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Ultrasound assisted one-pot, three-components synthesis of pyrimido[1,2-a]benzimidazoles and pyrazolo[3,4-b]pyridines: A new access *via* phenylsulfone synthon

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ABSTRACT

A simple, facile, efficient and three-components procedure for the synthesis of pyrimido[1,2-a]benzimidazoles and pyrazolo[3,4-b]pyridines utilizing phenylsulfone synthon, under ultrasonic irradiation was developed.

1. Introduction

Contemporaneous research in organic synthesis focuses on economy [1], the development of rapid and selective synthetic routes toward focused libraries of functionalized heterocyclic building blocks is of great importance to both medicinal and organic chemists, and still constitutes a challenge from academic and industrial points of view. In modern organic chemistry, because of economic and ecological increasing pressure, investigations are now directed to the discovery of methods that largely take into account the criterion of sustainable chemistry [2]. In this context, multicomponent reactions (MCRs) [3] involving domino processes [4], combining at least three different substrates in a one-pot operation, have emerged as powerful tools and complementary substrate-directed synthetic alternatives to other well-known methods [5–8]. Moreover, these transformations combine classical concerns such as efficiency, selectivity, molecular complexity and diversity [9,10].

Pyrimidobenzimidazoles have been found to be of pharmacological interest. For example, pyrimido[1,2-a]benzimidazoles have been described as antihypertensives [11,12], antidiabetics [12], antiinflammatory agents [13], antirheumatics [13] and as antibiotics against staphylococcus and mycobacterium ranae [14]. They have antiarrythmic effects [14], herbicidal activity [15] antidepressant effects [16], microfilaricidal and macrofilaricidal effects [17], they act as bactericides [18], fungicides [18], virucides [18] and as diuretics [19].

Pyrimido[1,2-a]benzimidazoles are commonly synthesized *via* cyclization of 2-aminobenzimidazole with 1,3-bielectrophiles. Up to now numerous data have been reported on regioselective cyclization of 2-aminobenzimidazole with α,β-unsaturated ketones (chalcones) [20–23] but one of the most drawbacks of this method formation of dihydro derivatives which need to oxidation upon certain treatment.

The pyrazolo[3,4-b]pyridine ring system is present in a number of pharmaceutically important compounds, for instance, to inhibit glycogen synthase kinase-3 (GSK-3) and cyclin-dependent kinases (CDKs) [24,25], GSK-3 is known to play a key role in chronic inflammatory processes [26], cancer [27], and Alzheimer's disease (AD) [28]. On the other hand, CDKs inhibitors are expected to be active in the nervous system, *via* inhibition of neurotrophic pathways, and antiapoptotic protection from neurofibrillary degeneration in AD [29]. It was found that attachment of sulfone moiety to pyrazolo[3,4-b]pyridine ring system in position 5 have a great importance, in which structure–activity studies for the class of pyrazolo[3,4-b]pyridines as CDKs inhibitors have shown that optimal CDKs inhibitory potency [30].

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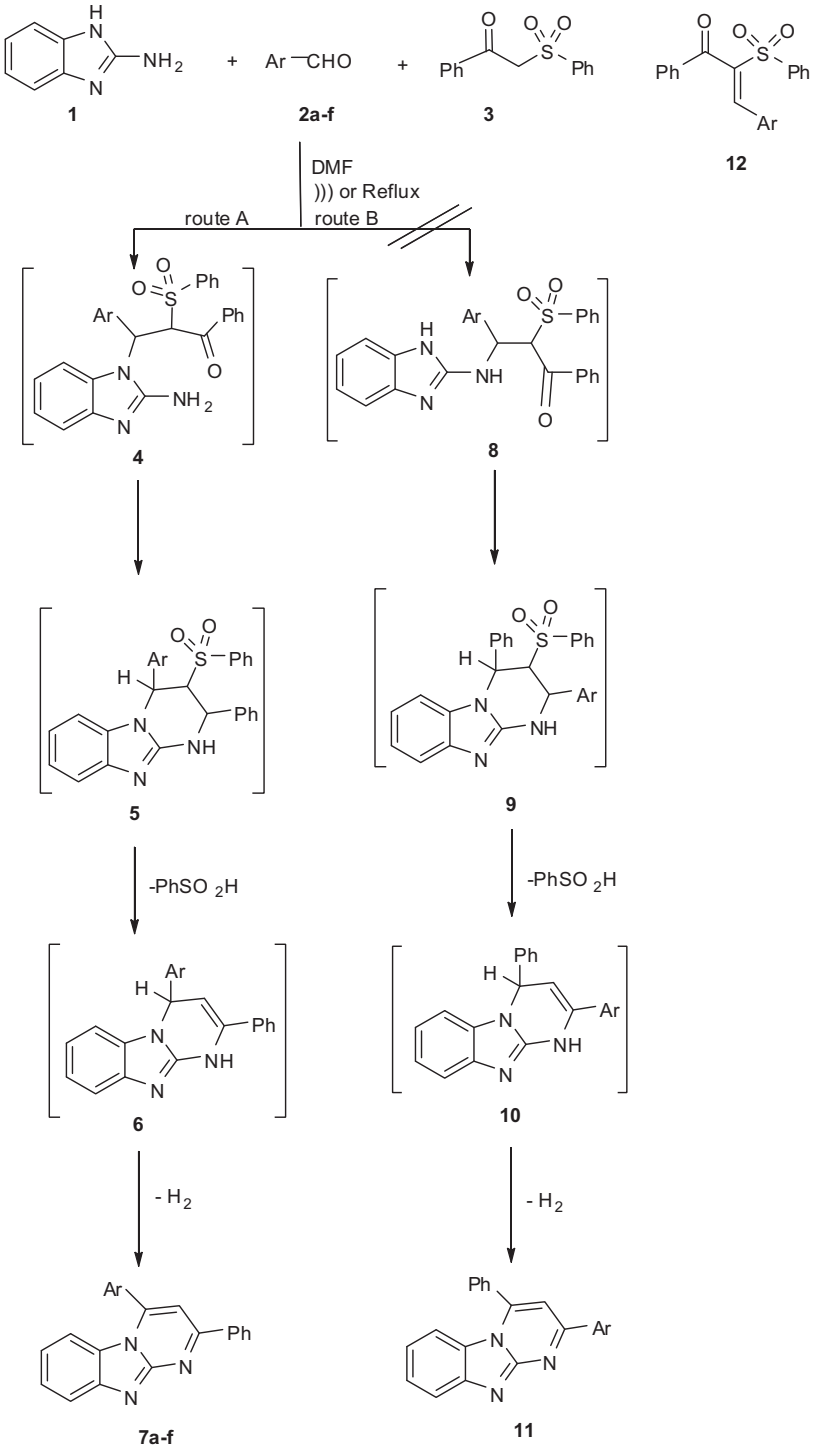


Scheme 1.

Hence, there remains a demand for development of methods for the synthesis of azolopyrimidines and azolopyridines.

In the last few years the application of ultrasound in synthetic organic chemistry became more and more interesting "Sonochemistry" is a new trend in organic chemistry, offering a versatile and facile pathway for a large variety of syntheses. Thus, a large number of organic reactions can be carried out under ultrasonic irradiation in high yields, short reaction times and mild conditions [31–38]. Motivated by the afore-mentioned findings, and in a continuation of our interest, in synthesis of a wide range of heterocyclic systems, for biological screening program in our laboratory [39–44], and as a part of our growing interest in sonochemistry [44–46]. We describe here a facile sonochemical one-pot, three-component synthesis of pyrimido[1,2-a]benzimidazoles and pyrazolo[3,4-b]pyridines *via* phenylsulfone synthon. The structure of the products was established on different analytical and spectroscopic data.

2. Result and discussion

The reaction of 2-aminobenzimidazole **(1)** with the aldehyde derivatives **2a–f** and 1-phenyl-2-(phenylsulfonyl)ethanone **(3)** in

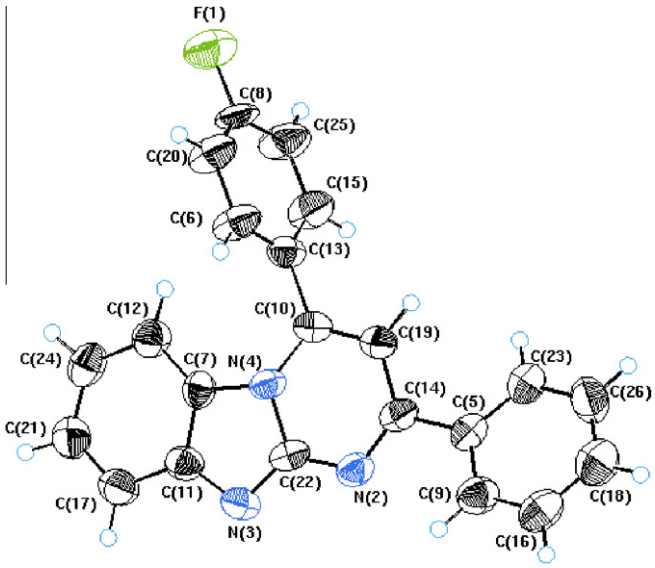


Fig. 1. X-ray structure of compound **7b**.

dimethyl formamide (DMF) as solvent under ultrasonic irradiation at room temperature afforded one product in each case (as evidenced by TLC) (Scheme 1). IR spectra of the latter products revealed absorption bands of C=N function in the region 1610–1613 cm^{-1} and no absorption bands due to sulfone group or NH group. Their ^1H NMR spectra exhibited no D_2O exchangeable signals and singlet signal in region of 7.68–8.16 in addition to aromatic multiplet in region 6.99–7.92 The latter spectroscopic data of the reaction products and their satisfactory elemental analyses supported the structure 2,4-diarylpyrimido[1,2-a]benzimidazoles **7a–f**. The proposed structure of pyrimido[1,2-a]benzimidazoles **7b** was further unequivocally confirmed by single crystal X-ray crystallography (Fig. 1), X-ray diffraction of compound **7b** add a sharp evidence not only for the proposed structure but also for the mechanism of formation of product **7** as postulated in Scheme 1.

The formation of 2,4-diarylpyrimido[1,2-a]benzimidazoles **7a–f** from Multi-component reactions (MCRs) [the reaction of 2-aminobenzimidazole, aldehyde derivatives and β-ketosulfone] seems to follow the sequence outlined in Scheme 1, which shows that the reaction starts with intermolecular condensation between aldehyde **2** derivatives and 1-phenyl-2-(phenylsulfonyl)ethanone **(3)** to form α,β-unsaturated carbonyl compound **12** then *via* an initial *Michael* addition of the *endocyclic* imino group in the 2-aminobenzimidazole **(1)** to α,β-unsaturated carbonyl compound **12** to yield the corresponding acyclic non-isolable intermediates **4** which undergo cyclization to intermediate **5** and loss of sulfinic acid molecule (intermediate **6**) which then underwent aromatization into the final products **7a–f** (Scheme 1).

X-ray diffraction of **7b** (Fig. 1) indicated without doubt that the regiodirectivity in cyclization of 2-aminobenzimidazole with β-ketosulfone, the reaction product formed through rout **a** and ruled out the other possible rout b (initial *Michael* addition of the *exocyclic* amino group in the 2-aminobenzimidazole **(1)** to α,β-unsaturated carbonyl compound **12** to yield the corresponding acyclic non-isolable intermediates **8** which undergo cyclization to intermediate **9** and loss of sulfinic acid molecule (intermediate 10) which then underwent aromatization into the final products **11** (Scheme 1).

To find the specific effect of ultrasound on this reaction, the mentioned reaction was carried out under the same conditions in the absence of ultrasound irradiation (Table 1), it was observed

Table 1
Synthesis of pyrimido[1,2-a]benzimidazoles derivatives under both ultrasonic irradiation and conventional method (Reflux).

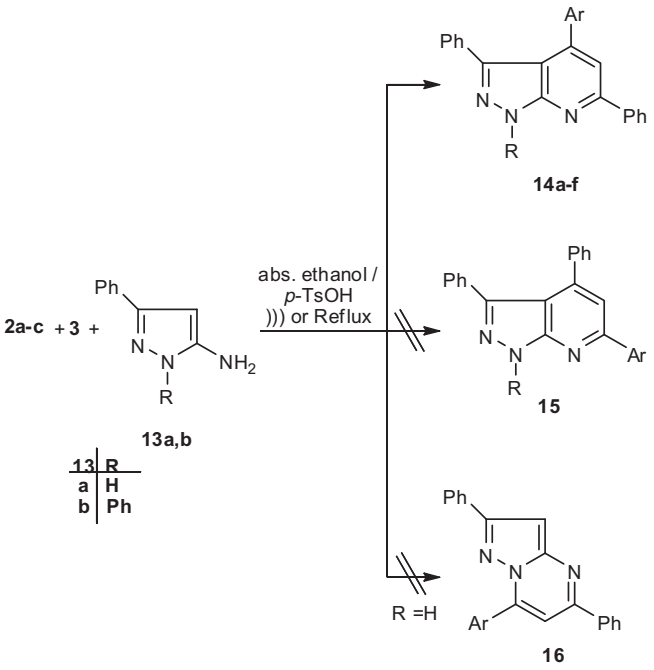
Compound	Ar	Ultrasonic irradiation		Reflux	
		Time (min)	Yield (%)	Time (h)	Yield (%)
7a	Ph	15	89	6	69
7b	4-FPh	10	92	6	75
7c	4-ClPh	10	90	7	72
7d	4-BrPh	15	88	8	70
7e	2-Cl-Ph	15	87	6	69
7f	4-MeOPh	15	88	7	70

that the reaction time increased considerably and yield of the products decreased. Thus, ultrasound was found to have beneficial effect on the synthesis of 2,4-diarylpyrimido[1,2-a]benzimidazoles **7a–f** in which decrease time of above reactions from 6 to 8 h in conventional procedure to less than 20 min, also, a noticeable improvement in yields of reactions under ultrasonic irradiations.

We extended our study to find out the reactivity of β-ketosulfone **3** towards 5-aminopyrazole derivatives **13a,b** *via* a one pot, three-component condensation reaction of an aldehyde **2a–c** and 5-amino-pyrazole derivatives **13** in the presence of 1-phenyl-2-(phenylsulfonyl)ethanone **(3)** in ethanol using *p*-toluenesulfonic acid (*p*-TsOH) as the catalyst under ultrasonic irradiation (Scheme 2), afforded in each case, only one isolable product (as examined by TLC).

The ^1H NMR of the products formed show presence of singlet signal in region 7.10–7.81 which give support for the assumed structures formed in Scheme 2 *via* loss of sulfonic acid molecule.

The one step cyclocondensation reaction can afford three isomers **14, 15** or **16** (Scheme 2) in which there are two possibilities for ring closure if the N1-position is unsubstituted like in **13a,** either to N1 or to C4-atom to afford compound **14** or **16** (Scheme 2). Structure **16** pyrazolo[1,5-a]pyrimidine derivative was easily ruled out depending on ^1H NMR spectra of the products formed (in case R=H) in which spectra show a D_2O exchangeable signal at δ 14.01–14.12 corresponding to the 1-NH proton, and no singlet



Scheme 2.

Table 2
Synthesis of 1*H*-pyrazolo[3,4-b]pyridine derivatives under both ultrasonic irradiation and conventional method (Reflux).

Compound	*R*	Ar	Ultrasonic irradiation		Reflux	
			Time (min)	Yield (%)	Time (h)	Yield (%)
14a	H	Ph	45	90	10	71
14b	H	4-FPh	30	97	6	76
14c	H	4-ClPh	30	94	6	75
14d	Ph	Ph	60	81	14	60
14e	Ph	4-FPh	45	84	10	63
14f	Ph	4-ClPh	45	84	12	62

Table 3
Effect of *p*-TsOH on the % yield of compound **14a**.

Entry	*p*-TsOH ratio	Solvent	Yield (%)	Time (min)
1	0	EtOH	29	90
2	0.1	EtOH	86	45
3	0.2	EtOH	90	45
4	0.3	EtOH	90	45
5	0	DMF	18	90
6	0.2	DMF	62	45

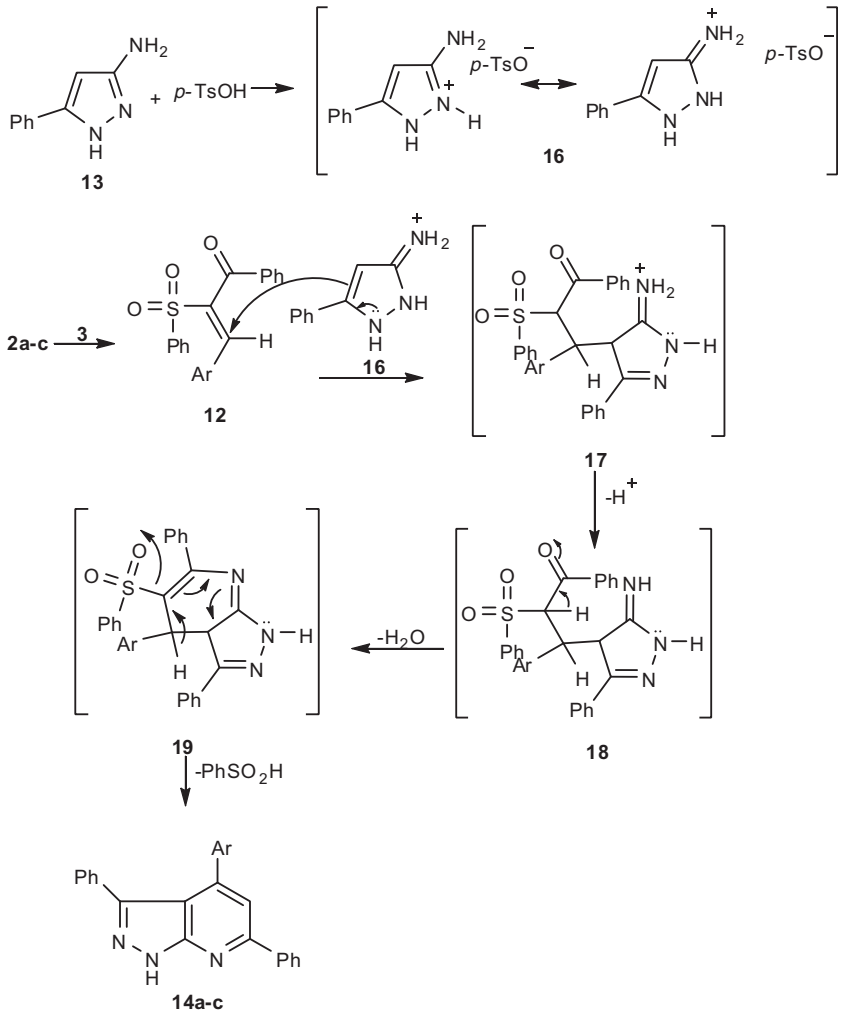
signal appear above 6 ppm for =CH of pyrazole that mean ring closure occur to C-4 atom. The cyclocondensation of amines **13a,b** with aldehyde **2** and β-ketosulfone **3** gave regiospecifically isomer **14** depending on the well established behavior and arising from our studies of the reaction of 5-aminopyrazole derivative with α,β-unsaturated carbonyl compounds [47–51] so other isomer **15** can be discarded.

The elemental analysis and spectral data of the reaction products were compatible with the 1*H*-pyrazolo[3,4-b]pyridine derivatives **14a–f,** For example, the IR spectra of **14a** revealed, the appearance of a band due to NH function at 3119 cm^{-1}. The mass spectra of the isolated product **14a** showed, a peak corresponding to the molecular ion at 347. It's ^1H NMR spectrum of the same compound revealed D_2O exchangeable singlet signal at δ 14.01 due to NH proton, a singlet signal at 7.84 due to CH-pyridine in addition to aromatic multiplet at δ 7.10–7.81 ppm (*cf.* experimental part).

Formation of compounds **14a–f** under ultrasonic irradiation, occur in excellent yields and shorter reaction time in comparing with conventional condition (silent reactions) (Table 2).

Table 2 shows that ultrasound technique reduced the time of reactions from several hours to minutes and improved the yields from 71–76% (under conventional conditions) to 81–97%.

It is noteworthy to mention that we optimize first the reaction conditions for the formation of 1*H*-pyrazolo[3,4-b]pyridine derivatives **14a–f** as in Table 3, to select the appropriate *p*-TsOH amounts necessary to perform these three-components one pot reaction



Scheme 3.

under ultrasound irradiation, different amounts of *p*-TsOH (mol/mol) ratios were tested.

Table 3 represents the effect of *p*-TsOH on the % yield of compound **14a**.

From the results cited in Table 3, it is clear that 0.2 mol equiv of *p*-TsOH furnishes the respective product in a quantitative yield (Table 3, entry 3). The influence of the nature of the solvent on the reaction yield and kinetic was studied to find the best reaction conditions which indicated that the best solvent for this reaction was ethanol under ultrasonic irradiation. As described for ultrasonic conditions, the catalytic system was inefficient in the absence of catalyst and produced only 29% of product after 90 min and in this case there is side product formed which detected as α,β-unsaturated carbonyl compound **12.**

There are no established mechanisms for the formation of 1 *H*-pyrazolo[3,4-b]pyridines; a reasonable possibility is shown in Scheme 3. The reaction presumably proceeds *via* initial reaction between *p*-TsOH and the 5-aminopyrazole derivative **13** to give the 3-aminopyrazolium salt **16**. Next, Michael addition of this compound to benzylidene compound **12**, itself produced by Knoevenagel condensation of aldehyde **2** and 1-phenyl-2-(phenylsulfonyl)ethanone **(3)** gives intermediate **17**. Elimination of one proton from the iminum group results in intermediate **18**. Subsequent cyclization of **18** results in condensed ring system **19** that finally, underwent aromatization with losing of sulfinic acid molecule to produce the 1*H*-pyrazolo[3,4-b]pyridine derivatives **14** (Scheme 3).

Finally, the above reactions show that phenylsulfone is an important synthon for use in a variety of reactions, including asymmetric synthesis.

The improvement induced by ultrasound in the above mentioned reactions can be attributed to the well established theory for the cavitation, The collapse of bubbles caused by cavitation produces intense local heating and high pressures, [52,53] so reaction time decreases clearly and high % yield obtained.

In addition, according to sonochemical reactions classification of Luche [54,55], the above mentioned reactions is considered false sonochemistry type in which cavitation effect provides the mechanical energy for all subsequent chemical reactions, including bond scission induced by viscous frictional forces.

3. Conclusion

A novel and efficient three-components condensation reaction of an aldehyde, amino azoles and β-ketosulfone has been developed for the synthesis of pyrimido[1,2-a]benzimidazoles and pyrazolo[3,4-b]pyridines under ultrasonic irradiation *via* utilization of β-ketosulfone as important synthon for synthesis of them.

The simple one-pot nature of the reaction makes it an interesting alternative to other multi-step approaches. In general, improvements in rates and yield of reactions are observed when reactions were carried out under sonication compared with classical condition.

4. Experimental

4.1. General

All organic solvents were purchased from commercial sources and used as received or dried using standard procedures, unless otherwise stated. All chemicals were purchased from Merck, Aldrich or Acros and used without further purification, thin-layer chromatography (TLC) was performed on precoated Merck 60 GF254 silica gel plates with a fluorescent indicator, and detection by means of UV light at 254 and 360 nm. All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded in KBr 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 dimethyl sulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMSQP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out on Elmentar instrument C, H, N, S analyzer Vario EL III.

X-ray crystallography was carried out on Kappa CCD Enraf Nonius FR 590 diffractometer, National Research Center, Dokki, Cairo, Egypt.

Sonication was performed by Branson sonicator (with a frequency of 40 kHz and a nominal power 180 W).

1-Phenyl-2-(phenylsulfonyl)ethanone **3** [56] and aminopyrazoles **13a,b** [57] were prepared according to the reported literature.

4.2. Typical procedure for synthesis of pyrimido[1,2-a]benzimidazoles derivatives 7a–f

4.2.1. Silent reactions

A mixture of 1-phenyl-2-(phenylsulfonyl)ethanone (1 mmol), aldehyde (1 mmol) and 2-aminobenzimidazole (1 mmol) in DMF (1 ml) was refluxed for appropriate time (*cf.* Table 1) until completion of the reaction (monitored by TLC). The precipitate formed was collected by filtration then washed, dried and purified by recrystallization from DMF/2-propanol (1:2).

4.2.2. Sonicated reactions

These processes were performed on the same scale described above for silent reactions. All The reactions were kept at room temperature 25–30 °C which attained by addition or removal of water in ultrasonic bath (the temperature inside reaction vessel was 28–30 °C). The sonochemical reactions were continued for suitable time (*cf.* Table 1) until the starting materials were no longer detectable by TLC. The products were obtained and purified as described above in silent reaction procedures.

The synthesized compounds with their physical data are listed below.

4.2.2.1. Synthesis of 2,4-diphenylpyrimido[1,2-a]benzimidazole (7a). M.p. = 297 °C; IR (KBr): 1610 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.12–7.82 (m, 14H, ArH's), 8.16 (s, 1H, H-3); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 103.25, 108.55, 116.87, 124.99, 125.11, 126.12, 126.14, 127.59, 127.69, 130.55, 131.08, 132.25, 138.26, 141.58, 145.08, 152.85, 159.94; MS (m/z): 321 (M^+). (Found: C, 82.41; H, 4.62; N, 12.97. $C_{22}H_{15}N_3$ requires C, 82.22; H, 4.70; N, 13.08.)

4.2.2.2. Synthesis of 4-(4-flurophenyl)-2-phenylpyrimido[1,2-a]benzimidazole (7b). M.p. = >300 °C; IR (KBr): 1613 (C=N)cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 6.99–7.88 (m, 13H, ArH's), 8.09 (s, 1H, H-3); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 102.55, 109.22, 111.29,116.88, 123.65, 126.32, 127.54, 128.02, 130.12, 132.18, 132.51 136.89, 136.98, 141.15, 146.00, 151.01, 159.90, 162.58; MS (m/z): 339 (M^+). (Found: C, 78.06; H, 4.09; N, 12.25. $C_{22}H_{14}FN_3$ requires C, 77.86; H, 4.16; N, 12.38.)

4.2.2.3. Synthesis of 4-(4-chlorophenyl)-2-phenylpyrimido[1,2-a]benzimidazole (7c). M.p. = 280–282 °C; IR (KBr): 1613 (C=N)cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.32–7.92 (m, 13H, ArH's), 8.02 (s, 1H, H-3); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 104.00, 113.54, 116.89, 124.22, 126.13, 126.85, 127.12, 128.45, 131.85, 133.87, 133.98, 138.58, 141.12, 146.00, 150.05, 155.24, 158.19; MS (m/z): 355 (M^+). (Found: C, 74.45; H, 3.89; N, 11.70. $C_{22}H_{14}ClN_3$ requires C, 74.26; H, 3.97; N, 11.81.)

4.2.2.4. Synthesis of 4-(4-bromophenyl)-2-phenylpyrimido[1,2-a]benzimidazole (7d). M.p. = >300 °C; IR (KBr): 1613 (C=N)cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.32–7.92 (m, 13H, ArH's), 7.99 (s, 1H, H-3); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 104.00, 113.54, 116.89, 124.22, 126.13, 126.85, 127.12, 128.45, 131.85, 133.87, 133.98, 138.58, 141.12, 146.00, 150.05, 156.10, 158.19; MS (m/z): 400 (M^+). (Found: C, 66.13; H, 3.49; N, 10.42. $C_{22}H_{14}BrN_3$ requires C, 66.01; H, 3.53; N, 10.50)

4.2.2.5. Synthesis of 4-(2-chlorophenyl)-2-phenylpyrimido[1,2-a]benzimidazole (7e). M.p. = 272 °C; IR (KBr): 1611 (C=N)cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 6.75–7.49 (m, 13H, ArH's), 7.68 (s, 1H, H-3); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 103.54, 112.14, 115.11, 122.12, 127.47, 127.87, 128.25, 129.82, 129.97, 131.15, 131.87, 133.45, 134.85, 136.14, 136.89, 140.11, 145.00, 151.09, 155.02, 158.00; MS (m/z): 355 (M^+). (Found: C, 74,41; H, 3.92; N, 11.71. $C_{22}H_{14}ClN_3$ requires C, 74.26; H, 3.97; N, 11.81.)

4.2.2.6. Synthesis of 4-(4-methoxyphenyl)-2-phenylpyrimido[1,2-a]benzimidazole (7f). M.p. = >300 °C; IR (KBr): 1613 (C=N)cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.95 (s, 3H, OCH_3), 7.32–7.89 (m, 13H, ArH's), 7.78 (s, 1H, H-3); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 52.12, 104.04, 112.55, 114.21, 116.58, 122.54, 127.37, 127.95, 128.45, 129.22, 131.59, 133.45, 133.89, 136.89, 145.21, 148.10, 151.55, 158.87; MS (m/z): 351 (M^+). (Found: C, 78.86; H, 4.76; N, 11.83. $C_{23}H_{17}N_3O$ requires C, 78.61; H, 4.88; N, 11.96.)

4.3. Typical procedure for synthesis of pyrazolo[3,4-b]pyridines derivatives 14a–f

4.3.1. Silent reactions

A solution of 1-phenyl-2-(phenylsulfonyl)ethanone (1 mmol), aldehyde (1 mmol), 5-aminopyrazole derivatives (1 mmol) and *p*-TsOH (0.2 mmol) in 15 ml of absolute ethanol was refluxed for appropriate time (*cf.* Table 2) until completion of the reaction. After completion of the reaction as indicated by TLC (EtOAc/n-hexene, 1:2), the reaction mixture was allowed to cool. The solvent was removed by evaporation and the residue was washed with H_2O (2 × 20 ml). The solid products were purified by recrystallization from 2-propanol.

4.3.2. Sonicated reactions

These processes were performed on the same scale described above for silent reactions. All The reactions were kept at room temperature 25–30 °C (the temperature inside reaction vessel was 28–30 °C). The sonochemical reactions were continued for suitable time (*cf.* Table 2) until the starting materials were no longer detectable by TLC. The products were obtained and purified as described above in silent reaction procedures.

The synthesized compounds with their physical data are listed below.

4.3.2.1. 3,4,6-triphenyl-1H-pyrazolo[3,4-b]pyridine (14a). M.p. = 278 °C; IR (KBr): 3119 (NH), 1595 (C=N)cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.10–7.81 (m, 15H, ArH's), 7.84 (s, 1H, H-5), 14.01 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 103.95, 117.25, 125.21, 125.88, 125.89, 125.97, 126.01, 127.70, 128.69, 128.97,128.99, 129.02, 130.15, 137.18, 140.87, 144.45, 149.85, 151.14, 154.07; MS (m/z): 347 (M^+). (Found: C, 83.19; H, 4.84; N, 11.97. $C_{24}H_{17}N_3$ requires C, 82.97; H, 4.93; N, 12.10.)

4.3.2.2. 4-(4-fluorophenyl)-3,6-diphenyl-1H-pyrazolo[3,4-b]pyridine (14b). M.p. = 289 °C; IR (KBr): 3174 (NH), 1592 (C=N)cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.19–7.79 (m, 14H, ArH's), 7.74 (s, 1H, H-5), 14.12 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 103.13, 115.46, 115.47, 120.59, 125.22, 126.01, 126.02, 126.88, 126.89, 127.98, 128.08, 128.09, 128.21, 130.03, 133.0, 138.11, 142.45, 149.85, 150.10, 155.12, 159.14; MS (m/z): 365 (M^+). (Found: C, 79.16; H, 4.29; N, 11.35. $C_{24}H_{16}FN_3$ requires C, 78.89; H, 4.41; N, 11.50.)

4.3.2.3. 4-(4-chlorophenyl)-3,6-diphenyl-1H-pyrazolo[3,4-b]pyridine (14c). M.p. = 283 °C; IR (KBr): 3148 (NH), 1590 (C=N)cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.22–7.81 (m, 14H, ArH's), 7.91 (s, 1H, H-5), 14.10 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 103.01, 116.11, 125.20, 126.13, 126.14, 126.94, 127.18, 128.08, 128.09, 128.89, 132.84, 136.05, 140.0, 141.12, 148.14, 151.13, 155.12, 156.78; MS (m/z): 381 (M^+). (Found: C, 75.78; H, 4.08; N, 10.85. $C_{24}H_{16}ClN_3$ requires C, 75.49; H, 4.22; N, 11.00.)

4.3.2.4. 1,3,4,6-tetraphenyl-1H-pyrazolo[3,4-b]pyridine (14d). M.p. = >300 °C; IR (KBr): 1610 (C=N)cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.05–7.72 (m, 20H, ArH's), 7.92 (s, 1H, H-5); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 109.00, 117.22, 120.25, 120.26, 125.25, 127.14, 127.15, 127.17, 127.18, 128.08, 128.09, 128.87, 128.88, 128.94, 128.99, 129.07, 129.08, 133.00, 138.58, 139.00, 141.55, 149.92, 150.70, 155.18; MS (m/z): 423 (M^+). (Found: C, 85.26; H, 4.94; N, 9.80. $C_{30}H_{21}N_3$ requires C, 85.08; H, 5.00; N, 9.92.)

4.3.2.5. 4-(4-fluorophenyl)-1,3,6-triphenyl-1H-pyrazolo[3,4-b]pyridine (14e). M.p. = >300 °C; IR (KBr): 1613 (C=N)cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.14–7.79 (m, 19H, ArH's), 7.81 (s, 1H, H-5); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 108.47, 115.14, 115.15, 120.14, 121.49, 121.50, 125.12, 126.34, 127.47, 127.48, 127.97, 127.98, 128.10, 128.11, 128.12, 129.22, 129.43, 130.07, 133.00, 139.50, 139.87, 140.95, 146.09, 149.89, 150.12, 155.01, 161.00; MS (m/z): 441 (M^+). (Found: C, 81.92; H, 4.39; N, 9.29. $C_{30}H_{20}FN_3$ requires C, 81.61; H, 4.57; N, 9.52.)

4.3.2.6. 4-(4-chlorophenyl)-1,3,6-triphenyl-1H-pyrazolo[3,4-b]pyridine (14f). M.p. = >300 °C; IR (KBr): 1610 (C=N)cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.09–7.80 (m, 19H, ArH's), 7.89 (s, 1H, H-5); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 109.02, 115.09, 116.58, 116.59, 120.25, 121.05, 123.98, 123.99, 124.12, 124.13, 127.55, 127.57, 128.45, 128.46, 128.70, 133.00, 134.78, 139.45, 140.12, 140.95, 144.81, 149.00, 151.78, 155.04; MS (m/z): 457 (M^+). (Found: C, 78.48; H, 4.35; N, 9.03. $C_{30}H_{20}ClN_3$ requires C, 78.68; H, 4.40; N, 9.18.)

5. X-ray crystallography

A single crystal of compound **7b** was obtained by slow evaporation from a mixture of ethanol:DMF (2:1). The crystal structure was solved and refined using maxus (nonius, Deflt and MacScience, Japan) [58] 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 793678 Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union, Road, Cambridge CB2 1EZ, UK [fax: 144 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ultsonch.2011.05.003.

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