Q-Tube Assisted green Synthesis of fused azines: New Synthetic Opportunities via Innovative Green Technology

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Supporting information

S1: Experimental details

S2: copies of NMR data

S3: Green Metrics

References

General:

All chemicals and solvents used in this study were of analytical grade supplied by Sigma-Aldrich or Merck and used as received. Thin-layer chromatography (TLC) was performed on precoated Merck 60 GF254 silica gel plates with a fluorescent indicator and detection utilizing UV light at 254 and 360 nm. The melting points were measured on a Stuart melting point apparatus and were uncorrected. IR spectra were recorded on a Smart iTR, which is an ultra-high-performance, versatile Attenuated Total Reflectance (ATR) sampling accessory on the Nicolet iS10 FT-IR spectrometer. The NMR spectra were recorded on two instruments the first was recorded on a Varian Mercury VXR-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in deuterated chloroform ($CDCl_3$) or dimethyl sulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. The second is a Bruker Avance III 400 (9.4 T, 400.13 MHz for 1H and 100.62 MHz for 13C) spectrometer with a 5-mm BBFO probe, at 298 K. Chemical shifts (δ in ppm) are given relative to internal solvent, DMSO-*d_6, 2.50* for ^{1}H and 39.50 for ^{13}C was used as an external standard. ^{1}H–^{1}H NOESY was acquired and processed using standard Bruker NMR software (Topspin 3.4). Sonication for the reused catalyst was performed by Elma sonicator (with a frequency of 37 kHz and ultrasonic peak max. 320 W). The reaction temperature was manually input depending on the boiling point of the solvent used and stabilized for more than an hour. Q-Tube-assisted reactions were performed in a Q-Tube-safe pressure reactor from Q Labtech (Washington, DC, USA) equipped with a cap/sleeve, pressure adapter (120 psi), needle, borosilicate glass tube, Teflon septum, and catch bottle. Microwave experiments were carried out using CEM Discover LabmateTM microwave apparatus (300W with ChemDriverTM Software). Mg-Al-HT [1], *E*-3-(4-fluorophenyl)-1-(furan-2-yl)prop-2-en-1-one (**1**) [2], and 5-aminopyrazole derivatives (**2a-c**) [3], were prepared according to the reported literature.

Typical procedure for the reactions

Method I (conventional): An equivalent amount of chalcone **1** (10 mmol) and amino azole (10 mmol) in the presence of 0.2g Mg-Al-HT catalyst were refluxed in 20 ml ethanol at 70 °C till completion of the reaction as examined by TLC. The mixture was filtered to remove the catalyst, then the filtrate was left at room temperature, and the solid formed was collected and recrystallized from 10:1ethanol/DMF mixture.

Method II (Q-tube): The same above mixture scale was placed in a Q-Tube at 100 °C/under the autogenic pressure (17 psi) for the appropriate time as examined by TLC. The products were worked up as in method I.

Method III (Microwave): The same above mixture scale was placed in a microwave tube at 100 °C/under the autogenic pressure (17-18 psi) for the appropriate time. The products were worked up as mentioned in method I.

Durability (reusing) of catalyst: After removing the catalyst from the reaction via filtration, the catalyst was washed with ethanol 3 times and then sonicated in 10 ml ethyl acetate for 5 min. to desorb all organic contaminant. Then dried at 80°C for 1 h.

Physical and spectral data of synthesized compounds using Q-tube are listed below

7-(4-Fluorophenyl)-2-phenyl-5-(furo-2-yl)-6,7-dihydropyrazolo[1,5-a]pyrimidine (3a)

m.p. 199-201 °C, Yield 95% in 10 min., IR (KBr) νmax/cm^{-1}: 1601 (C=N), ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.42 (dd, 1H, *J* =4.6, 9.8 Hz), 3.50 (dd, 1H, *J* =4.6, 11.00 Hz), 5.67 (dd, 1H, *J* =9.8, 11.00 Hz), 6.76 (s, 1H, Pyrazole CH-3), 6.95-7.82 (m, 12H, ArH's and furan protons). MS (m/z): 357 (M^+). Anal. Calcd. for $C_{22}H_{16}FN_3O$: C, 73.94; H, 4.51; N, 11.76. Found: C, 74.16; H, 4.46; N, 11.65 %.

2-Amino-3-(4-chlorophenylazo)-7-(4-fluorophenyl)-5-(furo-2-yl)-6,7-dihydropyrazolo[1,5-a]pyrimidine (3b)

m.p. 251-252 °C, Yield 93% in 10 min., IR (KBr) νmax/cm^{-1}: 3271, 3193 (NH_2), 1609 (C=N). ^{1}H NMR (300MHz, DMSO-d_6): δ 3.99 (dd, 1H, J = 4.7, 9.8 Hz), 4.18 (dd, 1H, J = 4.8, 11.8 Hz), 5.58 (dd, 1H, J = 9.8, 11.8 Hz), 6.36 (br's, 2H, D_2O-exchangable), 7.15-7.92 (m, 11H, ArH's and furan protons). MS (m/z): 434 (M^+). Anal. Calcd. for $C_{22}H_{16}ClFN_6O$: C, 60.76; H, 3.71; N, 19.33. Found: C, 60.97; H, 3.67; N, 19.24 %.

4-(4-Fluorophenyl)-4,5-dihydro-1,3-diphenyl-6-(furo-2-yl)-1H-pyrazolo[3,4-b]pyridine (3c)

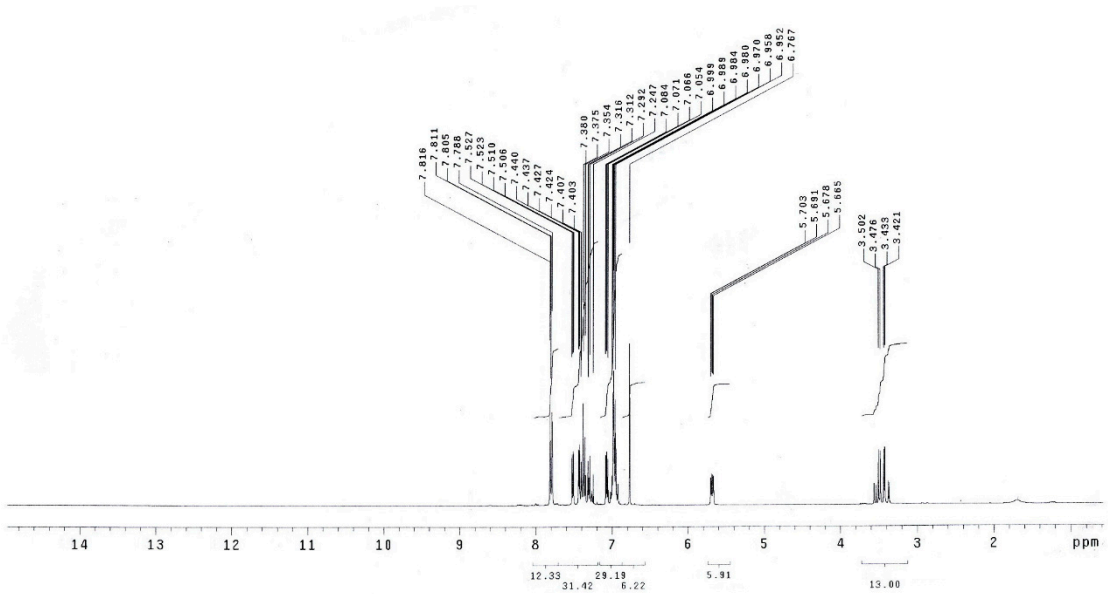
m.p. 212-214 °C, Yield 91% in 15 min., IR (KBr) νmax/cm^{-1}: 1594 (C=N). ^{1}H NMR (300MHz, $CDCl_3$): δ 3.14 (dd, 1H, J = 5.8, 8.6 Hz), 3.55 (dd, 1H, J = 5.8, 9.9 Hz), 4.85 (dd, 1H, J = 8.6, 9.9 Hz), 6.76-8.17 (m, 16H, ArH's and furan protons). MS (m/z): 433 (M^+). Anal. Calcd. for $C_{28}H_{20}FN_3O$: C, 77.58; H, 4.65; N, 9.69. Found: C, 77.77; H, 4.61; N, 9.59 %.

7-(4-Fluorophenyl)-5-(furo-2-yl)-1,2,4-triazolo[1,5-a]pyrimidine (7)

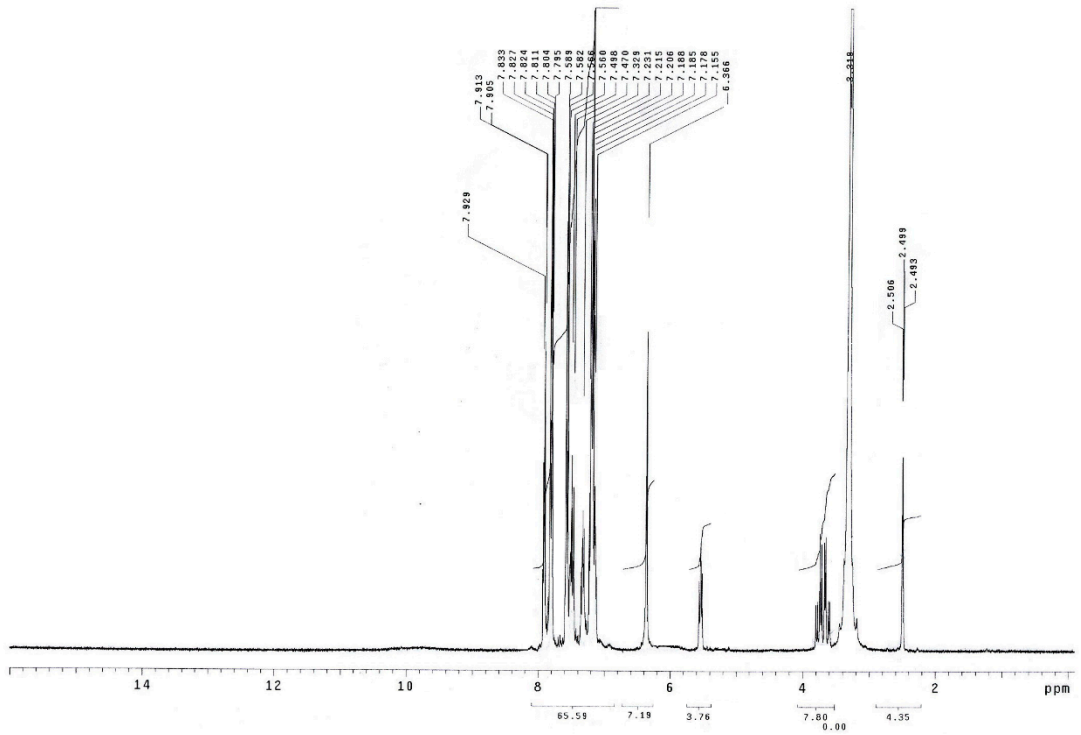
m.p. 165-167 °C, Yield 94% in 10 min., IR (KBr) νmax/cm^{-1}: 2231 (C≡N), 1621 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19-8.25 (m, 7H, ArH's and furan protons), 7.51 (s, 1H, pyrimidine CH-5), 8.48 (s, 1H, triazole CH-2). MS (m/z): 280 (M^+). Anal. Calcd. for $C_{15}H_9FN_4O$: C, 64.28; H, 3.24; N, 19.99. Found: C, 64.47; H, 3.20; N, 19.91 %.

4-(4-Fluorophenyl)-3,4-dihydro-2-thienylpyrimido[1,2-a]benzimidazole (9)

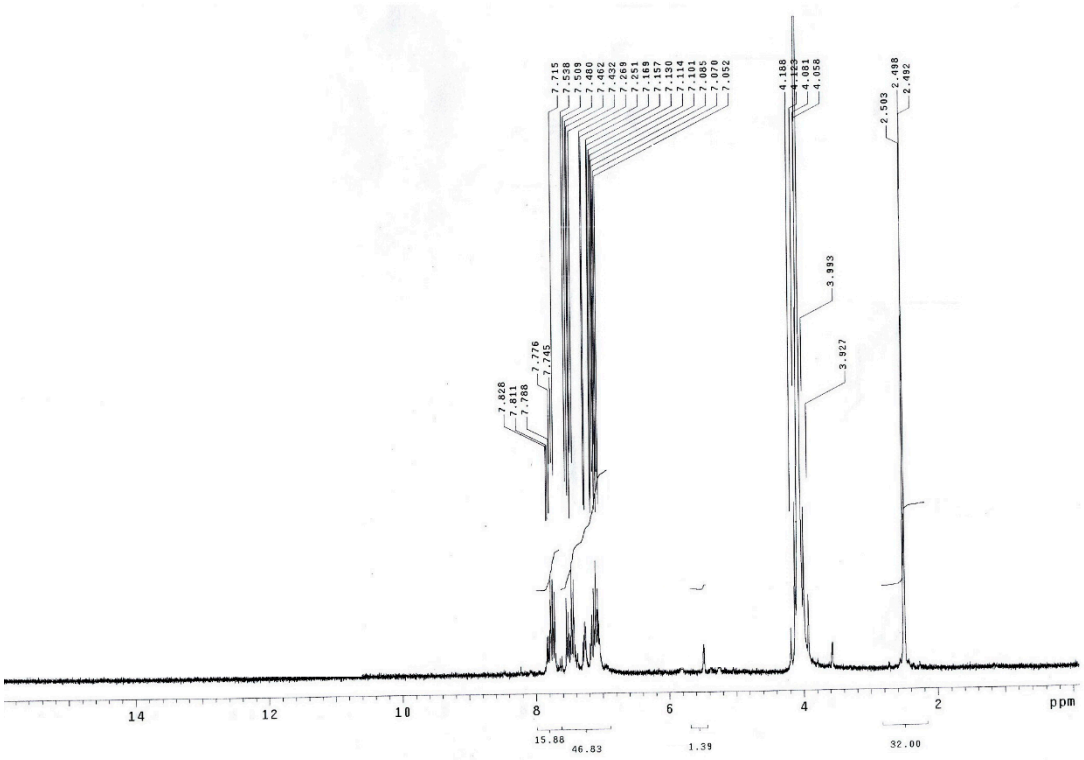
m.p. 223-225 °C, Yield 90% in 15 min., IR (KBr) νmax/cm–1: 1603 (C=N). 1H NMR (300 MHz, $CDCl_3$): δ 3.29 (dd, 1H, J = 9.8, 6.2 Hz), 3.52 (dd, 1H, J = 9.8, 4.5 Hz), 5.60 (dd, 1H, J = 6.2, 4.5 Hz), 5.19 (s, 1H, furan CH-3), 6.69 (s, 1H, furan CH-5), 6.72-7.77 (m, 9H, ArH's and furan proton CH-4). MS (m/z): 331 (M^+). Anal. Calcd. for $C_{20}H_{14}FN_3O$: C, 72.50; H, 4.26; N, 12.68. Found: C, 72.68; H, 4.22; N, 12.60 %.



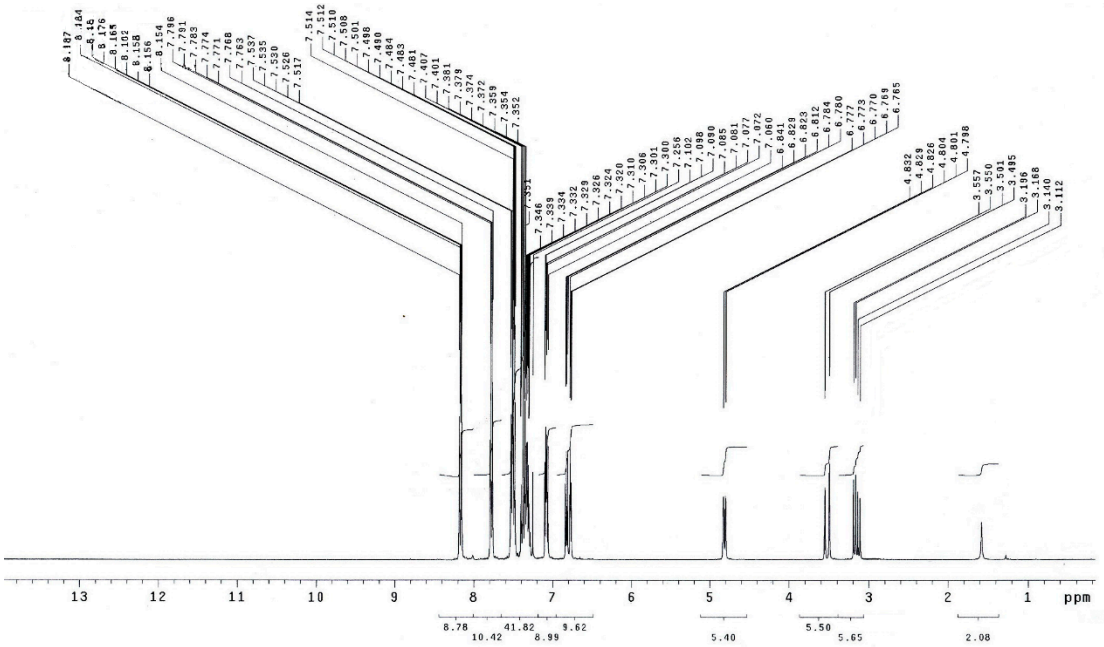
1H NMR of compound 3a



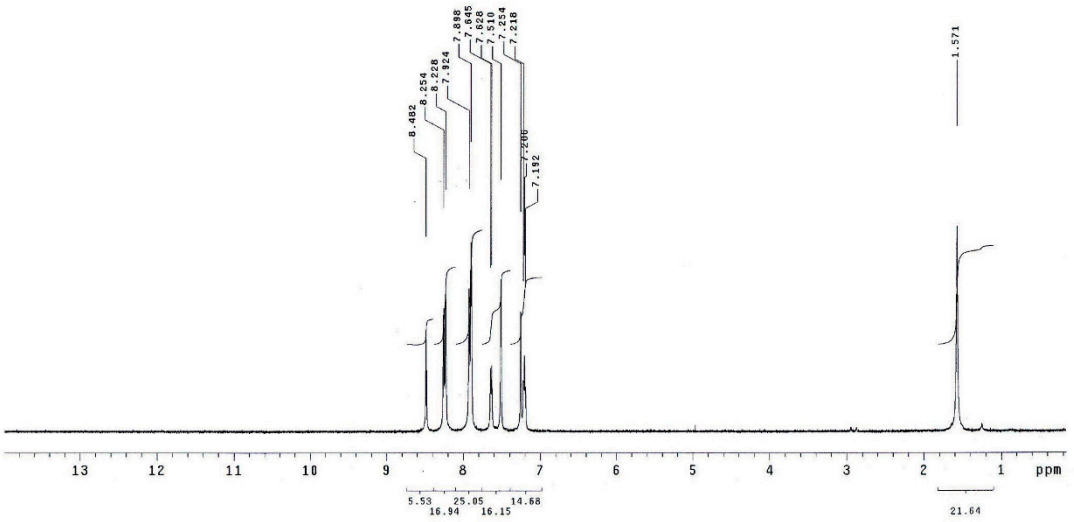
1H NMR of compound 3b



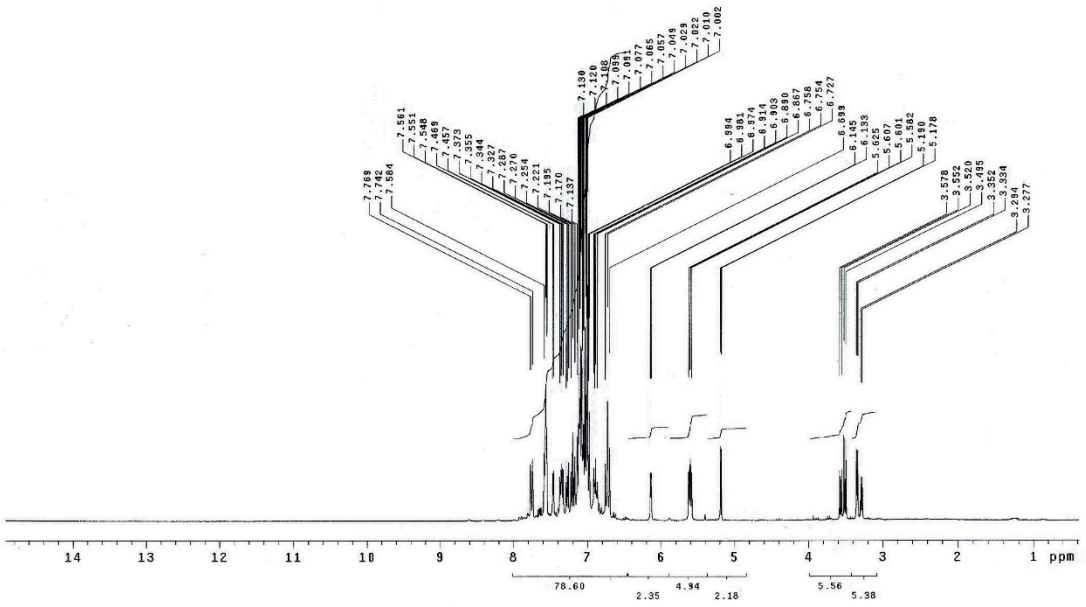
1H NMR of compound 3b (D_2O exchangeable)



1H NMR of compound 3c



1H NMR of compound 7



1H NMR of compound 9

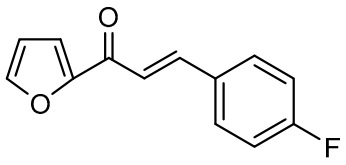
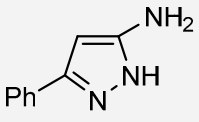
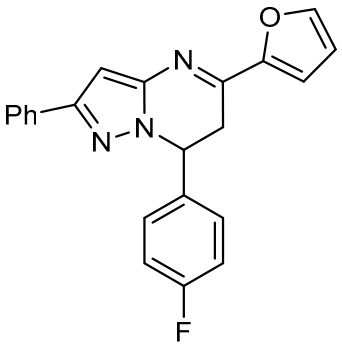
S3: Green Metrics

Atom economy % for organic reaction is given by Equation 1 [4]

$$\text{Atom Economy} = \frac{Mass\ of\ atoms\ of\ the\ desired\ product}{Mass\ of\ atoms\ of\ the\ reactants} \text{ X } 100 \qquad \textbf{Equation 1}$$

In our case: Taking compound 3a as an example

(Using Mg Al HT) by our protocol

	Reactants		Desired Product	Waste Product
	 1	 2a	 3a	H_2O
M.Wt	216	159	357	1* 18

$$\textbf{Atom economy} = \frac{357}{216+159} X\ 100 = 95.2\%$$

The Reaction Shows high atom economy

References

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