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ORIGINAL PAPER

Efficient access to pyrido[1,2-*a*]pyrimidines and imidazo[1,2-*a*]pyridines through Knoevenagel reaction/aza–ene addition/intramolecular cyclization

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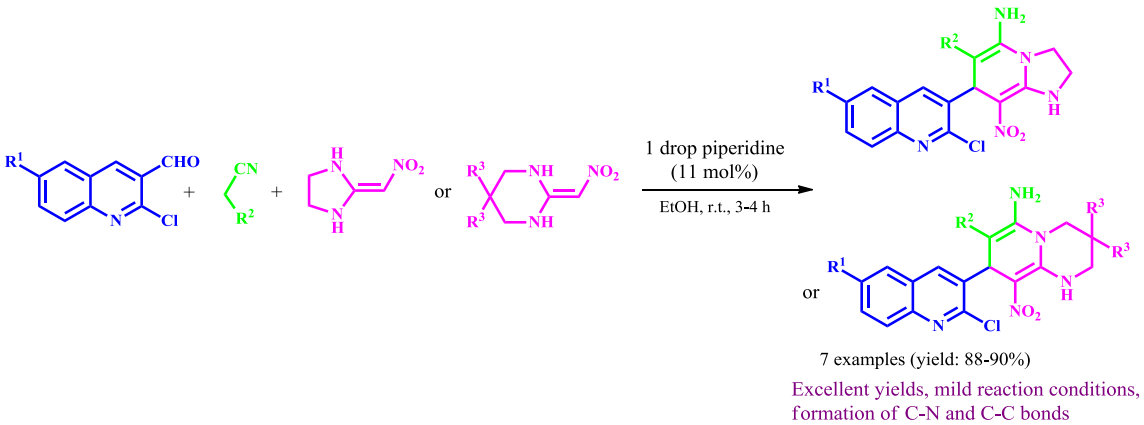
Abstract

An expeditious metal-free heteroannulation reaction for pyrido[1,2-*a*]pyrimidines/imidazo[1,2-*a*]pyridines was developed in green solvent under mild reaction conditions by using three-component reaction of 2-chloroquinoline-3-carbaldehyde, malononitrile and nitroketen aminals, which obtained from the reaction between 1,1-*bis*(methylthio)-2-nitroethylene and diamines in green solvent under EtOH reflux conditions. This one-pot strategy is very simple and occurs in two steps. The present sequence is visualized as an environmentally benign process with excellent purity and high yields.

Graphic abstract

An efficient, useful and general procedure for the synthesis of pyrido[1,2-*a*]pyrimidines/imidazo[1,2-*a*]pyridines via a one-pot three-component reaction of 2-chloroquinoline-3-carbaldehyde, malononitrile/ethyl 2-cyanoacetate and nitroketen aminals 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.



Keywords 2-Chloroquinoline-3-carbaldehyde · Malononitrile · 1,1-*bis*(methylthio)-2-nitroethylene · Imidazo[1,2-*a*]pyridines · Pyrido[1,2-*a*]pyrimidines

Introduction

Synthesis of bridgehead nitrogen fused heterocyclic compounds [1–3] is important as they have a lead role in medicinal chemistry due to their wide range of pharmacological activities. Among bridgehead nitrogen fused heterocycles, pyrido[1,2-*a*]pyrimidines and imidazo[1,2-*a*]pyridines are

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prevalent heterocycles in the medicinal chemistry [4–8]. Imidazo[1,2-*a*]pyridine scaffold exhibits a remarkably wide range of biological activities, such as antitumoral [5, 6, 9, 10], anti-inflammatory [11, 12], antiviral [13–16], antiulcer [4], antiprotozoal [17–19], antifungal [20], inhibitors of cyclin-dependent kinase [7, 21, 22], inhibitors of gastric acid secretion [23] and so on.

Also, pyridopyrimidine scaffolds are associated with a broad spectrum of biological properties such as antiallergic, antipsychotic, analgesic and antiasthmatic [24].

On the other hand, quinoline-based molecules are a significant class of *N*-heterocyclic products which display a library of bioactivities including bactericidal [25], anti-inflammatory [26], antitumor [27], anti-HIV [28], analgesic [29], anticancer [30] and antihypertensive [31]. When these units are fused into a single molecule, the potential activity of the created molecule is predicted to be increased. Traditional syntheses of polycyclic products bearing nitrogen atoms are time-consuming and expensive. Their syntheses produce a lot of waste, as well. This is a crucial difficulty for the expansion of this library of biologically active products. Therefore, there is a need to develop new, sustainable and efficient synthetic routes for the preparation of such compounds. To address this, polycyclic organic compounds have been constructed through one-pot multi-component reactions.

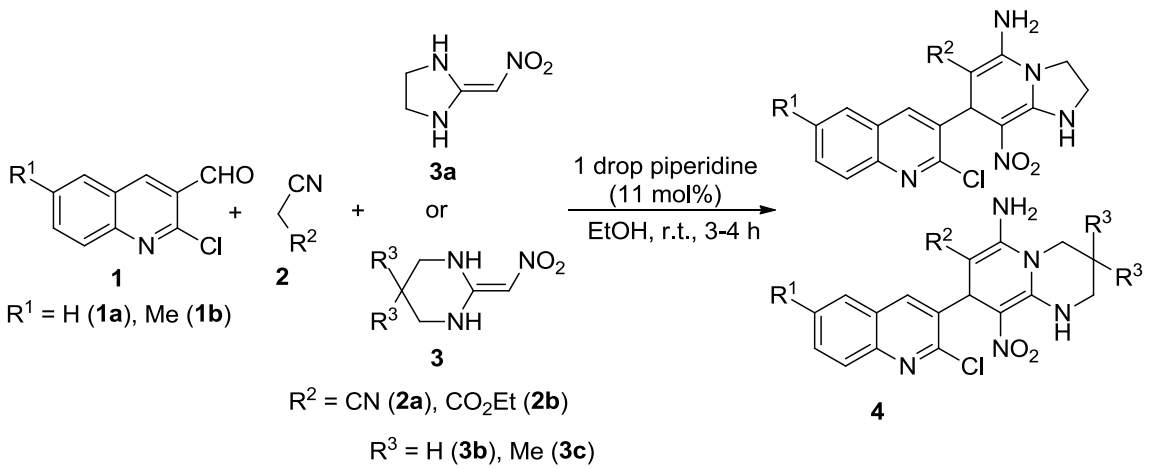
Multi-component reactions (MCRs) [32, 33] are the most influential and powerful chemical tools for accessing new complex products and have been widely used for the drug discovery process [34–36].

In this context, the goal of the present study includes the synthesis of highly functionalized pyrido[1,2-*a*]pyrimidines and imidazo[1,2-*a*]pyridines containing quinoline moiety. Continuing our studies directed toward the efficient and straightforward synthesis of biologically active molecules containing quinoline ring system through multi-component reactions [37–40], we carried out the synthesis of these molecules via MCRs of 2-chloroquinoline-3-carbaldehyde, malononitrile, 1,1-*bis*(methylthio)-2-nitroethylene and diamines in the presence of piperidine and EtOH as solvent (Scheme 1). The present methodology for the synthesis of these compounds offered several advantages such as simple procedure, using EtOH as a green and eco-friendly solvent, excellent yields, no need to the purification of the products and broad substrate scope.

Experimental section

Melting points measured on an Electrothermal 9100 apparatus. IR spectra were recorded as KBr pellets on a NICOLET FT-IR 100 spectrometer. Nuclear magnetic resonance spectra (^{1}H, ^{13}C) were recorded on 300 MHz NMR spectrometers. All NMR spectra at room temperature were determined in DMSO-d_6. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Elemental analyses for C, H and N performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. All chemicals were purchased from Merck or Aldrich and were used without further purification.

General Procedure for the Synthesis of Compound 4a–g 2-Chloroquinoline-3-carbaldehyde (1 mmol), malononitrile or ethyl 2-cyanoacetate (1 mmol) and piperidine (1 drop: 0.0093 g, 0.109 mmol, 11 mol%) were stirred in



Scheme 1 Synthesis of pyrido[1,2-*a*]pyrimidines and imidazo[1,2-*a*]pyridines **4**

ethanol at room temperature for 1 h to obtain Knoevenagel condensation compounds containing quinoline scaffold. Simultaneously, in another pot, nitroketen aminals were prepared through the reaction of aliphatic diamines (1 mmol) and 1,1-*bis*(methylthio)-2-nitroethylene (1 mmol) at reflux conditions for 3 h. After completion of the reactions (monitored by TLC), the solutions were mixed and stirred for 2–3 h to achieve pyrido[1,2-*a*]pyrimidines or imidazo[1,2-*a*] pyridines **4** depending on the diamine used for the reaction.

5-Amino-7-(2-chloroquinolin-3-yl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carbonitrile (4a) Yellow powder, dec. = 280–282 °C, 0.33 g, yield: 90%. IR (KBr) (ν_{max}, cm^{-1}): 3338 and 3189(NH_2), 2186 (CN), 1650 and 1466 (Ar), 1590 and 1336 (NO_2). Anal. calcd. for $C_{17}H_{13}ClN_6O_2$ (368.78): C, 55.37; H, 3.55; N, 22.79%. Found C, 55.34; H, 3.59; N, 22.77%. MS (EI, 70 eV): *m/z* (%): 367.9 (M^+-1, 2), 367.1 (M^+-2, 1), 366 (M^+-3, 3), 331 (31), 330 (11), 260 (21), 230 (12), 218 (10), 204 (15), 203 (13), 202 (11), 189 (12), 180 (13), 179 (10), 177.9 (14), 177.1 (35), 165 (17), 164 (11), 159 (25), 157.8 (13), 153 (18), 152 (18), 150.9 (13), 150 (14), 139.9 (15), 139 (12), 132 (17), 130 (21), 129 (13), 127 (13), 115 (10), 103.9 (16), 103 (15), 102 (19), 101 (12), 97 (16), 96 (100), 95 (15), 91 (15), 89 (11), 85 (12), 83 (12), 81 (12), 77.9 (14), 77 (25), 71 (15), 70 (18), 69 (48), 68 (26), 67 (14), 66 (17), 63 (15), 60 (12), 57 (30), 56 (15), 55 (36), 54 (20), 53 (13), 51.9 (14), 51 (13). ^{1}H NMR (300.13 MHz, DMSO-d_6): 3.86 (2H, t, $^3J_{HH}$ = 8.1 Hz, CH_2NH), 4.06 (2H, t, $^3J_{HH}$ = 8.4 Hz, CH_2N), 5.25 (1H, s, CH), 6.62 (2H, s, NH_2), 7.61 (1H, t, $^3J_{HH}$ = 7.5 Hz, CH^6 of quinoline), 7.76 (1H, t, $^3J_{HH}$ = 7.2 Hz, CH^7 of quinoline), 7.90 (1H, d, $^3J_{HH}$ = 8.3 Hz, CH^5 of quinoline), 8.01 (1H, d, $^3J_{HH}$ = 8.0 Hz, CH^8 of quinoline), 8.36 (1H, s, CH^4 of quinoline), 9.62 (1H, s, NH). ^{13}C NMR (75.46 MHz, DMSO-d_6): 40.0 (CH), 43.4 (CH_2–NH), 44.6 (CH_2–N), 57.0 (*C*–CN), 104.9 (C–NO_2), 120.4 (CN), 127.2 (C^{4a} of quinoline and C^6 of quinoline), 127.4 (C^5 of quinoline), 127.4 (C^7 of quinoline), 127.6 (C^8 of quinoline), 130.4 (C^4 of quinoline), 134.5 (C^3 of quinoline), 145.9 (C–NH_2), 149.4 (C^{8a} of quinoline), 149.8 (C^2 of quinoline), 151.8 (NH–C–N).

Ethyl 5-amino-7-(2-chloroquinolin-3-yl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylate (4b) Dark yellow powder, dec. = 198–200 °C, 0.37 g, yield: 90%. IR (KBr) (ν_{max}, cm^{-1}): 3424 (NH_2), 1633 (C=O), 1574 and 1351 (NO_2), 1412 (Ar), 1276 (C–N). Anal. calcd. for $C_{19}H_{18}ClN_5O_4$ (415.83): C, 54.88; H, 4.36; N, 16.84%. Found C, 54.81; H, 4.39; N, 16.88%. MS (EI, 70 eV): *m/z* (%): 413 (M^+-2, 1), 382 (3), 368 (3), 341 (11), 313 (10), 85 (69), 84.15 (91), 84 (17), 83 (42), 82 (10), 81 (12), 73 (10), 71 (17), 70 (22), 69 (24), 64 (35), 63 (12), 62 (100), 61 (10), 58 (29), 57 (78), 56 (80), 55 (24), 51 (12). ^{1}H NMR (300.13 MHz, DMSO-d_6): 1.45 (3H, t, $^3J_{HH}$ = 6.3 Hz, CH_3), 2.96 (2H, t, $^3J_{HH}$ = 8.1 Hz, CH_2NH), 3.78 (2H, t, $^3J_{HH}$ = 8.4 Hz, CH_2N), 3.90 (2H, q, $^3J_{HH}$ = 6.3 Hz, CH_2O), 5.30 (1H, s, CH), 7.55 (1H, t, $^3J_{HH}$ = 6.9 Hz, CH^6 of quinoline), 7.71 (1H, t, $^3J_{HH}$ = 6.2 Hz, CH^7 of quinoline), 7.89 (1H, d, $^3J_{HH}$ = 7.9 Hz, CH^5 of quinoline), 7.97 (1H, d, $^3J_{HH}$ = 7.2 Hz, CH^8 of quinoline), 8.24 (1H, s, CH^4 of quinoline), 8.31 (1H, s, NH), 8.74 (1H, bs, NH_2). ^{13}C NMR (75.46 MHz, DMSO-d_6): 14.3 (CH_3), 40.6 (CH), 43.1 (CH_2NH), 43.3 (CH_2N), 58.4 (CH_2O), 77.0 (*C*-CO_2Et), 105.8 (C–NO_2), 126.9 (C^{4a} of quinoline), 127.3 (C^6 of quinoline), 127.5 (C^5 of quinoline), 127.6 (C^7 of quinoline), 129.9 (C^8 of quinoline), 130.0 (C^4 of quinoline), 137.0 (C^3 of quinoline), 145.7 (C–NH_2), 150.0 (C^{8a} of quinoline), 151.7 (C^2 of quinoline), 153.9 (N–C–NH), 160.2 (C=O).

6-Amino-8-(2-chloroquinolin-3-yl)-9-nitro-1,3,4,8-tetrahydro-2*H*-pyrido[1,2-*a*]pyrimidine-7-carbonitrile (4c) Yellow powder, dec. = 267 °C, 0.34 g, yield: 88%. IR (KBr) (ν_{max}, cm^{-1}): 3398 and 3350 (NH_2), 2178 (CN), 1660, 1629 and 1494 (Ar), 1500 and 1441 (NO_2). Anal. calcd. for $C_{18}H_{15}ClN_6O_2$ (382.80): C, 56.48; H, 3.95; N, 21.95%. Found C, 56.40; H, 3.99; N, 21.99%. MS (EI, 70 eV): *m/z* (%): 382 (M^+, 3), 381 (M^+-1, 4), 380 (M^+-2, 23), 346 (22), 345 (100), 305 (11), 300 (11), 280 (20), 260 (12), 239 (13), 235 (11), 220 (14), 204 (18), 177 (21), 110 (10), 66 (25). ^{1}H NMR (300.13 MHz, DMSO-d_6): 2.05–2.12 (2H, m, CH_2), 3.63–3.86 (4H, m, CH_2–N and CH_2NH), 5.27 (1H, s, CH), 6.52 (2H, s, NH_2), 7.61 (1H, t, $^3J_{HH}$ = 7.8 Hz, CH^6 of quinoline), 7.76 (1H, t, $^3J_{HH}$ = 7.0 Hz, CH^7 of quinoline), 7.92 (1H, d, $^3J_{HH}$ = 8.4 Hz, CH^5 of quinoline), 8.02 (1H, d, $^3J_{HH}$ = 7.9 Hz, CH^8 of quinoline), 8.25 (1H, s, CH^4 of quinoline), 11.71 (1H, s, NH). ^{13}C NMR (75.46 MHz, DMSO-d_6): 19.5 (CH_2), 38.1 (CH), 38.4 (CH_2NH), 43.2 (CH_2N), 56.1 (*C*–CN), 107.1 (C–NO_2), 120.2 (CN), 127.2 (C^{4a} of quinoline), 127.3 (C^6 of quinoline), 127.4 (C^5 of quinoline), 127.8 (C^7 of quinoline), 130.5 (C^8 of quinoline), 135.8 (C^4 of quinoline), 137.7 (C^3 of quinoline), 145.9 (C–NH_2), 149.3 (C^{8a} of quinoline), 150.7 (C^2 of quinoline), 151.4 (N–C–NH).

Ethyl 6-amino-8-(2-chloroquinolin-3-yl)-9-nitro-1,3,4,8-tetrahydro-2*H*-pyrido[1,2-*a*]pyrimidine-7-carbonitrile (4d) Yellow powder, dec. = 288 °C, 0.39 g, yield: 90%. IR (KBr) (ν_{max}, cm^{-1}): 3356 (NH_2), 1668 (C=O), 1641 and 1481 (Ar), 1562 and 1347 (NO_2). Anal. calcd. for $C_{20}H_{20}ClN_5O_4$ (429.86): C, 55.88; H, 4.69; N, 16.29%. Found C, 55.89; H, 4.67; N, 16.27%. MS (EI, 70 eV): *m/z* (%): 431 (M^++2, 19), 430 (M^++1, 13), 429 (M^+, 53), 412 (10), 401 (16), 400 (11), 399 (46), 385 (28), 384 (50), 383 (81), 382 (83), 381 (14), 376 (22), 347 (12), 340 (16), 339 (33), 338 (45), 337 (74), 320 (8), 319 (22), 311 (11), 310 (17), 309 (13), 304 (23), 302 (15), 301 (45), 291 (26), 275 (26), 274 (14), 273 (28), 267 (37), 247 (13), 245

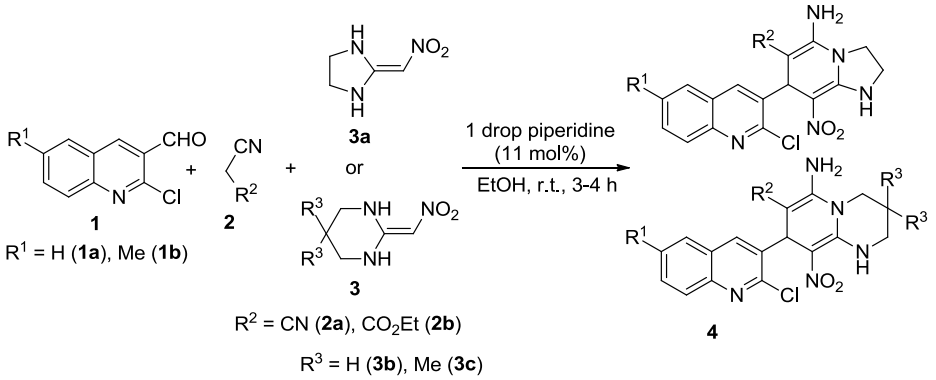
(12), 223 (20), 221 (53), 220 (31), 218 (11), 193 (16), 192 (11), 185 (100), 179 (18), 178 (11), 177 (17), 166 (17), 152 (13), 151 (12), 120 (11). ^{1}H NMR (300.13 MHz, DMSO-d_6): 1.02 (3H, t, $^{3}J_{HH}$ = 7.0 Hz, CH_3), 1.90–2.00 (1H, m, CH_2), 2.12–2.23 (1H, m, CH_2), 3.33–3.40 (1H, m, CH_2NH), 3.50–3.70 (1H, m, CH_2NH), 3.70–3.90 (2H, m, CH_2–N), 3.91 (2H, q, $^{3}J_{HH}$ = 7.0 Hz, OCH_2CH_3), 5.44 (1H, s, CH), 7.59 (1H, t, $^{3}J_{HH}$ = 7.1 Hz, CH^6 of quinoline), 7.72 (1H, t, $^{3}J_{HH}$ = 7.8 Hz, CH^7 of quinoline), 7.90 (1H, d, $^{3}J_{HH}$ = 8.5 Hz, CH^5 of quinoline), 7.94 (2H, s, NH_2), 8.04 (1H, d, $^{3}J_{HH}$ = 7.6 Hz, CH^8 of quinoline), 8.30 (1H, s, CH^4 of quinoline), 11.78 (1H, s, NH). ^{13}C NMR (75.46 MHz, DMSO-d_6): 14.3 (CH_3), 19.7 (CH_2), 37.9 (CH), 38.1 (CH_2–NH), 42.9 (CH_2–N), 58.8 (OCH_2-CH_3), 77.0 (C–C=O), 108.0 (C–NO_2), 126.7 (C^{4a} of quinoline), 126.9 (C^6 of quinoline), 127.2 (C^5 of quinoline), 127.7 (C^7 of quinoline), 130.1 (C^8 of quinoline), 135.3 (C^4 of quinoline), 141.2 (C^3 of quinoline), 145.5 (C–NH_2), 149.4 (C^{8a} of quinoline), 150.6 (C^2 of quinoline), 152.8 (N–C–NH), 168.2 (C=O).

6-Amino-8-(2-chloroquinolin-3-yl)-3,3-dimethyl-9-nitro-1,3,4,8-tetrahydro-2*H*-pyrido[1,2-*a*]pyrimidine-7-carbonitrile (4e) Yellow powder, dec. = 234 °C, 0.36 g, yield: 89%. IR (KBr) (ν_{max}, cm^{-1}): 3422 and 3347 (NH_2), 2180 (CN), 1661, 1626 and 1499 (Ar), 1590 and 1341 (NO_2). Anal. calcd. for $C_{20}H_{19}ClN_6O_2$ (410.86): C, 58.47; H, 4.66; N, 20.45%. Found C, 58.45; H, 4.63; N, 20.49%. MS (EI, 70 eV): *m/z* (%): 410 (M^+, 2), 409 (M^+-1, 2), 408 (M^+-2, 5), 373 (20), 204 (14), 200 (14), 189 (16), 179 (10), 178 (11), 177 (26), 176 (11), 165 (12), 153 (12), 152 (16), 151 (11), 150 (14), 140 (14), 139 (10), 138 (20), 127 (10), 105 (13), 102 (13), 101 (13), 99 (10), 97 (12), 95 (11), 89 (11), 85 (11), 84 (30), 83 (14), 82 (12), 81 (13), 77 (33), 76 (18), 75 (18), 74 (10), 71 (15), 70 (17), 69 (50), 68 (19), 67 (22), 66 (68), 65 (16), 64 (14), 63 (21), 62 (12), 57 (42), 56 (50), 55 (100), 54 (18), 53 (32), 52 (16), 51 (27). ^{1}H NMR (300.13 MHz, DMSO-d_6): 1.07 (3H, s, CH_3), 1.11 (3H, s, CH_3), 3.30 (2H, AB quartet, $^{2}J_{HH}$ = 12.7 Hz, CH_2–NH), 3.57 (2H, AB quartet, $^{2}J_{HH}$ = 12.2 Hz, CH_2N), 5.26 (1H, s, CH), 6.53 (2H, s, NH_2), 7.62 (1H, t, $^{3}J_{HH}$ = 7.4 Hz, CH^6 of quinoline), 7.77 (1H, t, $^{3}J_{HH}$ = 7.1 Hz, CH^7 of quinoline), 7.92 (1H, d, $^{3}J_{HH}$ = 8.5 Hz, CH^5 of quinoline), 7.95 (1H, d, $^{3}J_{HH}$ = 8.0 Hz, CH^8 of quinoline), 8.19 (1H, s, CH^4 of quinoline), 11.72 (1H, s, NH). ^{13}C NMR (75.46 MHz, DMSO-d_6): 23.1 (CH_3), 23.7 (CH_3), 27.1 (CMe_2), 38.5 (CH), 49.1 (CH_2NH), 52.9 (CH_2N), 58.9 (*C*–CN), 106.9 (C–NO_2), 120.2 (CN), 127.1 (C^{4a} of quinoline), 127.3 (C^6 of quinoline), 127.4 (C^5 of quinoline), 127.6 (C^7 of quinoline), 130.5 (C^8 of quinoline), 135.4 (C^4 of quinoline), 137.9 (C^3 of quinoline), 145.9 (C–NH_2), 149.1 (C^{8a} of quinoline), 149.8 (C^2 of quinoline), 151.3 (N–C–NH).

6-Amino-8-(2-chloro-6-methylquinolin-3-yl)-3,3-dimethyl-9-nitro-1,3,4,8-tetrahydro-2*H*-pyrido[1,2-*a*]pyrimidine-7-carbonitrile (4f) Yellow. powder, dec. = 258 °C, 0.37 g, yield: 88%. IR (KBr) (ν_{max}, cm^{-1}): 3398 and 3328 (NH_2), 3203 (NH), 2184 (CN), 1659 and 1627 (Ar), 1492 and 1344 (NO_2), 1111 (C–N). Anal. calcd. for $C_{21}H_{21}ClN_6O_2$ (424.88): C, 59.36; H, 4.98; N, 19.78%. Found C, 59.39; H, 4.97; N, 19.76%. MS (EI, 70 eV): *m/z* (%): 424 (M^+, 8), 422 (M^+-2, 7), 389 (13), 388 (27), 387 (100), 380 (12), 379 (17), 378 (41), 377 (39), 373 (12), 372 (41), 371 (24), 364 (19), 363 (13), 362 (60), 361 (38), 357 (18), 356 (21), 343 (12), 342 (22), 334 (15), 332 (8), 331 (31), 326 (12), 321 (26), 319 (12), 303 (12), 302 (27), 301 (14), 300 (21), 286 (17), 276 (6), 274 (34), 273 (29), 259 (26), 258 (19), 257 (16), 248 (26), 244 (15), 232 (14), 231 (18), 230 (29), 229 (11), 228 (12), 217 (14), 204 (12), 203 (16), 202 (24), 201 (13), 191 (19), 189 (14), 176 (15), 164 (21), 146 (19), 138 (35). ^{1}H NMR (300.13 MHz, DMSO-d_6): 1.07 (3H, s, Me), 1.11 (3H, s, Me), 2.47 (3H, s, Me), 3.30 (2H, AB quartet, $^{2}J_{HH}$ = 12.7 Hz, CH_2NH), 3.57 (2H, AB quartet, $^{2}J_{HH}$ = 11.8 Hz, CH_2N), 5.23 (1H, s, CH), 6.52 (2H, s, NH_2), 7.60 (1H, d, $^{3}J_{HH}$ = 8.0 Hz, CH^7 of quinoline), 7.70 (1H, s, CH^5 of quinoline), 7.80 (1H, d, $^{3}J_{HH}$ = 8.2 Hz, CH^8 of quinoline), 8.06 (1H, s, CH^4 of quinoline), 11.70 (1H, s, NH). ^{13}C NMR (75.46 MHz, DMSO-d_6): 21.0 (Me), 23.1 (Me), 23.7 (Me), 27.1 (CMe_2), 38.4 (CH), 49.1 (CH_2N), 52.8 (CH_2NH), 59.0 (*C*–CN), 106.9 (C–NO_2), 120.2 (CN), 126.2 (C^5 of quinoline), 127.1 (C^{4a} of quinoline and C^7 of quinoline), 132.6 (C^8 of quinoline), 135.3 (C^4 of quinoline), 136.9 (C^6 of quinoline), 137.1 (C^3 of quinoline), 144.5 (C–NH_2), 148.2 (C^{8a} of quinoline), 149.8 (C^2 of quinoline), 151.3 (N–C–NH).

Ethyl 6-amino-8-(2-chloroquinolin-3-yl)-3,3-dimethyl-9-nitro-1,3,4,8-tetrahydro-2*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate (4g) Yellow powder, dec. = 268 °C, 0.41 g, yield: 90%. IR (KBr) (ν_{max}, cm^{-1}): 3366 (NH_2), 1646 (C=O), 1600 and 1478 (Ar), 1559 and 1342 (NO_2). Anal. calcd. for $C_{22}H_{24}ClN_5O_4$ (457.91): C, 57.70; H, 5.28; N, 15.29%. Found C, 57.78; H, 5.24; N, 15.25%. MS (EI, 70 eV): *m/z* (%): 457 (M^+, 8), 411 (15), 374 (13), 366 (10), 365 (12), 319 (19), 309 (10), 308 (13), 291 (12), 286 (9), 280 (12), 263 (12), 249 (11), 248 (17), 247 (11), 224 (17), 223 (100), 195 (17), 194 (6), 193 (12), 180 (11), 179 (16), 177 (24), 166 (11), 152 (22), 151 (10), 125 (14), 68 (13), 55 (12). ^{1}H NMR (300.13 MHz, DMSO-d_6): 1.00 (3H, t, $^{3}J_{HH}$ = 6.3 Hz, CH_3CH_2), 1.12 (6H, s, 2Me), 3.30 (2H, AB quartet, $^{2}J_{HH}$ = 12.7 Hz, CH_2–NH), 3.62 (2H, AB quartet, $^{2}J_{HH}$ = 11.8 Hz, CH_2N), 3.90 (2H, q, $^{3}J_{HH}$ = 6.3 Hz, CH_2O), 5.47 (1H, s, CH), 7.59 (1H, t, $^{3}J_{HH}$ = 6.9 Hz, CH^6 of quinoline), 7.72 (1H, t, $^{3}J_{HH}$ = 6.2 Hz, CH^7 of quinoline), 7.86 (1H, d, $^{3}J_{HH}$ = 7.9 Hz, CH^5 of quinoline), 7.96 (1H, d, $^{3}J_{HH}$ = 7.2 Hz, CH^8 of quinoline), 7.97 (2H, s, NH_2), 8.24

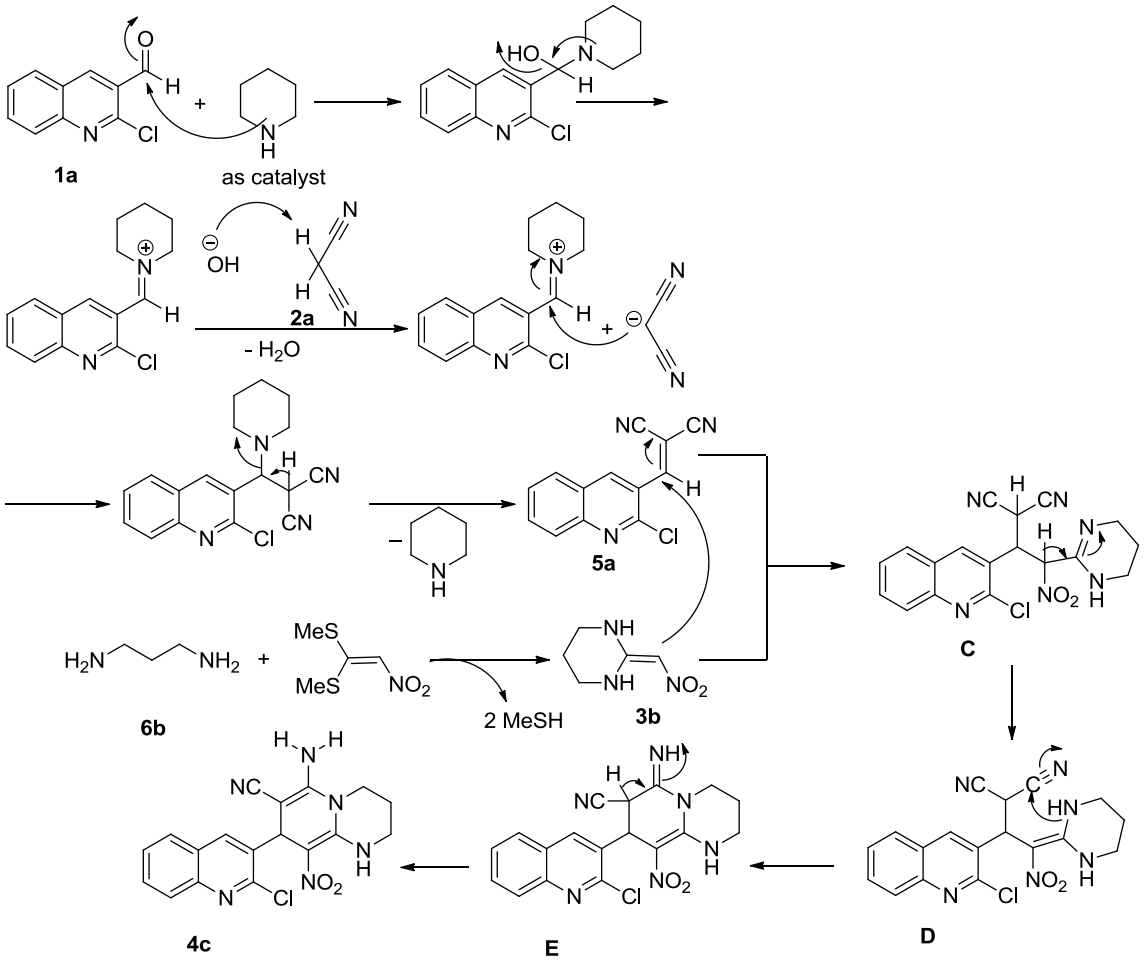
Table 1 Diversity of the products of the reaction



Entry	**1**, R^1	**2**, R^2	nitro ketene aminal **3**	Product **4**	Yield (%)[a]
1	**1a**, H	**2a**, CN	**3a**	**4a**	90
2	**1a**, H	**2b**, CO_2Et	**3a**	**4b**	90
3	**1a**, H	**2a**, CN	**3b**	**4c**	88
4	**1a**, H	**2b**, CO_2Et	**3b**	**4d**	90
5	**1a**, H	**2a**, CN	**3c**	**4e**	89
6	**1b**, Me	**2a**, CN	**3c**	**4f**	88
7	**1a**, H	**2b**, CO_2Et	**3c**	**4g**	90

2-Chloroquinoline-3-carbaldehyde (1 mmol), malononitrile or ethyl 2-cyanoacetate (1 mmol) and piperidine (1 drop: 0.0093 g, 0.109 mmol, 11 mol%) were stirred in ethanol at room temperature for 1 h to obtain Knoevenagel condensation compounds containing quinoline scaffold. Nitroketen aminals **3** were prepared through the reaction of aliphatic diamines (1 mmol) and 1,1-*bis*(methylthio)-2-nitroethylene (1 mmol) at EtOH reflux conditions for 3 h. The solutions were mixed and stirred for 2–3 h to achieve product **4**

[a]Isolated yield



Scheme 2 A plausible mechanism for the synthesis of pyrido[1,2-*a*]pyrimidines **4c**

(1H, s, CH^4 of quinoline), 11.75 (1H, s, NH). ^{13}C NMR (75.46 MHz, DMSO-d_6): 14.2 (CH_3CH_2O), 22.9 (Me), 24.1 (Me), 27.3 (CMe_2), 37.7 (CH), 48.7 (CH_2NH), 52.7 (CH_2N), 58.8 (CH_2O), 77.4 (*C*-CO_2Et), 108.3 (C–NO_2), 126.7 (CH^6 of quinoline), 127.0 (C^{4a} of quinoline), 127.2 (CH^5 of quinoline), 127.5 (CH^7 of quinoline), 130.1 (CH^8 of quinoline), 135.7 (C^4 of quinoline), 140.7 (C^3 of quinoline), 145.5 (C–NH_2), 149.4 (C^{8a} of quinoline), 149.6 (C^2 of quinoline), 152.9 (N–C–NH), 168.2 (C=O).

Results and discussion

Initially, Knoevenagel condensation compounds containing quinoline scaffold **5** and nitroketen aminals **3** were prepared according to the literature [41, 42]. Briefly, 2-chloroquinoline-3-carbaldehyde **1** and malononitrile **2a** or ethyl 2-cyanoacetate **2b** in the presence of one drop piperidine were stirred in ethanol at room temperature for 1 h to obtain Knoevenagel condensation compounds containing quinoline scaffold **5**. Simultaneously, nitroketen aminals **3** were prepared through the reaction of aliphatic diamines **6** and 1,1-*bis*(methylthio)-2-nitroethylene at reflux conditions for 3 h. After completion of the reactions (monitored by TLC), the solutions were mixed and stirred for 2–3 h to achieve pyrido[1,2-*a*]pyrimidines or imidazo[1,2-*a*]pyridines **4** depending on the diamine used for the reaction (Scheme 1).

Then, the precipitated products were separated by simple filtration and washed with ethanol. The pure products were achieved as yellow solids in excellent yields.

A variety of starting materials including 2-chloroquinoline-3-carbaldehydes, malononitrile/ethyl 2-cyanoacetate and three kinds of diamines were tested (Table 1). Notably, all the reactions proceeded cleanly under mild conditions to produce the corresponding products in excellent yields and no undesirable side products were detected. All the products were easily isolated simply by filtration and washing with ethanol.

The chemical structures of the products **4a–g** were deduced from their IR, mass, ^{1}H NMR, ^{13}C NMR and

elemental analyses. For example, the ^{1}H NMR spectrum of **4c** exhibited two multiplet peaks identified as three methylene groups at $\delta = 2.05–2.12$ (–CH_2–) and 3.63–3.86 (CH_2–NH and CH_2–N), a singlet at $\delta = 5.27$ is related to the CH of tetrahydropyridine ring, a broad singlet at $\delta = 6.52$ is related to the NH_2 group, 5 peaks at $\delta = 7.61–8.25$ are related to the aromatic hydrogens of quinoline ring, and a singlet at $\delta = 11.71$ is related to the NH group. The ^{1}H decoupled ^{13}C NMR spectrum of **4c** showed 18 distinct resonances in agreement with the proposed structure.

To the best of our knowledge, this new protocol provides the first example of synthesis of pyrido[1,2-*a*]pyrimidines and imidazo[1,2-*a*]pyridines **4** using a three-component reaction. More importantly, the reactions proceeded very cleanly at room temperature in the presence of piperidine as a catalyst. A rational mechanism for the probable sequence of events is given in Scheme 2. In the first step, the condensation of an active hydrogen compound **2** with 2-chloroquinoline-3-carbaldehyde **1** was performed efficiently in the presence of a basic catalyst to afford Knoevenagel condensation compounds containing quinoline scaffold **5**. The active hydrogen compounds **2** contain an active C–H bond which can be deprotonated in the presence of a basic catalyst. On the other hand, nitroketen aminal **3b** was formed through the nucleophilic addition of diamine **6b** to 1,1-*bis*(methylthio)-2-nitroethylene. Then, nitroketen aminal **3b** was reacted with Knoevenagel condensation compound **5** via aza–ene addition reaction forming the adduct (**C**). Intermediate (**C**) is changed to Intermediate (**D**) via imine–enamine tautomerization. Then, nucleophilic addition of amine group to the cyano moiety provides intermediate **E** after a successive intramolecular cyclization. Finally, an imine–enamine tautomerization provides corresponding pyrido[1,2-*a*]pyrimidines **4**.

Conclusions

In summary, a novel and efficient approach to synthesize pyrido[1,2-*a*]pyrimidines and imidazo[1,2-*a*]pyridines through Knoevenagel reaction/aza–ene addition/intramolecular cyclization under mild reaction conditions has been developed. The use of toxic transition metals was completely avoided in this procedure. All products were achieved in very good yields, and no column chromatography was needed. There was no need to purify the intermediates, as well.

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