161.22; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −60.04 (4-CF_3); MS (EI) *m/z*: 411 $[M+1]^+$; Elemental analysis calcd. for $C_{21}H_{13}F_3N_4S$: C, 61.46; H, 3.19; N, 13.65. Found: C, 61.38; H, 3.16; N, 13.62.*1-(Benzothiazol-2′-yl)-3-phenyl-4,6-bistrifluoromethyl-1H-pyrazolo[3,4-b]pyridine* **6b**: Characterisation data of **6b** is similar to that of **4b**.

1-(Benzothiazol-2′-yl)-3-(p-chlorophenyl)-6-methyl-4-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine **6c**: Mp 198 °C; IR (KBr, cm^{-1}): 1528, 3078 (–C═N); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.96 (s, 3H, 6-CH_3), 7.39–7.59 (m, 5H, C_6H_4, 5′, 6′, 5-H), 7.87–7.94 (m, 3H, C_6H_4, 7′-H), 8.15 (d, 1H, 4′-H, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.12 (6-CH_3), 95.19, 116.77, 121.15, 122.01 (q, $^1J_{C\text{-}F}$ = 272 Hz), 123.21, 124.99, 126.54, 127.47, 128.86, 129.06, 130.15, 132.69 (q, $^2J_{C\text{-}F}$ = 35 Hz), 133.20, 147.25, 150.24, 151.46, 156.76, 161.45; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −59.77 (4-CF_3); MS (EI) *m/z*: 445/447 (3:1) $[M+1]^+/[M+1+2]^+$; Elemental analysis calcd. for $C_{21}H_{12}ClF_3N_4S$: C, 56.70; H, 2.72; N, 12.59. Found: C, 56.67; H, 2.70; N, 12.56.

1-(Benzothiazol-2′-yl)-3-(p-chlorophenyl)-6-phenyl-4-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine **6d**: Mp 224 °C; IR (KBr, cm^{-1}): 1535, 3047(–C=N); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.46–7.66 (m, 8H, C_6H_4, C_6H_5, 6′-H), 8.01 (m, 1H, 5′-H) 8.15 (d, 1H, 7′-H, J = 8.4 Hz) 8.18 (s, 1H, 5-H), 8.36 (m, 1H, 4′-H), 8.48 (d, 2H, C_6H_4, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 110.17, 115.56, 121.27, 121.84 (q, $^1J_{C-F}$ = 272 Hz), 121.36, 123.24, 124.33, 126.68, 126.66, 128.29, 128.33, 129.55, 131.03, 132.38 (q, $^2J_{C-F}$ = 36 Hz), 132.46, 136.37, 138.22, 146.38, 148.41, 150.91, 154.76, 158.36; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −59.88 (4-CF_3); MS (EI) m/z: 507/509 (3:1) $[M+1]^+/[M+1+2]^+$; Elemental analysis calcd. for $C_{26}H_{14}ClF_3N_4S$: C, 61.60; H, 2.78; N, 11.05. Found: C, 61.58; H, 2.75; N, 11.02.

1-(Benzothiazol-2′-yl)-6-phenyl-3-(p-tolyl)-4-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine **6e**: Mp 214 °C; IR (KBr, cm^{-1}): 1528, 3078(–C=N); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.48 (s, 3H, 4″-CH_3), 7.30–7.68 (m, 9H, C_6H_4, Ph, 5′, 6′-H), 7.98 (d, 1H, 7′-H, J = 8.1 Hz), 8.12 (s, 1H, 5-H), 8.16 (d, 1H, 4′-H, J = 8.1 Hz) 8.37 (d, 2H, C_6H_4, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.49 (4″-CH_3), 110.59, 113.19, 123.04 (q, $^1J_{C-F}$ = 275 Hz), 123.16, 126.12, 126.56, 127.93, 127.97, 128.07, 128.62, 129.30, 129.69, 131.03, 133.32, 133.77 (q,$^2J_{C-F}$ = 35 Hz), 136.94, 139.30, 148.94, 149.78, 151.65, 155.37, 158.36; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −59.81 (4-CF_3); MS (EI) m/z: 487 $[M+1]^+$; Elemental analysis calcd. for $C_{27}H_{17}F_3N_4S$: C, 66.66; H, 3.52; N, 11.52. Found: C, 66.62; H, 3.48; N, 11.48.

1-(Benzothiazol-2′-yl)-6-(2″-thienyl)-3-(p-tolyl)-4-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine **6f**: Mp 227 °C; IR (KBr, cm^{-1}): 1535, 3063 (–C=N); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.48 (s, 3H, 4″-CH_3), 7.25–7.67 (m, 8H, C_6H_4, C_4H_3S, 5′, 6′-H), 7.95 (m, 2H, C_4H_3S, 5-H), 7.98 (d, 1H, 7′-H, J = 8.1 Hz), 8.15 (d, 1H, 4′-H, J = 8.4 Hz,);^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.48 (4″-CH_3), 109.25, 112.47, 121.07 (q, $^1J_{C-F}$ = 274 Hz), 121.22, 123.14, 123.87, 126.54, 127.68, 128.24, 128.78, 129.13, 129.68, 130.90, 133.36 (q, $^2J_{C-F}$ = 36 Hz), 133.47, 136.20, 139.29,142.82, 149.73, 150.29, 153.23, 158.16; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −60.01 (4-CF_3); MS (EI) m/z: 493 $[M+1]^+$; Elemental analysis calcd. for $C_{25}H_{15}F_3N_4S_2$: C, 60.96; H, 3.07; N, 11.38. Found: C, 60.92; H, 3.02; N, 11.34.

1-(6′-Fluorobenzothiazol-2′-yl)-6-methyl-3-(p-tolyl)-4-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine **6g**: Mp 208 °C; IR (KBr, cm^{-1}): 1531, 3068 (–C=N); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.47 (s, 3H, 4″-CH_3), 2.95 (s, 3H, 6-CH_3), 7.21–7.52 (m, 5H, C_6H_4, 5-H), 7.58 (m, 1H, 5′-H, J = 8.1 Hz), 7.82 (d, 1H, 7′-H, J = 7.8 Hz), 8.16 (dd, 1H, 4′-H, J = 4.8, 9.0, 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.46 (4″-CH_3), 25.13(6-CH_3), 107.70, 114.76, 120.27 (q, $^1J_{C-F}$ = 274 Hz), 122.65, 124.09, 124.21, 126.18 (d, $^2J_{C-F}$ = 24 Hz), 128.64, 129.40, 129.58, 134.21 (q, $^2J_{C-F}$ = 36 Hz), 146.79, 139.34, 149.14, 151.39, 154.39, 157.70, 161.26; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −59.99 (4-CF_3), −116.06 (6′-F); MS (EI) m/z: 443 $[M+1]^+$; Elemental analysis calcd. for $C_{22}H_{14}F_4N_4S$: C, 59.72; H, 3.19; N, 12.66. Found: C, 59.68; H, 3.15; N, 12.64.

1-(6′-Fluorobenzothiazol-2-yl)-6-phenyl-3-(p-tolyl)-4-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine **6h**: Mp 241 °C; IR (KBr, cm^{-1}): 1543, 3070 (–C=N); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.48 (s, 3H, 4″-CH_3), 7.30–7.66 (m, 9H, C_6H_4, Ph, 7′, 5′-H), 8.07 (d, 1H, 4′-H, J = 5.1 Hz), 8.12 (s, 1H, 5-H), 8.36 (d, 2H, J = 6.9 Hz, C_6H_4); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.49 (4″-CH_3), 107.41, 111.19 (q, $^1J_{C-F}$ = 271 Hz), 113.34, 123.91, 124.02, 124.14, 127.90 (d, $^2J_{C-F}$ = 24 Hz), 128.64, 129.33, 129.65, 131.10, 133.84 (q, $^2J_{C-F}$ = 35 Hz), 134.23, 134.37, 136.84, 139.38, 146.28, 149.06, 151.57, 154.88, 158.53, 161.78; ^{19}F NMR (282 MHz, $CDCl_3$) δ: −60.03 (4-CF_3), −116.09 (6′-F); MS (EI) m/z: 505 $[M+1]^+$; Elemental analysis calcd. for $C_{27}H_{16}F_4N_4S$: C, 64.28; H, 3.20; N, 11.11. Found: C, 64.24; H, 3.16; N, 11.06.

5-acetylamino-1-(benzothiazol-2′-yl)-3-phenyl-1H-pyrazole **7a**: Mp 191 °C (lit. [20] 192 °C).

5-acetylamino-1-(benzothiazol-2′-yl)-3-(p-chlorophenyl)-1H-pyrazole **7b**: Mp 206 °C (lit. [20] 208 °C).

5-acetylamino-1-(benzothiazol-2′-yl)-3-(p-tolyl)-1H-pyrazole **7c**: Mp 238 °C (lit. [20] 240 °C).

5-acetylamino-1-(6′-fluorobenzothiazol-2′-yl)-3-(p-tolyl)-1H-pyrazole **7d**: Mp 190 °C; IR (KBr, cm^{-1}): 3200 (NH),1698 (CO); ^1H NMR (300 MHz, $CDCl_3$) δ: 2.38 (3H, s, $COCH_3$), 2.42 (3H, s, 4″-CH_3), 7.24–7.84 (m, 8H, C_6H_4, 4′, 5′, 7′, 4-H); MS (EI) m/z: 367 $[M+1]^+$; Elemental analysis calcd. for $C_{19}H_{15}FN_4OS$: C, 62.28; H, 4.13; N, 15.29. Found: C, 62.24; H, 4.09; N, 15.26.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2012.04.007.

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