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A simple and efficient synthesis of novel naphthyridine-1-*H*-pyrazole-4-carboxylic acid esters/carbaldehydes using Vilsmeier-Haack reagent

Abstract: The reaction of hydrazide **4** with β-keto esters **5** gave hydrazones **6**. Cyclization of **6** with Vilsmeier-Haack reagent (DMF-$POCl_3$) for 20 min at room temperature gave 1-(4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-1*H*-pyrazole-4-carboxylic acid ethyl esters **7**. The treatment of **4** with substituted acetophenones **8** yielded the corresponding hydrazones **9** of substituted acetophenones. The treatment of **9** with Vilsmeier-Haack reagent (DMF-$POCl_3$) for 30 min at room temperature gave product **10**, the reaction of which with (diacetoxyiodo)benzene in ethanol at room temperature for 12 h in the presence of molecular iodine furnished **7**.

Keywords: (diacetoxyiodo)benzene; hydrazide; β-keto esters; naphthyridine; substituted acetophenone; Vilsmeier-Haack reagent.

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Introduction

Pyrazoles possess a wide range of useful biological activities such as antibacterial [1–5], anti-inflammatory [6–9], and antiviral [10, 11] properties. They are also useful luminescent and fluorescent [12] substances and an important class of chemicals in the development of cine films. Pyrimidinopyrazoles are being studied as drug candidates against cancer [13]. In continuation of earlier work on the synthesis of naphthyridinonoes [14, 15], it was considered worthwhile to prepare naphthyridine derivatives containing a pyrazolyl group as compounds with potentially useful biological properties.

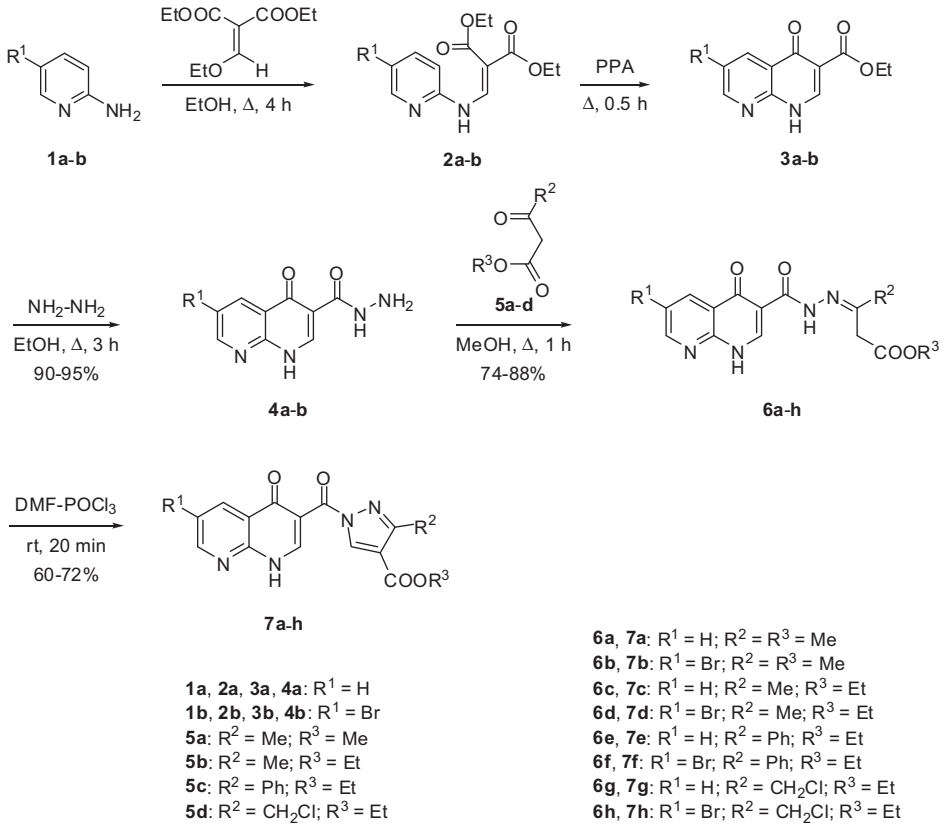
Results and discussion

The starting hydrazide **4** was prepared as described previously [16] as summarized in Scheme 1. Condensation of 2-aminopyridine **1** with ethoxymethylenemalonic ester in ethanol under reflux conditions for 4 h yielded the intermediate product **2** [17], the thermal cyclization of which in polyphosphoric acid for 30 min resulted in the formation of 1,8-naphthyridine derivative **3** [17]. Treatment of **3** with hydrazine hydrate in ethanol for 3 h yielded **4**.

Treatment of **4a** with methyl acetoacetate (**5a**) in methanol under reflux conditions for 1 h yielded product **6a**. Cyclization of **6a** using Vilsmeier-Haack reagent (DMF-$POCl_3$) at room temperature for 20 min yielded 3-methyl-1-(4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-1*H*-pyrazole-4-carboxylic acid methyl ester (**7a**). The ^{1}H NMR spectrum of **7a** shows the disappearance of the methylene proton signal and N-N-H proton signal that are observed in the spectrum of the substrate **6a**. The proton signal for the newly formed pyrazole ring appears at δ 8.27. This structure is also fully consistent with mass spectral and elemental analysis data.

This series of transformations was successfully extended on the preparations of the corresponding analogs **6b–h** and **7b–h**. All these products were fully characterized as discussed above for **6a** and **7a**.

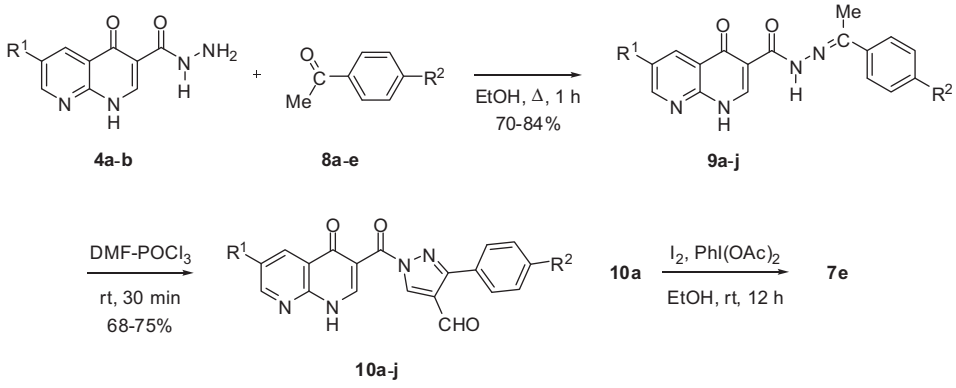
Substrates **4a,b** were also allowed to react with substituted acetophenones **8a–e** to give the corresponding hydrazides **9a–j** (Scheme 2). The treatment of **9a–j** with Vilsmeier-Haack reagent at room temperature for 30 min caused cyclization to yield the corresponding products **10a–j**. Further, **10a** was treated with (diacetoxyiodo) benzene in ethanol in the presence of molecular iodine at room temperature for 12 h. This reaction furnished product which was found to be identical with **7e** obtained is discussed above. This interesting transformation involves oxidation of the aldehyde function of **10a** followed by esterification of the resultant intermediate carboxylic acid or its derivative.



1a, **2a**, **3a**, **4a**: R^1 = H
1b, **2b**, **3b**, **4b**: R^1 = Br
5a: R^2 = Me; R^3 = Me
5b: R^2 = Me; R^3 = Et
5c: R^2 = Ph; R^3 = Et
5d: R^2 = CH_2Cl; R^3 = Et

6a, **7a**: R^1 = H; R^2 = R^3 = Me
6b, **7b**: R^1 = Br; R^2 = R^3 = Me
6c, **7c**: R^1 = H; R^2 = Me; R^3 = Et
6d, **7d**: R^1 = Br; R^2 = Me; R^3 = Et
6e, **7e**: R^1 = H; R^2 = Ph; R^3 = Et
6f, **7f**: R^1 = Br; R^2 = Ph; R^3 = Et
6g, **7g**: R^1 = H; R^2 = CH_2Cl; R^3 = Et
6h, **7h**: R^1 = Br; R^2 = CH_2Cl; R^3 = Et

Scheme 1



4a: R^1 = H
4b: R^1 = Br
8a: R^2 = H
8b: R^2 = Cl
8c: R^2 = NO_2
8d: R^2 = Me
8e: R^2 = OMe

9a, **10a**: R^1 = R^2 = H
9b, **10b**: R^1 = Br; R^2 = H
9c, **10c**: R^1 = H; R^2 = Cl
9d, **10d**: R^1 = Br; R^2 = Cl
9e, **10e**: R^1 = H; R^2 = NO_2

9f, **10f**: R^1 = Br; R^2 = NO_2
9g, **10g**: R^1 = H; R^2 = Me
9h, **10h**: R^1 = Br; R^2 = Me
9i, **10i**: R^1 = H; R^2 = OMe
9j, **10j**: R^1 = Br; R^2 = OMe

Scheme 2

Conclusion

Simple methods for the preparation of 3-methyl-1-(4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-1*H*-pyrazole-4-carboxylic acid methyl esters **7** and 1-(4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-phenyl-1*H*-pyrazole-4-carbaldehydes **10** using a Vilsmeier-Haack reagent are reported.

Experimental section

All reagents used in this work were obtained from commercial suppliers. Solvents were freshly distilled before use. Melting points are uncorrected and were determined using open capillary tubes in a sulfuric acid bath. TLC analyses were done on glass plates coated with silica gel GF-254 and visualization was done using treatment with iodine or illumination with a UV lamp. IR spectra were recorded on a Perkin-Elmer model 1000 instrument in KBr pellets. ^{1}H NMR spectra were recorded in DMSO-d_6 on a 400-MHz Varian Gemini spectrometer. Electrospray ionization mass spectra were recorded on an Agilent LC-MS instrument. Elemental analyses were performed on a Varian 3LV analyzer series CHN analyzer.

General procedure for the preparation of 6

A mixture of **4** (10 mmol), β-ketoester (**5a–d**) (10 mmol) and methanol (20 mL) was heated under reflux for 1 h and then poured into ice-cold water (25 mL). The separated solid was filtered, washed with water (2×20 mL) and dried, and crystallized from ethanol to give analytically pure product **6a–h**.

3-[(4-Oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-hydrazono]-butyric acid methyl ester (6a) Yield 2.23 g (74%); mp 164–166°C; IR: 3100–2800 (broad, medium, -NH- stretching), 1735 (strong, sharp, O-C=O stretching), 1678 cm^{-1} (strong, sharp, -CO- stretching); ^{1}H NMR: δ 1.25 (s, 3H, -C**H**$_3$), 2.00 (s, 3H, -C**H**$_3$), 4.20 (s, 2H, C**H**$_2$), 7.62–8.26 (m, 3H, **Ar-H**), 9.11 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.25 (s, 1H, -N**H**), 11.85 (sharp, s, 1H, -N**H**, D$_2$O exchangeable); MS: m/z 303 [M+H]$^+$. Anal. Calcd for $C_{14}H_{14}N_4O_4$: C, 55.63; H, 4.67; N, 18.53. Found: C, 55.60; H, 4.64; N, 18.51.

3-[(6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-hydrazono]-butyric acid methyl ester (6b) Yield 3.0 g (80%); mp 172–174°C; IR: 3400–3000 (broad, medium, -NH- stretching), 1710 (strong, sharp, -O-C=O stretching), 1677 (strong, sharp, -C=O) cm^{-1}; ^{1}H NMR: δ 1.25 (s, 3H, -C**H**$_3$), 2.10 (s, 3H, -C**H**$_3$), 4.32 (s, 2H, C**H**$_2$), 7.84–8.29 (m, 2H, **Ar-H**), 9.17 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.50 (s, 1H, C**H**), 11.90 (sharp, s, 1H, -N**H**, D$_2$O exchangeable); MS: m/z 382 [M+H]$^+$. Anal. Calcd for $C_{14}H_{13}BrN_4O_4$: C, 44.11; H, 3.44; N, 14.70. Found: C, 44.10; H, 3.42; N, 14.68.

3-[(4-Oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-hydrazono]-butyric acid ethyl ester (6c) Yield 2.6 g (82%); mp 178–180°C; IR: 3400–3100 (broad, medium, -NH- stretching), 1725 (strong, sharp, -O-C=O stretching), 1689 cm^{-1} (strong, sharp, -CO- stretching); ^{1}H NMR: δ 1.20 (s, 3H, -C**H**$_3$), 2.20 (t, 3H, -C**H**$_3$), 3.32 (q, 2H, -C**H**$_2$), 4.17 (s, 2H, C**H**$_2$), 7.42–8.26 (m, 3H, **Ar-H**), 8.65 (s, 1H, C**H**, α-proton to the enamine nitrogen), 9.89 (s, 1H, -N**H**), 11.85 (sharp, s, 1H, -N**H**, D$_2$O exchangeable); MS: m/z 317 [M+H]$^+$. Anal. Calcd for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.10; N, 17.71. Found: C, 56.94; H, 5.07; N, 17.68.

3-[(6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-hydrazono]-butyric acid methyl ester (6d) Yield 3.0 g (78%); mp 186°C; IR: 3458–3026 (broad, medium, -NH-), 1716 (strong, sharp, -O-C=O stretching), 1697 cm^{-1} (strong, sharp, -CO- stretching); ^{1}H NMR: δ 1.23 (s, 3H, -C**H**$_3$), 2.27 (t, 3H, -C**H**$_3$), 3.35 (q, 2H, -C**H**$_2$), 4.20 (s, 2H, C**H**$_2$), 7.78–8.16 (m, 2H, **Ar-H**), 8.74 (s, 1H, C**H**, α-proton to the enamine nitrogen), 9.79 (s, 1H, -N**H**), 11.90 (sharp, s, 1H, -N**H**, D$_2$O exchangeable); MS: m/z 396 [M+H]$^+$. Anal. Calcd for $C_{15}H_{15}BrN_4O_4$: C, 45.59; H, 3.83; N, 14.18. Found: C, 45.56; H, 3.80; N, 14.16.

3-[(4-Oxo-1,4-dihydro-[1,8]naphthyridine-3-cabonyl)-hydrazono]-3-phenyl-propionic acid ethyl ester (6e) Yield 3.34 g (88%); mp 256–258°C; IR: 3400–3100 (sharp, medium, -NH- stretching), 1690 (strong, sharp, -O-C=O stretching), 1667 cm^{-1} (strong, sharp, -CO- stretching); ^{1}H NMR: δ 1.30 (t, 3H, -C**H**$_3$), 2.70 (q, 2H, -C**H**$_2$), 4.15 (s, 2H, -C**H**$_2$), 7.16–8.35 (m, 8H, **Ar-H**), 8.67 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.76 (s, 1H, -N**H**), 12.00 (sharp, s, 1H, -N**H**, D$_2$O exchangeable); MS: m/z 379 [M+H]$^+$. Anal. Calcd for $C_{20}H_{18}N_4O_4$: C, 63.48; H, 4.79; N, 14.81. Found: C, 63.45; H, 4.76; N, 14.80.

3-[(6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-cabonyl)-hydrazono]-3-phenyl-propionic acid ethyl ester (6f) Yield 3.89 g (85%); mp 262–264°C; IR: 3300–3000 (sharp, medium, -NH- stretching), 1710 (strong, sharp, -O-C=O stretching), 1678 cm^{-1} (strong, sharp, -CO- stretching); ^{1}H NMR: δ 1.36 (t, 3H, -C**H**$_3$), 2.73 (q, 2H, -C**H**$_2$), 4.18 (s, 2H, -C**H**$_2$), 7.25–8.18 (m, 7H, **Ar-H**), 8.59 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.62 (s, 1H, -N**H**), 11.45 (sharp, s, 1H, -N**H**, D$_2$O exchangeable); MS: m/z 458 [M+H]$^+$. Anal. Calcd for $C_{20}H_{17}BrN_4O_4$: C, 52.53; H, 3.75; N, 12.25. Found: C, 52.51; H, 3.70; N, 12.23.

4-Chloro-3-[(4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-hydrazono]-butyric acid ethyl ester (6g) Yield 2.73 g (78%); mp 221–223°C; IR: 3400–3100 (sharp, medium, -NH- stretching), 1738 (strong, sharp, -O-C=O stretching), 1676 cm^{-1} (strong, sharp, -CO- stretching); ^{1}H NMR: δ 1.28 (t, 3H, -C**H**$_3$), 2.59 (q, 2H, -C**H**$_2$), 3.42 (s, 2H, -C**H**$_2$), 4.15 (s, 2H, -C**H**$_2$), 7.84–8.43 (m, 3H, **Ar-H**), 8.80 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.56 (s, 1H, -N**H**), 12.10 (sharp, s, 1H, -N**H**, D$_2$O exchangeable); MS: m/z 351 [M+H]$^+$. Anal. Calcd for $C_{15}H_{15}ClN_4O_4$: C, 51.36; H, 4.31; N, 15.97. Found: C, 51.34; H, 4.30; N, 15.96.

3-[(6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-hydrazono]-4-chloro-butyric acid ethyl ester (6h) Yield 3.23 g (75%); mp 230–232°C; IR: 3400–3100 (sharp, medium, -NH- stretching), 1738 (strong, sharp, -O-C=O stretching), 1676 cm^{-1} (strong, sharp, -CO- stretching); ^{1}H NMR: δ 1.30 (t, 3H, -C**H**$_3$), 2.78 (q, 2H, -C**H**$_2$), 3.60 (s, 2H, -C**H**$_2$), 4.27 (s, 2H, -C**H**$_2$), 7.94–8.27 (m, 2H, **Ar-H**), 8.87 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.66 (s, 1H, -N**H**), 11.25 (sharp, s, 1H, -N**H**, D$_2$O exchangeable); MS: m/z 431 [M+H]$^+$. Anal. Calcd for $C_{15}H_{14}ClBrN_4O_4$: C, 41.93; H, 3.28; N, 13.04. Found: C, 41.90; H, 3.26; N, 13.00.

General procedure for the preparation of 7

$POCl_3$ (4.5 mL, 30 mmol) was added dropwise to an ice-cold, stirred DMF (4 mL) and the mixture was stirred for 30 min before portionwise treatment with hydrazone **6a–h** (10 mmol) for approximately 15 min. The mixture was stirred for an additional 20 min at room temperature and then poured onto crushed ice (25 mL) and neutralized with aqueous solution of NaOH (5%, 10 mL). The separated solid of **7a–h** was filtered, washed with water (2×10 mL) and dried, and crystallized from hot ethanol.

3-Methyl-1-(4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-1*H*-pyrazole-4-carboxylic acid methyl ester (7a) Yield 1.86 g (60%); mp 174–176°C; IR: 3431–2800 (broad, medium, -NH- stretching), 1710 (strong, sharp, -O-C=O stretching), 1685 and 1660 cm^{-1} (sharp, strong, -CO- stretching); ^1H NMR: δ 1.34 (s, 3H, -C**H**$_3$), 4.26 (s, 3H, -C**H**$_3$), 7.42–7.97 (m, 3H, **Ar-H**), 8.15 (s, 1H, pyrazole-C**H**), 9.26 (s, 1H, C**H**, α-proton to the enamine nitrogen), 12.27 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 313 $[M+H]^+$. Anal. Calcd for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87; N, 17.94. Found: C, 57.66; H, 3.86; N, 17.90.

1-(6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-methyl-1*H*-pyrazole-4-carboxylic acid methyl ester (7b) Yield 2.43 g (62%); mp 190–192°C; IR: 3400–2800 (broad, medium, -NH- stretching), 1710 (sharp, strong, -O-C=O stretching), 1698 and 1665 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 1.20 (s, 3H, -C**H**$_3$), 3.35 (s, 3H, -C**H**$_3$), 7.78–8.29 (m, 2H, **Ar-H**), 8.24 (s, 1H, pyrazole -C**H**), 9.10 (s, 1H, C**H**, α-proton to the enamine nitrogen), 11.90 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 392 $[M+H]^+$. Anal. Calcd for $C_{15}H_{11}BrN_4O_4$: C, 46.06; H, 2.83; N, 14.32. Found: C, 46.04; H, 2.82; N, 14.30.

3-Methyl-1-(4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester (7c) Yield 2.15 g (66%); mp 202–204°C; IR: 3300–2900 (broad, medium, -NH- stretching), 1718 (sharp, strong, -O-C=O stretching), 1695 and 1676 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 1.22 (t, 3H, -C**H**$_3$), 3.27 (s, 2H, -C**H**$_3$), 4.12 (q, 2H, -C**H**$_2$), 7.48–8.37 (m, 3H, **Ar-H**), 8.55 (s, 1H, pyrazole -C**H**, α-proton to the enamine nitrogen), 8.90 (s, 1H, -C**H**), 12.50 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 327 $[M+H]^+$. Anal. Calcd for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 58.87; H, 4.30; N, 17.15.

1-(6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-methyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (7d) Yield 2.91 g (72%); mp 212–214°C; IR: 3500–3200 (broad, medium, -NH- stretching), 1728 (sharp, strong, -O-C=O stretching), 1699 and 1665 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 1.27 (t, 3H, -C**H**$_3$), 3.40 (s, 2H, -C**H**$_3$), 4.16 (q, 2H, -C**H**$_2$), 7.88–8.24 (m, 3H, **Ar-H**), 8.47 (s, 1H, pyrazole -C**H**), 9.00 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 12.15 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 406 $[M+H]^+$. Anal. Calcd for $C_{16}H_{13}BrN_4O_4$: C, 47.43; H, 3.23; N, 13.83. Found: C, 47.42; H, 3.20; N, 13.81.

1-(4-Oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-phenyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (7e) Yield 2.32 g (60%); mp 233–235°C; IR: 3400–3100 (broad, medium, -NH- stretching), 1746 (sharp, strong, -O-C=O stretching), 1690 and 1669 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 1.17 (t, 3H, -C**H**$_3$), 4.19 (q, 2H, -C**H**$_2$), 7.37–8.25 (m, 8H, **Ar-H**), 8.45 (s, 1H, pyrazole -C**H**), 9.10 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 12.15 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 389 $[M+H]^+$. Anal. Calcd for $C_{21}H_{16}N_4O_4$: C, 64.94; H, 4.15; N, 14.43. Found: C, 64.90; H, 4.12; N, 14.40.

1-(6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-phenyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (7f) Yield 3.12 g (67%); mp 237–239°C; IR: 3400–3000 (broad, medium, -NH- stretching), 1716 (sharp, strong, -O-C=O stretching), 1686 and 1660 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 1.18 (t, 3H, -C**H**$_3$), 4.25 (q, 2H, -C**H**$_2$), 7.45–8.16 (m, 7H, **Ar-H**), 8.34 (s, 1H, pyrazole -C**H**), 8.95 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 12.20 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 468 $[M+H]^+$. Anal. Calcd for $C_{21}H_{15}BrN_4O_4$: C, 53.98; H, 3.24; N, 11.99. Found: C, 53.95; H, 3.21; N, 11.97.

3-Chloromethyl-1-(4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester (7g) Yield 2.08 g (58%); mp 192–194°C; IR: 3300–3100 (broad, medium, due to -NH- stretching), 1705 (sharp, strong, due to -O-C=O stretching), 1694 and 1676 cm^{-1} (strong, sharp, due to -CO- stretching); ^1H NMR: δ 1.12 (t, 3H, -C**H**$_3$), 4.12 (s, 2H, -C**H**$_2$), 4.18 (q, 2H, -C**H**$_2$), 7.74–8.23 (m, 3H, **Ar-H**), 8.21 (s, 1H, pyrazole-C**H**), 8.94 (s, 1H, C**H**, α-proton to the enamine nitrogen), 12.13 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: *m/z* 361 $[M+H]^+$. Anal. Calcd for $C_{16}H_{13}ClN_4O_4$: C, 53.27; H, 3.63; N, 15.53. Found: C, 53.25; H, 3.62; N, 15.51.

1-(6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-chloromethyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (7h) Yield 2.64 g (60%); mp 149–151°C; IR: 3400–3100 (broad, medium, -NH- stretching), 1726 (sharp, strong, -O-C=O stretching), 1698 and 1686 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 1.19 (t, 3H, -C**H**$_3$), 4.16 (s, 2H, -C**H**$_2$), 4.25 (q, 2H, -C**H**$_2$), 7.90–8.13 (m, 2H, **Ar-H**), 8.35 (s, 1H, pyrazole-C**H**), 9.10 (s, 1H, C**H**, α-proton to the enamine nitrogen), 11.55 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 440 $[M+H]^+$. Anal. Calcd for $C_{16}H_{12}BrClN_4O_4$: C, 43.71; H, 2.75; N, 12.74. Found: C, 43.69; H, 2.73; N, 12.72.

General procedure for the preparation of 9

A mixture of **4** (10 mmol), substituted acetophenone **8a–j** (10 mmol) and ethanol (20 mL) was heated under reflux for 1 h, then cooled and poured onto crushed ice (25 mL). The separated solid of **9a–j** was filtered, washed with water (2×10 mL), dried and crystallized from ethanol.

4-Oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (1-phenyl-ethylidene)-hydrazide (9a) Yield 2.23 g (73%); mp 135–137°C; IR: 3400–3100 (broad, medium, -NH- stretching), 1684 (strong, sharp, -CO- stretching), 1665 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 1.22 (s, 3H, -C**H**$_3$), 7.29–8.30 (m, 8H, **Ar-H**), 9.24 (s, 1H, -C**H**, α-proton of the enamino nitrogen), 12.27 (s, 1H, -N**H**), 13.04 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 307 $[M+H]^+$. Anal. Calcd for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.64; H, 4.59; N, 18.26.

6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (1-phenyl-ethylidene)-hydrazide (9b) Yield 2.88 g (75%); mp 142–144°C; IR: 3400–3100 (broad, medium, -NH- stretching), 1688 (strong, sharp, -CO- stretching), 1675 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 1.27 (s, 3H, -C**H**$_3$), 7.29–8.32 (m, 7H, **Ar-H**), 9.24 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 10.24 (s, 1H, -N**H**), 12.10 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 386 $[M+H]^+$. Anal. Calcd for $C_{17}H_{13}BrN_4O_2$: C, 53.00; H, 3.40; N, 14.54. Found: C, 52.98; H, 3.36; N, 14.5.

4-Oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid [1-(4-chloro-phenyl)-ethylidene]-hydrazide (9c) Yield 2.65 g (78%); mp 136–138°C; IR: 3400–3100 (broad, medium, -NH- stretching), 1684 (strong, sharp, -CO- stretching), 1669 cm^{-1} (strong, sharp, -O- stretching); ^1H NMR: δ 1.20 (s, 3H, -C**H**$_3$), 7.25–8.39 (m, 7H, **Ar-H**), 8.91 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 10.16 (s,

1H, -N**H**), 11.12 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 341 $[M+H]^+$. Anal. Calcd for $C_{17}H_{13}ClN_4O_2$: C, 59.92; H, 3.85; N, 16.44. Found: C, 59.90; H, 3.80; N, 16.40.

6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid [1-(4-chloro-phenyl)-ethylidene]-hydrazide (9d) Yield 2.98 g (71%); mp 148–150°C; IR: 3400–3000 (broad, medium, -NH- stretching), 1684 (strong, sharp, -CO- stretching), 1670 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 1.26 (s, 3H, -C**H**$_3$), 7.48–8.30 (m, 6H, **Ar-H**), 8.88 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 10.26 (s, 1H, -N**H**), 11.79 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 420 $[M+H]^+$. Anal. Calcd for $C_{17}H_{12}BrClN_4O_2$: C, 48.65; H, 2.88; N, 13.35. Found: C, 48.64; H, 2.86; N, 13.30.

4-Oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid [1-(4-nitro-phenyl)-ethylidene]-hydrazide (9e) Yield 2.94 g (84%); mp162–164°C; IR: 3400–2900 (broad, medium, -NH- stretching), (strong, sharp, -CO- stretching), 1668 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 1.26 (s, 3H, -C**H**$_3$), 7.28–8.40 (m, 7H, **Ar-H**), 8.90 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 10.25 (s, 1H, -N**H**), 12.10 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 352 $[M+H]^+$. Anal. Calcd for $C_{17}H_{13}N_5O_4$: C, 58.12; H, 3.73; N, 19.93. Found: C, 58.10; H, 3.71; N, 19.90.

6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid [1-(4-nitro-phenyl)-ethylidene]-hydrazide (9f) Yield 3.50 g (81%); mp 177–179°C; IR: 3300–3000 (broad, medium, -NH- stretching), 1694 (strong, sharp, -CO- stretching), 1678 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 1.30 (s, 3H, -C**H**$_3$), 7.18–8.35 (m, 6H, **Ar-H**), 8.11 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.98 (s, 1H, -N**H**), 11.45 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 431 $[5+H]^+$. Anal. Calcd for $C_{17}H_{12}BrN_5O_4$: C, 47.46; H, 2.81; N, 16.28. Found: C, 47.43; H, 2.80; N, 16.26.

4-Oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid [1-(4-methyl-phenyl)-ethylidene]-hydrazide (9g) Yield 2.30 g (72%); mp 134–136°C; IR: 3400–3200 (broad, medium, -NH- stretching), 1692 (strong, sharp, -CO- stretching), 1665 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 1.25 (s, 3H, -C**H**$_3$), 2.30 (s, 3H, -C**H**$_3$), 7.28–8.19 (m, 7H, **Ar-H**), 8.90 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 10.16 (s, 1H, -N**H**), 12.55 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 321 $[M+H]^+$. Anal. Calcd for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.46; H, 5.00; N, 17.46.

6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid [1-(4-methyl-phenyl)-ethylidene]-hydrazide (9h) Yield 3.15 g (79%); mp 138–140°C; IR: 3400–3000 (broad, medium, -NH- stretching), 1699 (strong, sharp, -CO- stretching), 1670 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 1.32 (s, 3H, -C**H**$_3$), 2.29 (s, 3H, -C**H**$_3$), 7.19–8.40 (m, 6H, **Ar-H**), 8.86 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 10.05 (s, 1H, -N**H**), 12.65 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 400 $[M+H]^+$. Anal. Calcd for $C_{18}H_{15}BrN_4O_2$: C, 54.15; H, 3.79; N, 14.03. Found: C, 54.12; H, 3.76; N, 14.00.

4-Oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid [1-(4-methoxy-phenyl)-ethylidene]-hydrazide (9i) Yield 2.35 g (70%); mp 152–154°C; IR: 3400–3150 (broad, medium, -NH- stretching) 1690 (strong, sharp, -CO- stretching), 1674 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 1.25 (s, 3H, -C**H**$_3$), 2.56 (s, 3H, -C**H**$_3$), 7.10–8.20 (m, 7H, **Ar-H**), 8.80 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 10.15 (s, 1H, -N**H**), 12.55 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 337 $[M+H]^+$. Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.24; H, 4.73; N, 16.64.

6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid [1-(4-methoxy-phenyl)-ethylidene]-hydrazide (9j) Yield 2.98 g (72%); mp 158–160°C; IR: 3400–3150 (broad, medium, -NH- stretching), 1710 (strong, sharp, -CO- stretching), 1676 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 1.20 (s, 3H, -C**H**$_3$), 2.31 (s, 3H, -C**H**$_3$), 7.27–8.40 (m, 6H, **Ar-H**), 8.90 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 10.50 (s, 1H, -N**H**), 12.99 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 416 $[M+H]^+$. Anal. Calcd for $C_{18}H_{15}BrN_4O_3$: C, 52.06; H, 3.64; N, 13.49. Found: C, 52.02; H, 3.62; N, 13.46.

General procedure for the preparation of 10

Products **10** were obtained from **9** by using the procedure described above for the preparation of **7**.

1-(4-Oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-phenyl-1*H*-pyrazole-4-carbaldehyde (10a) Yield 2.33 g (68%); mp 182–184°C; IR: 3400–3100 (broad, medium, -NH- stretching), 1695 (strong, sharp, -CO- stretching), 1684 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 7.10–8.32 (m, 8H, **Ar-H**), 8.60 (s, 1H, -C**H**, α-proton to the enamino nitrogen), 9.10 (s, 1H, -C**H**O), 9.30 (s, 1H, pyrazole-C**H**), 10.20 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 345 $[M+H]^+$. Anal. Calcd for $C_{19}H_{12}N_4O_3$: C, 66.28; H, 3.50; N, 16.27. Found: C, 66.26; H, 3.46; N, 16.24.

1-(6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-phenyl-1*H*-pyrazole-4-carbaldehyde (10b) Yield 3.00 g (71%); mp 190–192°C; IR: 3400–3100 (broad, medium, -NH- stretching), 1693 (strong, sharp, -CO- stretching), 1659 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 7.11–8.32 (m, 7H, **Ar-H**), 8.62 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.12 (s, 1H, -C**H**O), 9.30 (s, 1H, pyrazole -C**H**), 11.10 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 424 $[M+H]^+$. Anal. Calcd for $C_{19}H_{11}BrN_4O_3$: C, 53.92; H, 2.62; N, 13.24. Found: C, 53.90; H, 2.60; N, 13.22.

3-(Chloro-phenyl)-1-(4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-phenyl-1*H*-pyrazole-4-carbaldehyde (10c) Yield 2.64 g (70%); mp 198–200°C; IR: 3300–3200 (broad, medium, -NH-stretching), 1695 (strong, sharp, -CO- stretching), 1665 cm^{-1} (strong, sharp, due to -CO- stretching); ^1H NMR: δ 7.20–8.45 (m, 7H, **Ar-H**), 8.72 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.10 (s, 1H, -C**H**O), 9.25 (s, 1H, pyrazole -C**H**), 11.25 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 379 $[M+H]^+$. Anal. Calcd for $C_{19}H_{11}ClN_4O_3$: C, 60.25; H, 2.93; N, 14.79. Found: C, 60.21; H, 2.90; N, 14.76.

1-(6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-(4-chloro-phenyl)-1*H*-pyrazole-4-carbaldehyde (10d) Yield 3.29 g (72%); mp 204–206°C; IR: 3400–2900 (broad, medium, -NH-stretching), 1692 (strong, sharp, -CO- stretching), 1670 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 7.26–8.30 (m, 6H, **Ar-H**), 8.72 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.15 (s, 1H, -C**H**O), 9.27 (s, 1H, pyrazole -C**H**), 11.55 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 458 $[M+H]^+$. Anal. Calcd for $C_{19}H_{10}ClBrN_4O_3$: C, 49.86; H, 2.20; N, 12.24. Found: C, 49.84; H, 2.18; N, 12. 22.

3-(Nitro-phenyl)-1-(4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-phenyl-1*H*-pyrazole-4-carbaldehyde (10e) Yield 2.91 g (75%); mp 212–214°C; IR: 3400–3000 (broad, medium, -NH- stretching), 1698 (strong, sharp, -CO- stretching), 1669 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 7.23–8.40 (m, 7H, **Ar-H**), 8.68 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.10 (s, 1H, -C**H**O), 9.25 (s, 1H, pyrazole-C**H**), 10.50 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 390 $[M+H]^+$. Anal. Calcd for $C_{19}H_{11}N_5O_5$: C, 58.62; H, 2.85; N, 17.99. Found: C, 58.60; H, 2.81; N, 17.96.

1-(6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-(4-nitro-phenyl)-1*H*-pyrazole-4-carbaldehyde (10f) Yield 3.65 g (78%); mp 218–220°C; IR: 3200–3100 (broad, medium, -NH- stretching), 1698 (strong, sharp, -CO- stretching), 1676 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 7.13–8.30 (m, 6H, **Ar-H**) 8.79 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.10 (s, 1H, -C**H**O), 9.28 (s, 1H, pyrazole-C**H**), 11.95 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 469 $[M+H]^+$. Anal. Calcd for $C_{19}H_{10}BrN_5O_5$: C, 48.74; H, 2.15; N, 14.96. Found: C, 48.73; H, 2.13; N, 14.95.

3-(Methyl-phenyl)-1-(4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-phenyl-1*H*-pyrazole-4-carbaldehyde (10g) Yield 2.68 g (75%); mp 186–188°C; IR: 3400–3100 (broad, medium, -NH- stretching), 1698 (strong, sharp, -CO- stretching), 1675 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 2.45 (s, 3H, -CH_3), 7.25–8.35 (m, 7H, **Ar-H**), 8.54 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.16 (s, 1H, -C**H**O), 9.42 (s, 1H, pyrazole-C**H**), 12.00 (sharp, s, 1H, -N**H**, D_2O exchangeable); M: m/z 359 $[M+H]^+$. Anal. Calcd for $C_{20}H_{14}N_4O_3$: C, 67.03; H, 3.94; N, 15. 63. Found: C, 67.00; H, 3.90, N, 15.60.

1-(6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-(4-methyl-phenyl)-1*H*-pyrazole-4-carbaldehyde (10h) Yield 3.05 g (70%); mp 194–196°C; IR: 3100–2900 (broad, medium, -NH- stretching), 1710 (strong, sharp, -CO- stretching), 1686 cm^{-1} (strong, sharp, -CO- stretching); ^1H NMR: δ 2.70 (s, 3H, -CH_3), 7.30–8.14 (m, 6H, **Ar-H**), 8.60 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.20 (s, 1H, -C**H**O), 9.35 (s, 1H, pyrazole-C**H**), 11.20 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 438 $[M+H]^+$. Anal. Calcd for $C_{20}H_{13}BrN_4O_3$: C, 54.94; H, 3.00; N, 12.81. Found: C, 54.90; H, 2.97; N, 12.80.

3-(Methoxy-phenyl)-1-(4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-phenyl-1*H*-pyrazole-4-carbaldehyde (10i) Yield 2. 61 g (70%); mp 166–168°C; IR: 3430–3100 (broad, medium, -NH- stretching), 1697 (strong, sharp, -CO- stretching), 1655 cm^{-1} (strong, sharp, -CO-); ^1H NMR (DMSO–d_6/TMS): δ 3.15 (s, 3H, -OCH_3), 7.27–8.11 (m, 7H, **Ar-H**), 8.54 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.26 (s, 1H, -C**H**O), 9.28 (s, 1H, pyrazole-C**H**), 11.55 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 375 $[M+H]^+$. Anal. Calcd for $C_{20}H_{14}N_4O_4$: C, 64.14; H, 3.77; N, 14.97. Found: C, 64.10; H, 3.75; N, 14.94.

1-(6-Bromo-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carbonyl)-3-(4-methoxy-phenyl)-1*H*-pyrazole-4-carbaldehyde (10j) Yield 3.34 g (75%); mp 175–177°C; IR: 3430–3100 (broad, medium, -NH- stretching), 1698 (strong, sharp, due to -CO- stretching), 1666 cm^{-1} (strong, sharp, due to -CO- stretching); ^1H NMR: δ 3.20 (s, 3H, -OCH_3), 7.45–8.24 (m, 6H, **Ar-H**), 8.58 (s, 1H, -C**H**, α-proton to the enamine nitrogen), 9.21 (s, 1H, -C**H**O), 9.30 (s, 1H, pyrazole-C**H**), 11.35 (sharp, s, 1H, -N**H**, D_2O exchangeable); MS: m/z 454 $[M+H]^+$. Anal. Calcd for $C_{20}H_{13}BrN_4O_4$: C, 53.00; H, 2.89; N, 12.36. Found: C, 52.97; H, 2.86; N, 12.31.

Preparation of 7 from 10

A mixture of **10a** (10 mmol), iodine (5 mmol), (diacetoxyiodo)benzene (15 mmol), and ethanol (25 mL) was stirred for 12 h, then poured onto crushed ice (25 mL) and extracted with $CHCl_3$ (2×10 mL). The organic extract was dried over anhydrous Na_2SO_4, concentrated, and the residue of **7e** crystallized from ethanol.

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