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Note

Mild and efficient synthesis of 1,2,4-triazolo[4,3-*a*][1,8] naphthyridines using $FeCl_3$ in the solid state

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An efficient, rapid and mild method for the synthesis of 1,2,4-triazolo-[4,3-*a*][1,8]naphthyridines **4** by the oxidative cyclization of vanillin 3-aryl-1,8-naphthyridine-2-yl hydrazones **3** with $FeCl_3.6H_2O$ in the solid state by grinding at room temperature has been described. The products are obtained in good yields with high purity.

Keywords: 3-Aryl-2-hydrazino-1,8-napthyridines, vanillin, vanillin 3-aryl-1,8-naphthyridin-2-ylhydrazones, $FeCl_3.6H_2O$, 1,2,4-triazolo[4,3-*a*][1,8]-naphthyridines, solid state

With the increasing public concern over environmental degradation, one of the challenges for chemists is to come up with new approaches that are less hazardous to human health and the environment. The solvents used in organic synthesis are high on the list of environmental pollutants, because they are employed in large amounts and usually are volatile liquids. In recent years organic reactions in the solid state (solvent-free) by grinding have been attracting the synthetic organic chemists because of their simplicity and synthetic value[1,2]. Furthermore, the solid state reaction by grinding has many advantages; reduced pollution, low costs, and simplicity in process and handling. These factors are beneficial to industry as well as to environment.

The 1,8 naphthyridine nucleus is associated with a wide spectrum of biological activity such as antibacterial[3], antihypertensive[4] and antiinflammatory[5]. 1,2,4-Triazoles are important heterocycles possessing diverse biological and pharmacological activity[6,7]. Therefore, it may be interesting to bring these two biologically active moieties within a molecular framework with a view to studying their additive effect on biological properties. In view of this, and in continuation of the interest on solid state organic reactions on 1,8-naphthyridine derivatives[8-11], herein is reported a mild, efficient and convenient procedure for the synthesis of 1,2,4-triazolo[4,3-*a*]-[1,8] naphthyridines under solid state grinding conditions at RT.

Condensation of 3-aryl-2-hydrazino-1,8-naphthyridines **1** with vanillin (4-hydroxy-3-methoxybenzaldehyde) **2** in the solid state at RT afforded the corresponding vanillin 3-aryl-1,8-naphthyridin-2-ylhydrazones **3** in excellent yields.

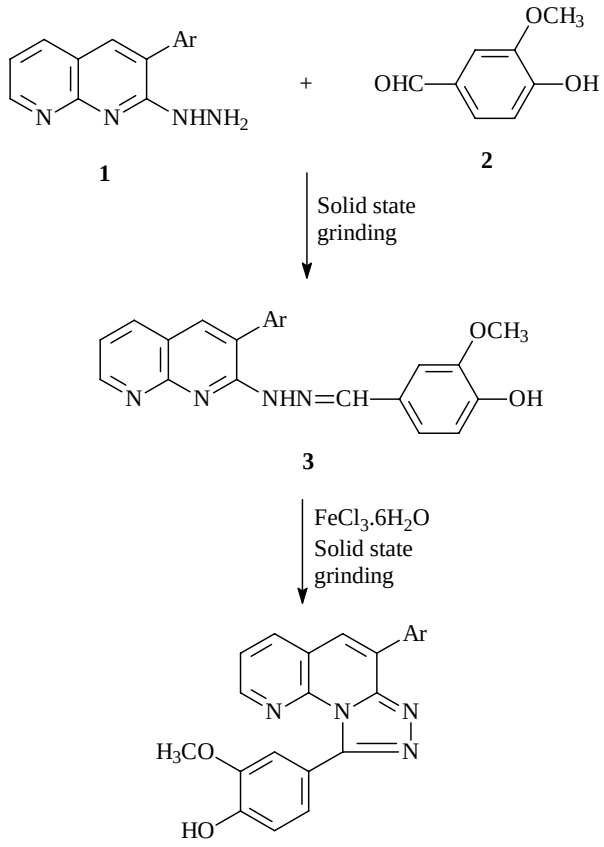
The hydrazones **3** on oxidative cyclization with $FeCl_3.6H_2O$ under solid state grinding conditions at RT furnished the respective 6-aryl-9-(4-hydroxy-3-methoxyphenyl)-1,2,4-triazolo[4,3-*a*] [1,8] naphthyridines **4** (**Scheme I**).

A mixture of **3a** and $FeCl_3.6H_2O$ was ground in a mortar by pestle at RT for 4 min. The product obtained was combined with water and filtered to give 6-phenyl-9-(4-hydroxy-3-methoxyphenyl)-1,2,4-triazolo [4,3-*a*] [1,8]naphthyridine **4a** in 86% yield. When the reaction was carried out in ethanol for the same duration as above (4 mm), under reflux, the product was obtained in only 8% yield. It is clear that the reaction in the solid state is more efficient than in solution.

The oxidative transformation is very clean and rapid. The reaction proceeds efficiently with good yields at RT and completes within a few minutes. The process is environmentally benign. The reaction conditions and work-up procedures are mild, simple and convenient. The products were obtained with a high degree of purity by this procedure and no further purification was needed.

To the best of the knowledge this is the first report on rapid synthesis of 1,2,4-triazolo[4,3-*a*][1,8]-naphthyridines using $FeCl_3.6H_2O$ under solid state grinding conditions at RT. The structural assignments of compounds **3** and **4** were based on their elemental analyses and spectral (IR and ^1H NMR) data.

In conclusion, a highly practical procedure has been developed for the synthesis of 1,2,4-triazolo[4,3-*a*][1,8]naphthyridines using $Fecl_3.6H_2O$ in the solid state at RT. Moreover, mild reaction conditions, short reaction times, simple experimental work-up procedure, cheapness and non-toxicity of the reagent, high yields and excellent purity of the products are noteworthy advantages of this environment-friendly protocol.



Scheme I

Experimental Section

Melting points were determined in open capillaries using a Cintex melting point apparatus and are uncorrected. Homogeneity of compounds was checked using precoated TLC plates (Merk, 60 F-254). IR spectra (KBr) were recorded on a Perkin-Elmer BX series FT-IR spectrophotometer and ^{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as an internal standard. 3-Aryl-2-hydrazino-1,8-naphthyridines **1** were prepared by a previously reported procedure[9,12-16].

General procedure for the synthesis of vanillin 3-aryl-1,8-naphthyridin-2-ylhydrazones 3. A mixture of appropriate 3-aryl-2-hydrazino-1,8-naphthyridine **1** (0.01 mole) and vanillin **2** (0.01 mole) was ground by pestle and mortar at RT for the specified time indicated in **Table I**. On completion of reaction, as monitored by TLC, the reaction mixture was treated with water. The solid that precipitated was filtered, washed with water and the crude material purified by recrystallization from ethanol to give **3** (**Table I**).

3a: IR (KBr): 3434 (OH, NH), 1612 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ 3.95 (s, 3H, OCH_3) 8.20 (m, 2H, C_4-H, C_5-H), 8.32 (m, H, C_7-H), 6.82-7.76 (m, 9H, C_6-H, 8Ar-H), 8.38 (s, 1H, N=CH), 9.40 (s, 1H, OH), 10.20 (s, 1H, NH).

3b: IR (KBr): 3342 (OH,NH), 1622 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.82 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 8.15 (m, 1H, C_6-H), 8.30 (m, 2H, C_4-H, C_5-H), 8.62 (m, 1H, C_7-H), 6.80-7.62 (m, 7H, Ar-H), 8.45 (s, 1H, N=CH), 9.38 (S, 1H, OH), 10.15 (s, 1H, NH).

3c: IR (KBr): 3430 (OH, NH), 1627 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.92 (s, 3H, OCH_3), 7.70 (m, 2H, C_4-H, C_5-H), 8.35 (m, 1H, C_7-H), 6.79-7.43 (m, 8H, C_6-H, 7Ar-H), 8.20 (s, 1H, N=CH), 9.15 (s, 1H, OH), 10.05 (s, 1H, NH).

3d: IR (KBr): 3376 (OH, NH), 1622 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.90 (s, 3H, OCH_3), 7.65 (m, 2H, C_4-H, C_5-H), 8.05 (m, 1H, C_7-H), 6.80-7.42 (m, 8H, C_6-H, 7Ar-H), 8.30 (s, 1H, N=CH), 9.25 (s, 1H, OH), 10.12 (s, 1H, NH).

3e: IR (KBr): 3376 (OH, NH), 1623 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ 3.98 (s, 3H, OCH_3), 7.60 (m, 2H, C_4-H, C_5-H), 8.36 (m, 1H, C_7-H), 6.85-7.42 (m, 8H, C_6-H, 7Ar-H), 8.25 (s, 1H, N=CH), 9.30 (s, 1H, OH), 10.08 (s, 1H, NH).

3f: IR (KBr): 3396 (OH, NH), 1620 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ 3.90 (s, 3H, OCH_3), 7.72 (m, 2H, C_4-H, C_5-H), 8.42 (m, 1H, C_7-H), 6.88-7.45 (m, 8H, C_6-H, 7Ar-H), 8.34 (s, 1H, N=CH), 9.20 (s, 1H, OH), 10.05 (s, 1H, NH).

General procedure for the synthesis of 6-aryl-9-(4-hydroxy-3-methoxyphenyl)-1,24-triazolo[4,3-*a*]-[1,8]naphthyridines 4. A mixture of appropriate hydrazone **3** (0.01 mole) and $FeCl_3.6H_2O$ (0.02 mole) was ground by pestle and mortar at RT for the time indicated in **Table I**. After complete conversion as indicated by TLC, the reaction mixture was digested with water. The resultant solid was filtered, washed with water and the crude material purified by recrystallization from methanol to afford **4** (**Table I**).

4a: IR (KBr): 3429 (OH), 1608 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ 3.96 (s, 3H, OCH_3), 8.10 (m, 3H, C_3-H, C_4-H, C_5-H), 8.46 (m, 1H, C_2-H), 7.35-7.60 (m, 8H, Ar-H), 9.15 (s, 1H, OH).

4b: IR (KBr): 3432 (OH), 1609 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 8.20 (m, 2H, C_3-H, C_5-H), 8.42 (m, 1H, C_4-H), 8.52 (m, 1H, C_2-H), 6.90-7.62 (m, 7H, Ar-H), 9.20 (S, 1H, OH).

Table I — Characterization data of compounds **3** and **4**

Compd	Ar	Reaction period (min)	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calcd) C	H	N
3a	C_6H_5	2.0	120	96	$C_{22}H_{18}N_4O_2$	71.52 (71.35	4.90 4.86	15.20 15.14)
3b	*p*-$CH_3OC_6H_4$	1.5	200	94	$C_{23}H_{20}N_4O_3$	69.18 (69.00	5.05 5.00	14.09 14.00)
3c	*o*-ClC_6H_4	1.5	140	94	$C_{22}H_{17}N_4O_2Cl$	65.44 (65.27	4.25 4.20	13.90 13.84)
3d	*m*-ClC_6H_4	2.0	178	95	$C_{22}H_{17}N_4O_2Cl$	65.45 (65.27	4.24 4.20	13.92 13.84)
3e	*p*-ClC_6H_4	2.0	170	98	$C_{22}H_{17}N_4O_2Cl$	65.43 (65.27	4.26 4.20	13.90 13.84)
3f	*p*-BrC_6H_4	1.5	182	95	$C_{22}H_{17}N_4O_2Br$	59.10 (58.93	3.84 3.79	12.57 12.50)
4a	C_6H_5	4.0	160	86	$C_{22}H_{16}N_4O_2$	71.90 (71.74	4.40 4.35	15.32 15.22)
4b	*p*-$CH_3OC_6H_4$	5.0	263	85	$C_{23}H_{18}N_4O_3$	69.52 (69.35	4.56 4.52	14.15 14.07)
4c	*o*-ClC_6H_4	4.5	165	84	$C_{22}H_{15}N_4O_2Cl$	65.76 (65.59	3.78 3.73	13.98 13.91)
4d	*m*-ClC_6H_4	4.0	240	85	$C_{22}H_{15}N_4O_2Cl$	65.78 (65.59	3.79 3.73	13.96 13.91)
4e	*p*-ClC_6H_4	5.0	230	88	$C_{22}H_{15}N_4O_2Cl$	65.77 (65.59	3.77 3.73	13.99 13.91)
4f	*p*-BrC_6H_4	4.5	250	86	$C_{22}H_{15}N_4O_2Br$	59.38 (59.19	3.41 3.36	12.63 12.56)

4c: IR (KBr): 3402 (OH), 1608 cm^{-1} (C=N); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.90 (s, 3H, OCH_3), 7.65 (m, 1H, C_3-H), 8.00 (s, 1H, C_5-H), 8.38 (m, 1H, C_4-H), 8.50 (m, 1H, C_2-H), 7.30-7.55 (m, 7H, Ar-H), 9.22 (s, 1H, OH).

4d: IR (KBr): 3448 (OH), 1606 cm^{-1} (C=N); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.92 (s, 3H, OCH_3), 7.67 (m, 1H, C_3-H), 8.02 (s, 1H, C_5-H), 8.18 (m, 1H, C_4-H), 8.52 (m, 1H, C_2-H), 7.25-7.60 (m, 7H, Ar-H), 9.18 (s, 1H, OH).

4e: IR (KBr): 3371 (OH) 1599 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 3.90 (s, 3H, OCH_3), 8.18 (m, 2H, C_3-H, C_5-H), 8.37 (m, 1H, C_4-H), 8.52 (m, 1H, C_2-H), 7.22-7.90 (m, 7H, Ar-H), 9.00 (s, 1H, OH).

4f: IR (KBr): 3415 (OH), 1605 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 3.95 (s, 3H, OCH_3), 7.98 (m, 2H, C_3-H, C_5-H), 8.40 (m, 1H, C_4-H), 8.56 (m, C_2-H), 7.20-7.72 (m, 7H, Ar-H), 9.15 (s, 1H, OH).

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