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ORIGINAL PAPER

An efficient one-pot synthesis of highly substituted [1,8] naphthyridin-1-phenyl-1-ethanone derivatives via a four-component reaction

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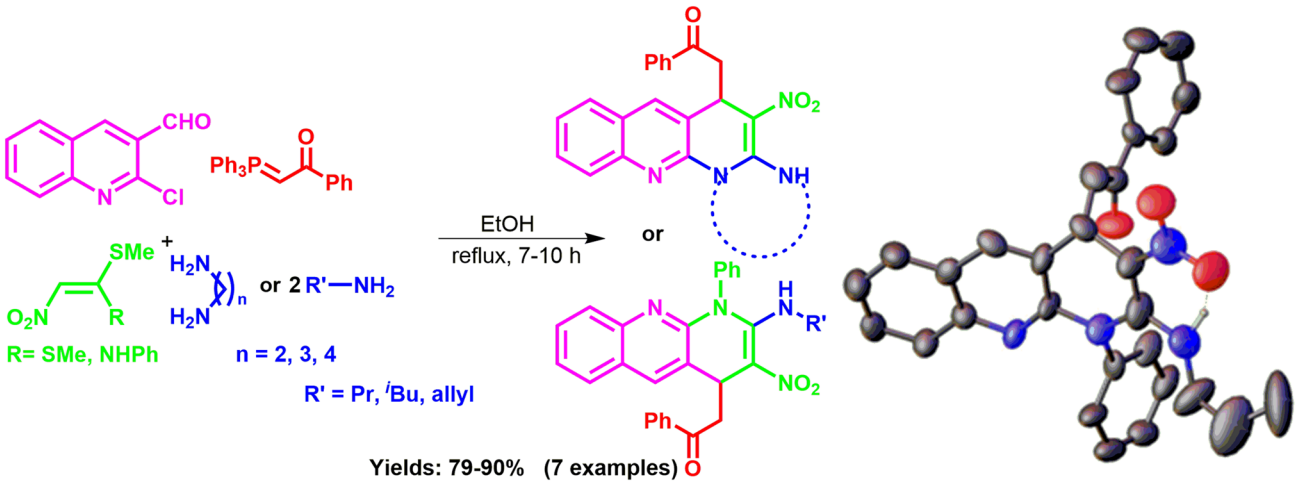
Abstract An operationally simple one-pot protocol for the synthesis of highly substituted [1,8]naphthyridin-1-phenyl-1-ethanones dealing with 2-chloroquinoline-3-carbaldehyde and 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene) ethan-1-one, 1,1-bis(methylthio)-2-nitroethylene or ketene *N*,*S*-acetals, and aromatic/aliphatic amine or diamines under mild and catalyst-free conditions in excellent yields is described. The structures of products were corroborated spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and by X-ray analysis.

Graphical Abstract An efficient, useful and general procedure for the synthesis of [1,8]naphthyridin-1-phenyl-1-ethanones via a one-pot four-component reaction of 2-chloroquinoline-3-carbaldehyde and 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one, 1,1-bis(methylthio)-2-nitroethylene or ketene *N*,*S*-acetals, and aromatic/aliphatic amine or diamines under mild and catalyst-free conditions in excellent yields is described. The major advantages of this protocol are high yields, mild and catalyst-free conditions, short reaction times, and application of green solvent.



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Keywords 2-Chloroquinoline-3-carbaldehyde · 1-Phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one · 1,1-Bis(Methylthio)-2-nitroethylene · Ketene *N*,*S*-acetals · Aliphatic amine or diamines · Multicomponent reaction

Introduction

Nitrogen-based heterocyclic compounds have been extremely used in pharmaceuticals, and designing unprecedented heterocyclic units has become a progressively crucial purpose for pharmacists and biologists [1, 2]. Among them, 1,8-naphthyridine architectures are noteworthy synthetic objectives because these compounds have an extensive range of biological activities consisting of antibacterial [3–6], antimycobacterial [7], antimalarial [8], antitumor [9–11], anti-inflammatory [12–14], antiplatelet [15], antiproliferative [16], antihypertensive [17], gastric antisecretary [18], antiallergic [19], antioxidant [20], neurotoxic [21], and neuroprotective [22, 23] activities. They also have been designed and developed in directions as divergent as new catalysts [24–26], fluorescent dyes [27, 28], and sensors [29] because of their noticeable catalytic and optical characteristics. The 1,8-naphthyridine derivatives are also inhibitors of acid secretion in stomach named as gastric antisecretary [18], and besides they are used for treatment of *Alzheimer*'s disease [30]. A number of 1,8-naphthyridine derivatives have been reported as adjustors of plant growth, fungicides, herbicides, insecticides, and nematicides [31–34].

Although there are several accesses to the construction of 1,8-naphthyridine moieties [5, 9, 13, 35–37], in view of their extensive biological significance, the development of a simple and efficient method for the construction of this class of compounds using readily available starting materials is very much desirable.

Multicomponent reactions (MCRs) are an eminent method for the generation of structurally diverse and bioactive scaffolds from simple substrates, thereby providing the benefits of minimizing the synthetic steps, simple operation, short reaction periods, environmental friendliness, high molecular diversity, atom economy, and high chemical efficiency [38–43]. Generally, in the MCRs increasing the number of substrates leads to inefficiency and more side reactions [44, 45]. So, the investigation of MCRs with more than three components, is still in demand.

Taking the above description and as part of our continued research in developing novel, discriminating, and environmentally friendly methods for the preparation of bioactive molecules using ketene aminals [46, 47], we report herein a novel and facile protocol for the synthesis of 1,8-naphthyridine derivatives via a four-component reaction of 2-chloroquinoline-3-carbaldehyde, 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one, 1,1-bis(methylthio)-2-nitroethylene or ketene *N*,*S*-acetals, and aromatic/aliphatic amine or diamines.

Experimental section

The aromatic/aliphatic amine or diamines and 1,1-bis(methylthio)-2-nitroethylene were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on an Agilent Technologies 5975C VL MSD mass spectrometer operating at an ionization potential of 70 eV. ^{1}H NMR (300 and 500.13 MHz) and ^{13}C NMR (75 and 125 MHz) spectra were obtained using Bruker DRX-300 AVANCE and Bruker DRX-500 AVANCE spectrometers. IR spectra were recorded as KBr pellets on a NICOLET FT-IR 100 spectrometer; absorbencies are reported in cm^{-1}.

General Procedure for the Synthesis of compound 5 (for example 5a): A solution of 2-chloroquinoline-3-carbaldehyde (**1**, 1 mmol) and 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene) ethan-1-one (**2**, 1 mmol) in EtOH (4 mL) was stirred for 2 h at room temperature. Then, nitro ketene dithioacetal (**3**; 1 mmol) and 1,3-propanediamine (**4a**; 1 mmol) were added in sequence and refluxed for 5–7 h. Upon completion of the reaction, monitored by TLC, the mixture was filtered and the precipitate washed with EtOH (4 mL) to afford the pure product **5a**.

2-(5-Nitro-2,3,4,6-tetrahydro-1*H*-benzo[g]pyrimido[1,2-*a*][1,8]naphthyridin-6-yl)-1-phenylethanone (5a): Light yellow powder; mp 222–224 °C; 0.36 g, yield 90%. IR (KBr): 3477 (NH), 1674 (C=O), 1542, 1338 (NO_2), 1605, 1420 (Ar). ^{1}H NMR (500.1 MHz, DMSO-d_6): 1.94–1.96 (*m*, 1 H); 2.12–2.16 (*m*, 1 H); 3.29–3.34 (*m*, 2 H); 3.42–3.65 (*m*, 2 H); 4.09–4.20 (*m*, 2 H); 5.06 (*s*, 1 H); 7.39 (*d*, $^3J = 7.3$, 1 H); 7.41 (*d*, $^3J = 7.7$, 1 H); 7.43 (*t*, $^3J = 6.9$, 1 H); 7.54 (*t*, $^3J = 6.8$, 1 H); 7.64 (*t*, $^3J = 7.8$, 1 H); 7.78–7.80 (*m*, 4 H); 8.19 (*s*, 1 H); 11.67 (*s*, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): 19.3, 34.0, 38.3, 42.1, 43.5, 106.0, 121.2, 125.3, 125.5, 127.3, 127.4, 127.9, 128.6, 129.8, 133.2, 136.1, 136.5, 144.9, 147.8, 152.0, 198.2. EI-MS (70 eV): 293 (16), 260 (5), 259 (46), 258 (100), 257 (8), 256 (4), 230 (12), 216 (9), 152 (31), 151 (3), 125 (8), 105 (16), 77 (28). Anal. Calcd. for $C_{23}H_{20}N_4O_3$ (400.43): C, 68.99; H, 5.03; N, 13.99; found: C, 68.98; H, 4.91; N, 13.93.

2-(2,2-Dimethyl-5-nitro-2,3,4-tetrahydro-1*H*-benzo[*g*]pyrimido[1,2-*a*][1,8]naphthyridin-6-yl)-1-phenyl-1-ethanone (5b): Cream powder; mp 226–228 °C; 0.38 g, yield 90%. IR (KBr): 3433 (NH), 1686 (C=O), 1535, 1344 (NO_2), 1611, 1440 (Ar). ^{1}H NMR (500.1 MHz, $CDCl_3$): 1.23 (*s*, 3 H); 1.26 (*s*, 3 H); 3.27 (*q*, $^2J = 12.5$, 2 H); 3.50 (*d*, $^2J = 16.2$, 1 H); 3.79 (*dd*, $^2J = 16.2$, $^3J = 6.2$, 1 H); 4.08 (*q*, $^2J = 13.0$, 2 H); 5.15 (*s*, 1 H); 7.37–7.41 (*m*, 3 H); 7.49 (*t*, $^3J = 6.6$, 1 H); 7.61 (*t*, $^3J = 6.9$, 1 H); 7.67 (*d*, $^3J = 7.7$, 1 H); 7.87 (*d*, $^3J = 6.7$, 2 H); 7.87–7.88 (*m*, 2 H), 12.18 (*s*, 1 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): 23.9, 25.0, 27.6, 34.6, 43.7, 50.5, 52.5, 107.3, 121.4, 125.6, 126.1, 127.3, 128.0, 128.2, 128.7, 129.9, 133.3, 136.2, 136.7, 145.6, 147.9, 152.1, 197.9. EI-MS (70 eV): 428 (5, M^+), 382 (25), 381 (39), 310 (26), 309 (100), 306 (21), 305 (17), 276 (35), 263 (20), 221 (8), 180 (24), 105 (47), 77 (24), 51 (4). Anal. Calcd. for $C_{25}H_{24}N_4O_3$ (428.49): C, 70.08; H, 5.65; N, 13.08; found: C, 70.10; H, 5.70; N, 13.12.

2-(6-Nitro-1,2,3,4,5,7-hexahydrobenzo[g] [1,3] diazepino[1,2-*a*][1,8]naphthyridin-7-yl)-1-phenylethanone (5c): White powder; mp 135–137 °C; 0.35 g, yield 85%. IR (KBr): 3337 (NH), 1604 (C=O), 1486, 1363 (NO_2), 1671, 1443 (Ar). ^{1}H NMR (500.1 MHz, $CDCl_3$): 1.65–1.68 (*m*, 2 H); 1.99–2.00 (*m*, 2 H); 3.28 (*t*, $^3J = 10.4$, 2 H); 3.42 (*dd*, $^2J = 18.5$, $^3J = 1.4$, 1 H); 3.76–3.78 (*m*, 2 H); 5.01 (*d*, $^3J = 10.3$, 4 H); 5.16 (*dd*, $^2J = 18.6$, $^3J = 10.7$ $^3J = 8.8$, 1 H); 7.51 (*t*, $^3J = 7.6$, 2 H); 7.54 (*t*, $^3J = 8.0$, $^4J = 1.0$, 1 H); 7.62 (*t*, $^3J = 7.3$, 1 H); 7.68 (*dt*, $^3J = 7.0$, $^4J = 1.2$, 1 H); 7.90 (*d*, $^3J = 7.6$, 1 H); 7.95 (*d*, $^3J = 8.4$, 1 H); 8.10 (*d*, $^3J_{HH} = 7.2$, 2 H); 8.56 (*s*, 1 H); 9.47 (*bs*, 1 H). ^{13}C NMR (75.46 MHz, DMSO-d_6): 27.4, 35. 8, 39.2, 46.4, 46.4, 110.6, 127.0, 127.1, 127.9, 128.1, 128.6, 128.9, 130.2, 130.9, 134.2, 136.4, 140.2, 146.4, 150.5, 164.7, 201.8. EI-MS (70 eV): 295 (27), 293 (8), 292 (5), 291 (5), 260 (3), 259 (24), 258 (100), 230 (7), 229 (6), 228 (6), 221 (2), 220 (6), 218 (2), 217 (2), 158 (2), 157 (26), 153 (6), 152 (24), 151 (3), 128 (4), 126 (5), 125 (7), 77 (29), 41 (9), 69 (4). Anal. Calcd. for $C_{24}H_{22}N_4O_3$ (414.45): C, 69.55; H, 5.35; N, 13.52; found: C, 69.41; H, 5.37; N 13.55.

2-(3-Nitro-1-propyl-2-(propylamino)-1,4-dihydrobenzo[*b*][1,8]naphthyridin-4-yl)-1-phenylethanone (5d): Yellow powder; mp 165 °C; 0.35 g, yield 78%. IR (KBr): 3435 (NH), 1674 (C=O), 1589, 1392 (NO_2), 1629, 1436 (Ar). ^{1}H NMR (500.1 MHz, $CDCl_3$): 1.02 (*t*, $^3J = 7.0$, 6 H); 1.80 (*q*, $^3J = 7.0$, 4 H); 3.22–3.26 (*m*, 2 H); 3.41 (*d*, $^2J = 18.2$, 1 H); 3.41–3.44 (*m*, 2 H); 4.86 (*d*, $^3J = 10.6$, 1 H), 5.30 (*dd*, $^2J = 18.2$, $^3J = 10.4$, 1 H), 7.51 (*t*, $^3J = 7.6$, 2 H); 7.54 (*t*, $^3J = 7.7$, 1 H); 7.62 (*t*, $^3J = 7.2$, 1 H); 7.68 (*t*, $^3J = 7.4$, 1 H); 7.91 (*d*, $^3J = 7.9$, 1 H); 7.95 (*d*, $^3J = 8.3$, 1 H); 8.11 (*d*, $^3J = 7.6$, 2 H); 8.61 (*s*, 1 H), 8.83 (*bs*, 1 H). ^{13}C NMR (75.46 MHz, $CDCl_3$): 11.6, 22.9, 37.1, 38.4, 47.30, 47.31, 108.0, 127.1, 127.2, 127.9, 128.1, 128.6, 128.9, 130.2, 131.4, 134.2, 136.3, 139.7, 146.4, 150.3, 161.5, 202.4. EI-MS (70 eV): 436 (1), 398 (9), 397 (5), 354 (4), 313 (2), 293 (10), 259 (26), 258 (100), 230 (7), 229 (6), 228 (6), 216 (5), 170 (7), 152 (20), 128 (2), 125 (6), 105 (19), 100 (2), 99 (2), 77 (22). Anal. Calcd. for $C_{26}H_{28}N_4O_3$ (444.53): C, 70.25; H, 6.35; N, 12.60; found: C, 70.24; H, 6.36; N, 12.55.

2-(3-Nitro-2-(phenylamino)-1-propyl-1,4-dihydrobenzo[*b*][1,8]naphthyridin-4-yl)-1-phenylethanone (5e): Light yellow powder; mp 192–194 °C; 0.42 g, yield 88%. IR (KBr): 3361, 3437 (NH), 1628 (C=O), 1492, 1340 (NO_2), 1610, 1450 (Ar). ^{1}H NMR (500.13 MHz, $CDCl_3$): 0.84 (*t*, $^3J = 8.0$, 3 H); 1.42–1.51 (*m*, 2 H); 2.42–2.47 (*m*, 1 H); 2.89–2.95 (*m*, 1 H); 3.58 (*dd*, $^2J = 16.4$, $^3J = 3.7$, 1 H); 3.65 (*dd*, $^2J = 16.3$, $^3J = 7.6$, 1 H); 5.41 (*dd*, $^3J = 7.4$, $^3J = 3.6$, 1 H); 7.37 (*t*, $^3J = 6.8$, 1 H); 7.39 (*t*, $^3J = 7.4$, 2 H); 7.45 (*t*, $^3J = 7.4$, 1 H); 7.50 (*t*, $^3J = 7.3$, 1 H); 7.55 (*t*, $^3J = 7.7$, 3 H); 7.68 (*d*, $^3J = 7.7$, 1 H); 7.80 (*d*, $^3J = 8.4$, 1 H); 7.92 (*d*, $^3J = 7.3$, 2 H); 7.96 (*d*, $^3J = 7.7$, 2 H);.8.03 (*s*, 1 H); 11.56 (*s*, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): 11.3, 22.9, 34.9, 44.6, 47.4, 112.2, 123.3, 125.9, 126.4, 127.3, 128.2, 128.3, 128.5, 128.8, 129.0, 129.7, 133.4, 136.7, 140.6, 145.6, 149.8, 156.6, 197.6. EI-MS (70 eV): 477 (4), 445 (4), 430 (100), 433 (4), 432 (22), 431 (57), 403 (4), 402 (13), 401 (3), 389 (4), 388 (8), 360 (7), 359 (23), 314 (3), 313 (12), 312 (24), 271 (4), 270 (16), 269 (5),), 268 (4), 257 (4), 256 (3), 255 (5), 105 (20), 77 (14). Anal. Calcd. for $C_{29}H_{26}N_4O_3$ (478.54): C, 72.79; H, 5.48; N, 11.71; found: C, 72.74; H, 5.45; N 11.79. Crystal data for **3e** $C_{29}H_{26}N_4O_3$ (CCDC 1486604): $M_W = 478.33$, monoclinic, Cc, $a = 14.474(3)$ Å, $b = 22.434(4)$ Å, $c = 8.8587(18)$ Å, $\alpha = 90.00$, $\beta = 120.14(3)$, $\gamma = 90.00$, $V = 2487.6(11)$ Å^3, $Z = 4$, $Dc = 1.277$ mg/m^3,. $F(000) = 1008$, crystal dimension $0.42 \times 0.18 \times 0.17$ mm, radiation, Mo Kα ($\lambda = 0.71073$ Å), $1.815 \leq 2\theta \leq 24.982$, intensity data were collected at 293(2) K with a Bruker APEX area-detector diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of $-17 \leq h \leq 17$, $-24 \leq k \leq 26$, $-10 \leq l \leq 10$; the structure was solved by a direct method; all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 4081 observed reflections with R (into) = 0.1976 by a full-matrix least-squares technique converged to $R = 0.0487$ and Raw = 0.0657 [$I > 2$sigma(I)].

2-(1-Isobutyl-3-nitro-2-(phenylamino)-1,4-dihydrobenzo[*b*][1,8]naphthyridin-4-yl)-1-phenylethanone (5f): Light yellow powder; mp 185–187 °C (decom.); 0.41 g, yield 85%. IR (KBr): 3431 (NH), 1683 (C=O), 1500, 1342 (NO_2), 1617, 1449 (Ar). ^{1}H NMR (300.1 MHz, DMSO-d_6): 0.72 (*s*, 6 H); 1.58–1.61 (*m*, 1 H); 2.26–2.27 (*m*, 1 H); 2.70–2.71 (*m*, 1 H); 3.35–3.61 (*m*, 2 H), 5.26 (*s*, 1 H); 7.40–7.48 (*m* 5 H); 7.51–7.60 (*m*, 4 H); 7.89–7.92 (*m*, 5 H); 8.33 (*s*, 1H); 11.26 (*s*, 1 H). ^{13}C NMR (75.46 MHz, DMSO-d_6): 19.4, 27.8, 34.3, 44.3, 52.1, 111.1, 123.3, 125.8, 125.9, 127.4, 127.5, 128.0, 128.17, 128.18, 128.6, 128.9, 129.7, 133.3, 136.2, 136.6, 139.8, 144.6, 149.4, 155.9, 197.9. EI-MS (70 eV): 537 (1), 491 (11), 446 (32), 445 (10), 444 (5), 389 (4), 373 (91), 371(5), 370 (16), 326 (100), 327 (61), 280 (2), 281 (2), 282 (11), 283 (13), 270 (70), 269 (12), 268 (10), 180 (6), 105 (37), 41 (6). Anal. Calcd. for $C_{30}H_{28}N_4O_3$ (492.57): C, 73.15; H, 5.73; N, 11.37; found: C, 73.18; H, 5.71; N, 11.39.

2-(1-Allyl-3-nitro-2-(phenylamino)-1,4-dihydrobenzo[*b*][1,8]naphthyridin-4-yl)-1-phenylethanone (5g): Yellow powder; mp 193–195 °C; 0.41 g, yield 89%. IR (KBr): 3431, 1681 (C=O), 1492, 1339 (NO_2), 1606, 1402 (Ar). ^{1}H NMR (500.1 MHz, $CDCl_3$): 3.15–3.21 (*m*, 1 H); 3.55–3.61 (*m*, 2 H); 3.62–3.67 (*m*, 1 H); 5.11–5.19 (*dd*, ^2J = 19.7, ^3J = 10.4, 2 H); 5.43 (*dd*, ^3J = 7.4, ^3J = 3.7, 1 H); 5.59–5.67 (*m*, 1 H); 7.40 (*t*, ^3J = 7.1, 1 H); 7.41 (*t*, ^3J = 7.7, 2 H); 7.45 (*t*, ^3J = 7.3, 1 H); 7.51 (*t*, ^3J = 7.4, 1 H); 7.56 (*t*, ^3J = 7.7, 2 H); 7.58 (*t*, ^3J = 6.8, 1 H); 7.70 (*d*, ^3J = 8.0, 1 H); 7.80 (*d*, ^3J = 8.3, 1 H); 7.92 (*d*, ^3J = 7.6, 2 H); 7.92 (*d*, ^3J = 7.7, 2 H); 8.03 (1 H); 11.44 (*s*, 1 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 34.8, 44.6, 47.7, 112.6, 118.0, 123.4, 125.9, 126.5, 127.3, 128.3, 128.5, 128.8, 129.2, 129.7, 129.8, 132.1, 133.4, 136.7, 136.8, 140.5, 145.6, 149.8, 156.4, 197.6. EI-MS (70 eV): 476 (3), 475 (7), 432 (2), 431 (10), 430 (31), 429 (6), 428 (12), 359 (3), 358 (14), 357 (55), 335 (13), 327 (13), 326 (13), 324 (15), 311 (38), 310 (100), 297 (26), 296 (26), 295 (9), 294 (11), 271 (14), 270 (60), 269 (24), 268 (13), 255 (9), 206 (3), 152 (4), 105 (33), 77 (27), 41 (7). Anal. Calcd. for $C_{29}H_{24}N_4O_3$ (476.53): C, 73.09; H, 5.08; N 11.76, found: C, 73.05; H, 5.08; N, 11.78.

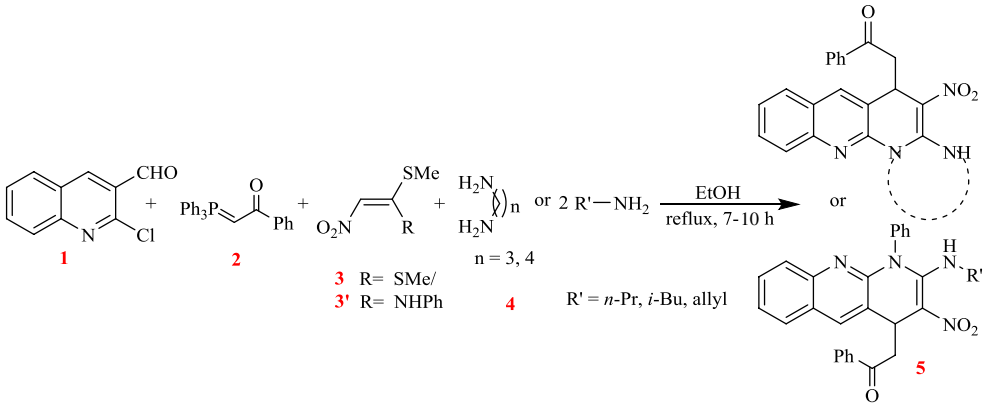
7-(2-Chloroquinolin-3-yl)-8-nitro-5-phenyl-1,2,3,5,6,7-hexahydroimidazo[1,2-*a*]pyridine-5-ol (6): White powder; mp 226–228 °C; 0.37 g, yield 89%. IR (KBr): 3343 (NH), 1595 (Ar), 1525, 1396 (NO_2). ^{1}H NMR of minor isomer (500.1 MHz, DMSO-d_6): 2.10–2.20 (*m*, 2 H); 3.15–3.17 (*m*, 2 H); 3.44–3.49 (*m*, 2 H); 4.76 (*s*, 1 H); 6.33 (*bs*, 1 H); 7.19–8.12 (*m*, 10 H); 9.40 (s, 1 H). ^{1}H NMR of major isomer (500.1 MHz, DMSO-d_6): 2.29–2.35 (*m*, 2 H); 3.17–3.28 (*m*, 2 H); 3.65–3.69 (*m*, 2 H); 4.63 (*s*, 1 H); 6.93 (*bs*, 1 H); 7.19–8.12 (*m*, 10 H); 9.45 (*s*, 1 H). ^{13}C NMR of minor isomer (75.4 MHz, DMSO-d_6): 35.4, 45.6, 42.5, 44.0, 84.1, 105.7, 125.90, 125.92, 126.9, 127.3, 127.4, 127.7, 128.1, 128.5, 129.8, 135.7, 141.9, 145.8, 150.2, 157.6. ^{13}C NMR of major isomer (75.4 MHz, DMSO-d_6): 35.7, 41.9, 42.7, 44.2, 83.3, 103.9, 125.9, 126.0, 127.00, 127.04, 127.33, 127.6, 127.9, 128.3, 129.9, 135.0, 142.6, 145.5, 150.3, 158.3. EI-MS (70 eV): 422 (1, M^+), 387 (3), 358 (4), 357 (5), 356 (6), 355 (10), 320 (2), 295 (4), 294 (4), 260 (3), 259 (30), 258 (100), 256 (4), 242 (12), 230 (9), 229 (8), 228 (8), 227 (3), 217 (3), 202 (3), 170 (11), 153 (7), 152 (28), 151 (3), 129 (6), 127 (4), 126 (6), 125 (8), 105 (22), 77 (35), 51 (10). Anal. Calcd. for $C_{22}H_{19}ClN_4O_3$ (422.86): C, 62.49; H, 4.53; N, 13.25; found: C, 62.42; H 4.59; N, 13.28.

Results and discussion

We report herein a novel one-pot procedure for the synthesis of substituted [1,8]naphthyridin-1-phenyl-1-ethanone derivatives **5**. The products were obtained via a one-pot protocol including a four-component condensation reaction of 2-chloroquinoline-3-carbaldehyde **1** and 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one **2**, 1,1-bis(methylthio)-2-nitroethylene **3** or ketene *N*,*S*-acetals **3′**, and aliphatic amine or diamines **4** under catalyst-free and mild reaction conditions and in excellent yields at reflux temperature in EtOH (Scheme 1).

To explore the scope of nitro ketene aminals **7** or **7′** for this multicomponent reaction, we used 1,1-bis(methylthio)-2-nitroethylene **3** or ketene *N*,*S*-acetals **3′** and different amines.

The reaction of nitro ketene aminal **7** or **7′**, which was prepared by the addition of diamine or primary amine **4** to 1,1-bis(methylthio)-2-nitroethylene **3** or ketene *N*,*S*-acetals **3′**, with 2-chloroquinoline-3-carbaldehyde **1** and 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one **2** in EtOH at 80°C for 7–10 h was performed in catalyst-free conditions. The progress of the reaction was monitored by TLC. After completion of the reaction, product **5** was obtained in 80–90% yield. The amine moiety in the starting materials can be varied. We have shown that the uses of a wide range of amines **4** in this four-component reaction make possible the synthesis of libraries



Scheme 1 Synthesis of substituted 1,4-dihydrobenzo[*b*][1,8]naphthyridin-4-yl)-1-phenylethanones **5**

of compounds. When we used 1,1-bis(methylthio)-2-nitroethylene **3** and diamines **4a**, **4b,** and **4c** or 2 mmol of primary amine **4d**, we obtained, respectively, products **5a**, **5b**, **5d,** and **5c** or **5d** according to Table 1.

But, when we used ketene *N*,*S*-acetals **3′** and 1 mmol of primary amines like **4d**, **4e,** and **4f**, products **5e**, **5f,** and **5g** were obtained, respectively (Table 2).

When we used ethylenediamine in this reaction, a different process was occurred and the product as a mixture of two diastereomers was obtained as shown in Scheme 2.

As anticipated from our initial results, these reactions progressed very cleanly under reflux conditions and no undesirable side reactions were observed. The structures of all products **5a**–**g** and **6** were deduced from their IR, mass, ^{1}H NMR, and ^{13}C NMR spectra and unambiguously confirmed by X-ray crystal structure analysis of **5e** (Fig. 1).

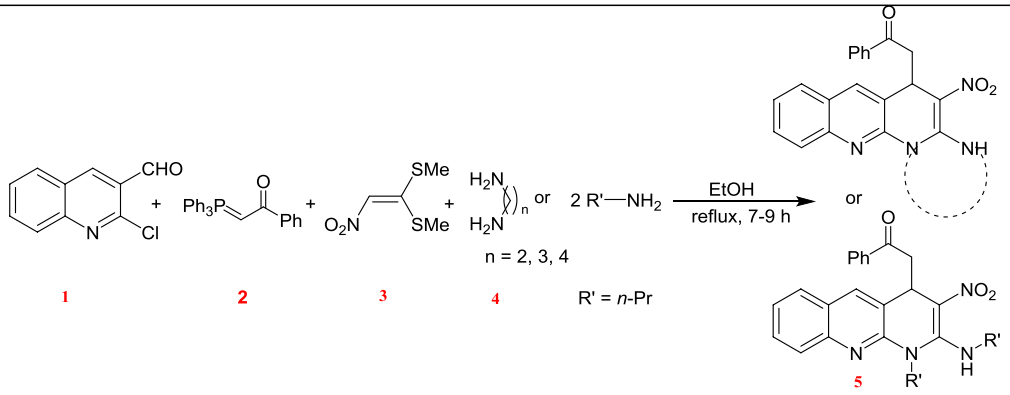
The mass spectrum of **5b** displayed the molecular ion peak at the appropriate *m/z* value. In the IR spectrum of **5b**, an absorption band at 3433 cm^{-1}, two absorption bands at 1611 and 1499 cm^{-1}, and two absorption bands at 1535 and 1344, which are related to NH, C=O, Ph, and NO_2 stretching frequencies, clearly indicated the most significant functional groups of the product. The ^{1}H NMR spectrum of **5b** exhibited four sharp singlet signals at 1.23, 1.25, 5.15, and 12.19 ppm, readily recognized as two methyl, CH^{6}, and NH groups. Four other signals in the range of 3–4 ppm belong to the CH_2–N, CH_2–NH, and CH_2-C=O, and ten aromatic hydrogens gave rise to characteristic signals in the aromatic region of the spectrum. Observation of 23 distinct signals in the ^{1}H-decoupled ^{13}C NMR spectrum of **5b** is in agreement with the proposed structure.

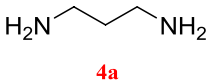
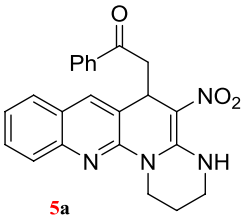
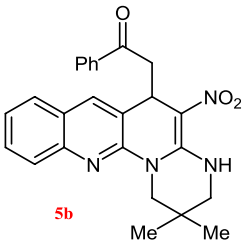
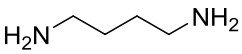
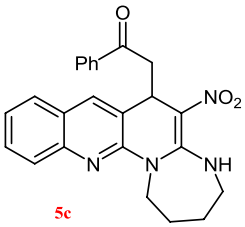
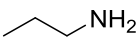
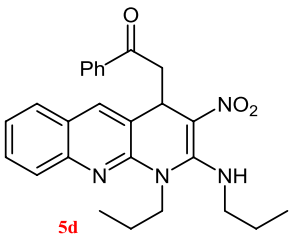
On the basis of the results obtained above, the detailed mechanism of this one-pot four-component reaction is outlined in Schemes 3 and 4.

The formation of the [1,8]naphthyridin-1-phenyl-1-ethanone nucleus **5** can be explained by the initial Michael addition of the nitro ketene aminal (NKA) **7**, resulted from the coupling of nitro ketene dithioacetal **3** and diamine **4**, at the electrophilic center of the adduct **8** that is formed in situ through the condensation of 2-chloroquinoline-3-carbaldehyde **1** and 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene) ethan-1-one **2** followed by chemoselective nucleophilic attack of the NH of the resulted intermediate **9** at the C–Cl function that afford product **5**.

A plausible reaction scenario for the formation of compound **6** is outlined in Scheme 5. It is conceivable that initially the 2-chloroquinoline-3-carbaldehyde **1** and 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one **2** undergo Wittig reaction and loss of triphenylphosphine oxide to give adduct **8**, which acts as Michael acceptor. Next, the formation of nitro ketene aminal **7g** occurs through condensation of ethylenediamine **4g** with 1,1-bis(methylthio)-2-nitroethylene **3**. Then, the nitro ketene aminal **7g** attacks to quinolinyl chalcone **8** in a Michael-type addition to produce an open chain intermediate **9g** which transformed to intermediate **9′g** through the rotation about C–C bound. At this stage, considering the previous derivatives, we would normally expect to form **9′g** which then undergoes *N*-cyclization via attack to the C–Cl band and give the desired 1,4-dihydrobenzo[*b*][1,8]naphthyridin-4-yl)-1-phenylethanones **6′** (path A). But considering IR, ^{1}H, and ^{13}C NMR spectra, this product was not created and another considerable event occurs. In fact, in this stage, chemoselective nucleophilic addition of the amino group to the C=O band afforded product **6** (path B).

Table 1 Synthesis of [1,8]naphthyridin-1-phenyl-1-ethanones **5**

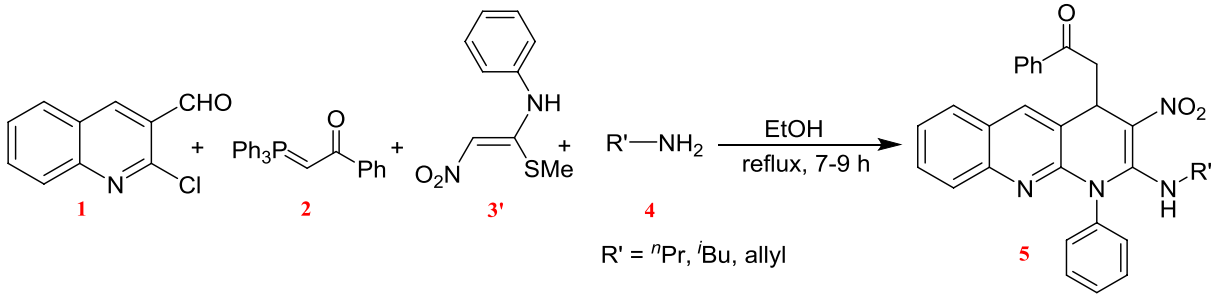


Entry	Diamine or Amine **4**	Product **5**	Yield (%)
1	 **4a**	 **5a**	90
2	 **4b**	 **5b**	90
3	 **4c**	 **5c**	85
4	 **4d**	 **5d**	78

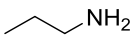
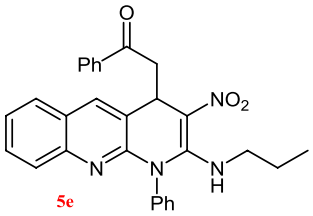
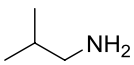
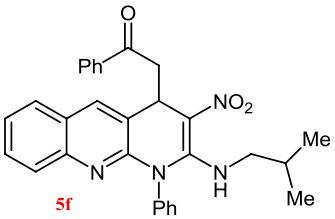
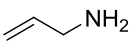
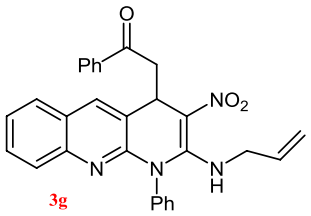
Conclusions

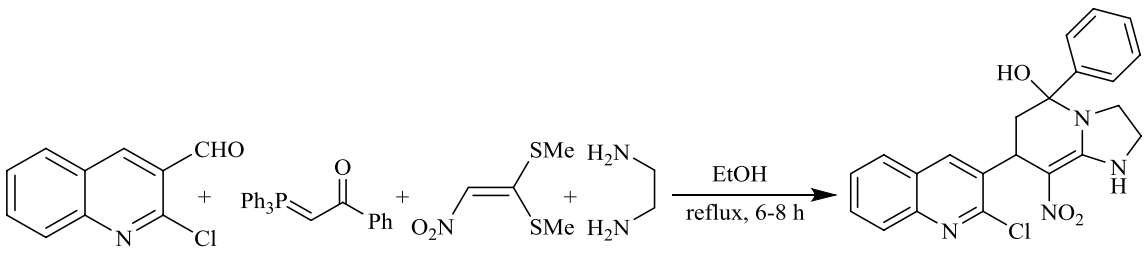
In summary, we have developed a metal and catalyst-free synthesis of various [1,8]naphthyridin-1-phenyl-1-ethanone derivatives, based on a novel four-component reaction. This new protocol provides a diverse collection of naphthyridine derivatives with excellent yields by simply heating a mixture of 2-chloroquinoline-3-carbaldehyde,

Table 2 Synthesis of 2-(1-alkyl-3-nitro-2-(phenylamino)-1,4-dihydrobenzo[*b*][1,8]naphthyridin-4-yl)-1-phenylethanone **5**



1 2 3' 4 5

Entry	Amine **2**	Product **3**	Yield (%)
1	 **4d**	 **5e**	88
2	 **2e**	 **5f**	85
3	 **2f**	 **3g**	89



1 2 3 4g 6

Scheme 2 Synthesis of 7-(2-chloroquinoline-3-yl)-8-nitro-5-phenyl-1,2,3,5,6,7-hexahydroimidazo[1,2-a]pyridine-5-ol (**6**)

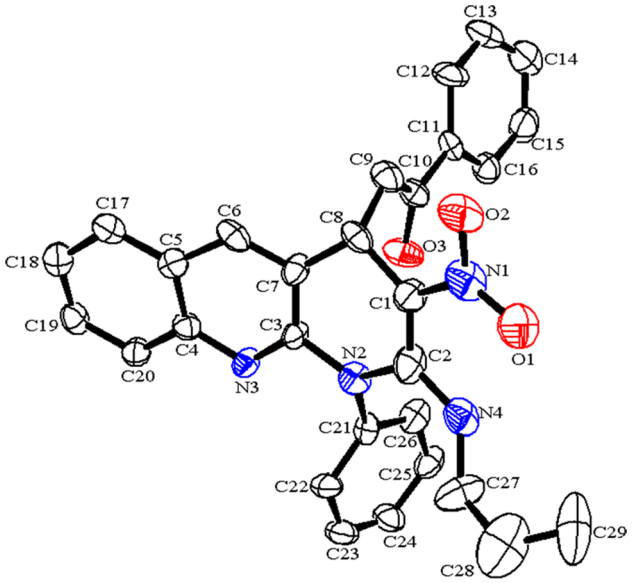
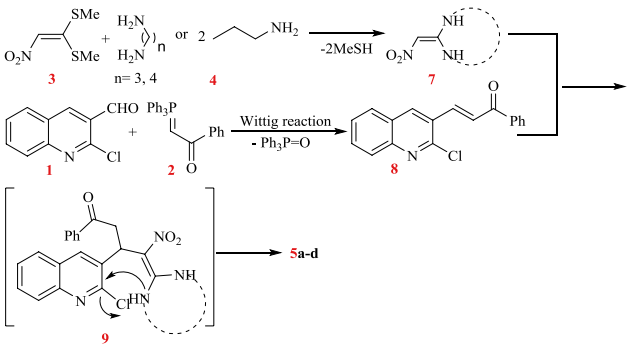
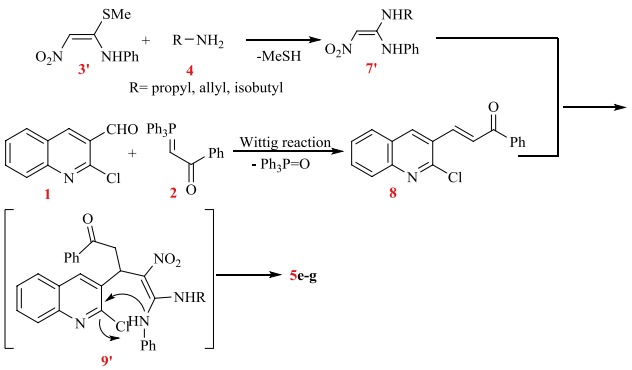


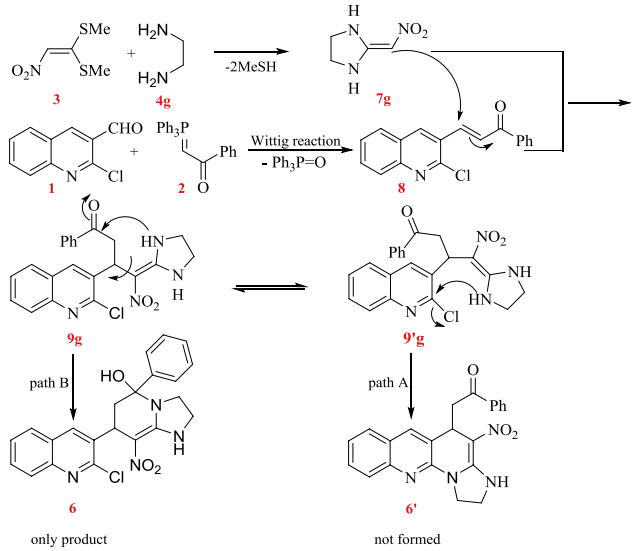
Fig. 1 ORTEP diagram of **5e**



Scheme 3 Mechanistic rationale for the synthesis of **5a-d**



Scheme 4 Mechanistic rationale for the synthesis of **5e-g**



Scheme 5 Mechanistic rationale for the synthesis of compound **6**

1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one, 1,1-bis(methylthio)-2-nitroethylene or ketene *N,S*-acetals, and aliphatic amine or diamines in EtOH, without any catalyst and base at reflux conditions.

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