Efficient synthesis of 3,4-dihydro-1*H*-quinoxalin-2-ones and 1*H*-quinolin-2-ones and evaluation of their anti-bacterial activity

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Economical and environmentally friendly syntheses of three 3,4-dihydro-1*H*-quinoxalin-2-ones and six 1*H*-quinolin-2-ones have been developed by a 1:1 reaction of *o*-, *m*-, or *p*-phenylenediamine with dialkyl acetylenedicarboxylates under solvent-free conditions. Some of the products were antibacterial towards both Gram positive and Gram negative microorganisms.

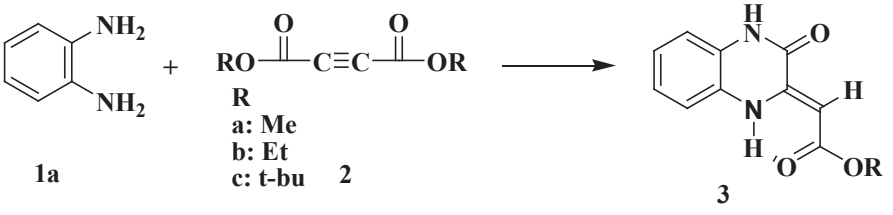
Keywords: phenylenediamines, 3,4-dihydro-1*H*-quinoxalin-2-ones, 1*H*-quinolin-2-ones, dialkyl acetylenedicarboxylates, solvent-free synthesis

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis.[1] Solvent-free and one-pot multi-component condensations are powerful green chemical technology procedures from both economical and synthetic points of view and may be the instrument to perform a near-ideal synthesis.[2–4] Due to the growing concern over the influence of the organic solvent on the environment as well as on the human body, organic reactions without the use of conventional organic solvents have attracted the attention of synthetic organic chemists. Although a number of modern solvents, such as fluorous media, ionic liquids and water have been extensively studied, not using a solvent at all would be the best option. Development of solvent-free organic reactions is thus gaining prominence.[5,6]

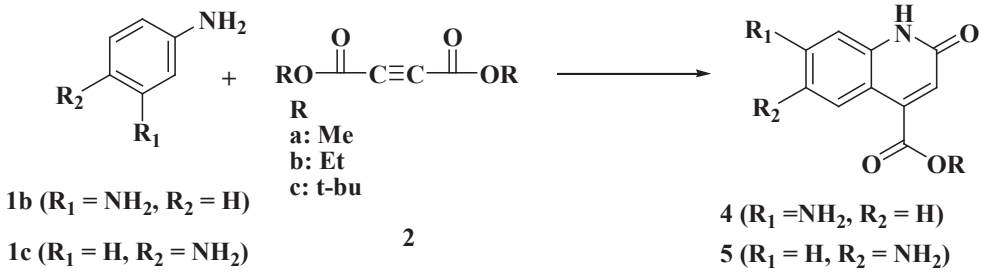
Heterocyclic compounds containing nitrogen heteroatoms are common in nature, and derivatives feature in many pharmaceuticals as well as agrochemicals.[7,8] The presence of a nitrogen heterocyclic nucleus in the framework of various pharmacologically active compounds with antimalarial, antitumour, anthelmintic, antibacterial, antiasthmatic, and antiplatelet activities continue to justify their synthesis.[9–11] Due to these useful pharmacophoric properties, they have been extensively studied.[12] In view of the emerging importance of *N*-heterocyclic compounds[13–15] and our general interest in solvent-less chemical process,[13–15] we envisioned expediting the synthesis of quinoxaline and quinoline derivatives from the reaction of phenylenediamines, and dialkylacetylene dicarboxylates under catalyst- and solvent-free conditions. All the synthesised compounds have been evaluated for their antibacterial activity towards two Gram positive and two Gram negative bacteria.

Results and discussion

We report here an efficient and rapid method for the preparation of 3,4-dihydro-1*H*-quinoxalin-2-ones and 1*H*-quinolin-2-ones that involves grinding of *o*-, *m*-, or *p*-phenylenediamine and three dialkyl acetylenedicarboxylates using a pestle and mortar (Schemes 1 and 2). This solvent-free approach requires only a few minutes of reaction time. This type of reaction is expected



Scheme 1 Reaction between *o*-phenylenediamine **1a** and dialkyl acetylenedicarboxylates **3**.



Scheme 2 Reaction between *m*- and *p*-phenylenediamine **1b**,**c** and dialkyl acetylenedicarboxylates **3**.

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to be the most economical method since neither catalyst nor solvent is used. The products were characterised by their IR, ^{1}H and ^{13}C NMR spectra along with their elemental analyses.

The wholly symmetrical isomers, *o*- and *p*-phenylenediamine, as expected, yielded a single product. Thus, a 1 : 1 reaction of *o*-phenylenediamine **1a** with dimethyl, diethyl or di-*tert*-butyl acetylenedicarboxylate **2a**–**c** yielded (*Z*)-alkyl 2-(3-oxo-3,4-dihydroquinoxalin-2(1*H*)-ylidene)acetates **3a**–**c** in an excellent yield (94–97%) (Scheme 1). Also, a 1 : 1 reaction of *p*-phenylenediamine **1c** and dimethyl, diethyl or di-t-butyl acetylenedicarboxylates **2a**–**c** afforded alkyl 6-amino-2-oxo-1,2-dihydroquinoline-4-carboxylates **4a**–**c** in a very good yield (85–89%) (Scheme 2). In theory, a 1 : 1 reaction between *m*-phenylenediamine **1b** and dialkyl acetylenedicarboxylates **2a**–**c** could have afforded two products **A** and **B** (Scheme 3), but again, only one product, alkyl 7-amino-2-oxo-1,2-dihydroquinoline-4-carboxylate **5a**–**c** was formed, again in an excellent yield (91–96%) (Scheme 2).

Regioselectivity

The regioselectivity observed leading to structure **A** is probably due to steric hindrance which attacks at the 2-position of *m*-phenylenediamine **1b**. NMR spectroscopy demonstrated that the major product was indeed compound **A**.

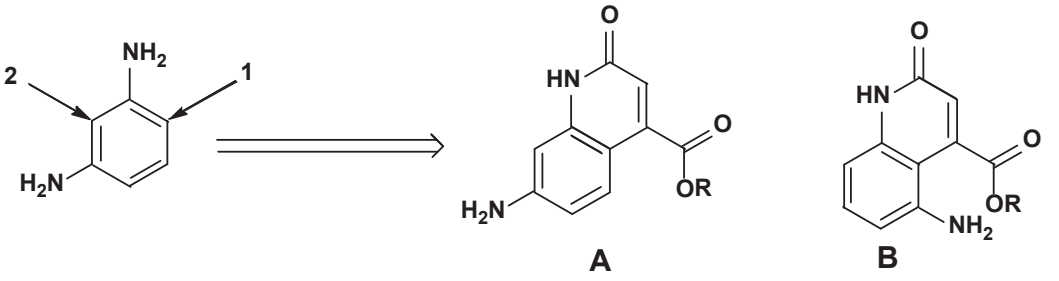
Thus, in the simple ^{1}H NMR spectrum of compound **4b**, the vicinal protons of the benzene ring form an AX system featuring a doublet at 7.59 (J = 8.8 Hz) and a doublet of doublets at 6.24 (J = 8.8, 2 Hz), the latter also coupling with the proton located between the N atoms which appears as a doublet at 6.22 (J = 2 Hz). This pattern of peaks is only possible for compound **4b** and not the other isomer **B** which has four vicinal aromatic protons.

The formation of products **3a**–**c** can be rationalised by a Michael-type addition, with initial formation of intermediate **5** followed by cyclisation to **7** and elimination of RO^{-} products **3a**–**c** (Scheme 4).

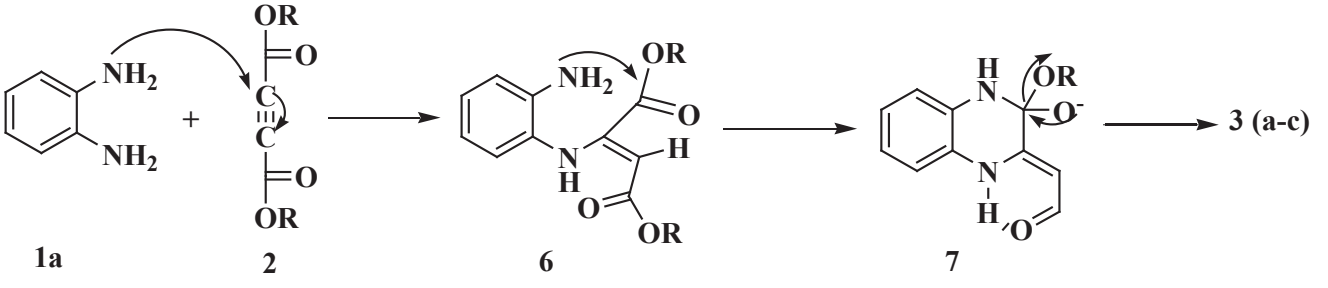
We believe that the formation of the quinoline derivatives **4a**–**c**, **5a**–**c** proceeds by the pathways illustrated in Scheme 5.

m- or *p*-Phenylenediamine **1b**,**c** reacts with dialkyl acetylenedicarboxylate **2** to generate intermediate **8** which cyclises to afford the intermediate **9** which can undergo intramolecular nucleophilic substitution to afford the corresponding quinolines **4a**–**c** and **5a**–**c**.

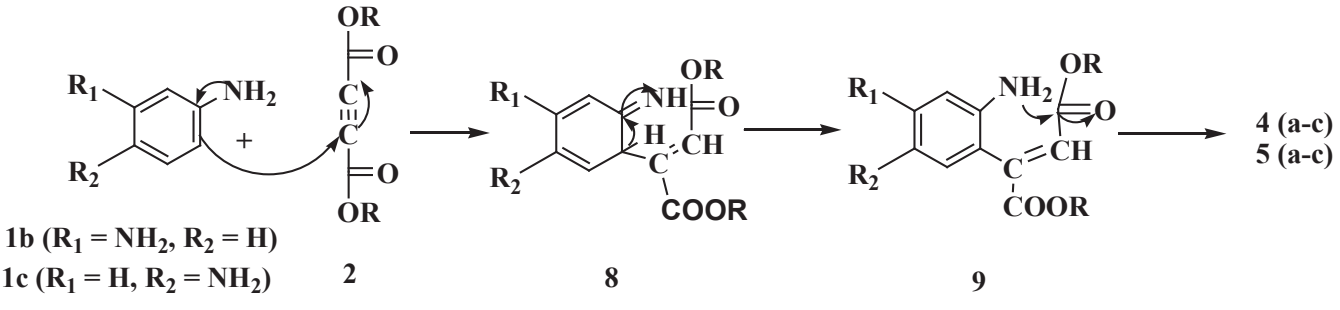
Finally, all synthesised compounds were screened for antimicrobial activity against two Gram-positive bacteria (*Pseudomonas aeruginosa* PTCC 1077*, Escherichia coli* PTCC 1330) and two Gram-negative bacteria (*Staphylococcus aureus* PTCC 1133, *Bacillus cereus* PTCC 1015) and their activity



Scheme 3 The two possible products of reaction from *m*-phenylenediamine **1b** and dialkyl acetylenedicarboxylates **2**.



Scheme 4 Suggested mechanism for the synthesis of (*Z*)-alkyl 2-(3-oxo-3,4-dihydroquinoxalin-2(1*H*)-ylidene)acetate **3a**–**c**.



Scheme 5 Suggested mechanism for the synthesis of 1*H*-quinolin-2-ones **4a**–**c** and **5a**–**c**.

compared with gentamycin and ampicillin as reference drugs for Gram-negative and Gram-positive bacteria, respectively. The minimum inhibitory concentration (MIC) of the synthesised compounds and reference drugs were determined by the microdilution method.[16] As can be seen from Table 1, good antibacterial activity was observed for **5c** against all species of Gram-positive and Gram-negative bacteria, and compounds **3a**–**c** showed good antibacterial activity against two Gram-positive bacteria. Indeed, **3a** was found to have the same activity against *S. aureus* as ampicillin, and compounds **3b**–**c**, **4f** and **5c** have the same activity against *B. cereus* as ampicillin.

Table 1 Evaluation of the antibacterial activity of 3,4-dihydro-1*H*-quinoxalin-2-ones **3a**–**c** and 1*H*-quinolin-2-ones **4a**–**c**, **5a**–**c** using the microdilution method[16]

Compound	MIC/mg mL^{-1}			
	P. aeruginosa	*q*	*B. cereus*	*S. aureus*
3a	>100	>50	>25	>3.125
3b	>100	>50	>12.5	>6.5
3c	>50	>25	>12.5	>6.5
4a	>50	>100	>100	>50
4b	>25	>100	>50	>25
4c	>50	>50	>100	>50
5a	>25	>50	>25	>25
5b	>25	>12.5	>50	>25
5c	>12.5	>6.25	>12.5	>6.25
Ampicillin[b]	–	–	12.5>	3.125>
Gentamycin[c]	6.25>	6.25>	–	–

[a]Examined bacteria: *Staphylococcus aureus* (PTCC 1133), *Bacillus cereus* (PTCC 1015), *Pseudomonas aeruginosa* (PTCC 1077) and *Escherichia coli* (PTCC 1330).

[b]Reference drug for Gram-positive bacteria.

[c]Reference drug for Gram-negative bacteria.

Conclusions

We have described a simple, one-pot, two-component reaction between dialkyl acetylene dicarboxylates and all three isomers of phenylenediamine which gave very good to excellent yields of medicinally important nitrogen heterocycles. The advantages of the reported method are readily available starting materials, short reaction time, simple work-up, neutral reaction conditions and high yields. Nearly all the compounds exhibited moderate to good antibacterial activity against all four of the tested strains.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser. IR spectra were recorded on a Shimadzu IR-470 spectrometer. NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer (^{1}H NMR at 500 Hz, ^{13}C NMR at 125 Hz) in $CDCl_3$ or in $CDCl_3$/DMSO-d_6 using TMS as internal standard. Chemical shifts (d) are given in ppm and coupling constants (*J*) in Hz. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Synthesis of compounds **3a**–**c**, **4a**–**c**, **5a**–**c***; general procedure*

A mixture of *o*-, *m*- or *p*-phenylenediamine (2 mmol) and dialkyl acetylenedicarboxylate (2 mmol) was crushed for 2 min using a pestle and mortar. The reaction takes place almost immediately. The mixture was treated with dichloromethane (5 mL), filtered and the filtrate evaporated to give the product. In the case of the products **5a**–**c**, the residue was purified by silica gel column chromatography using hexane and ethyl acetate as the eluents.

(Z)-Methyl 2-(3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidene)acetate (**3a):** Yellow powder, 0.212 g, yield 97%; m.p. 225–227 °C; IR (ν_{max}): 3211, 3164, 3046, 3010, 2945, 2874, 2783, 1688, 1647, 1619, 1443 cm^{-1}; ^{1}H NMR ($CDCl_3$): 3.80 (s, 3H, O*CH*$_3$), 5.86 (s, 1H, C=C–H), 6.96–7.27 (m, 4H, arom), 8.88 (s, 1H, NH exchangeable with D_2O), 11.14 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$+DMSO (3%)): 51.2, 84.9, 114.7, 116.1, 122.8, 124.1, 125.5, 125.6, 144.6, 156.9, 171.3. Anal. calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84; found: C, 60.45; H, 4.78; N, 12.69%.

(Z)-Ethyl 2-(3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidene)acetate (**3b):** Yellow powder, 0.220 g, yield 94%; m.p. 218 °C; IR (ν_{max}): 3210, 3164, 3046, 3010, 2878, 2781, 1687, 1646, 1619, 1463; ^{1}H NMR ($CDCl_3$): 1.14 (t, *J*=7.1, 3H, *CH*$_3$), 4.03 (q, *J*=7.1, 2H, *O–CH*$_2$), 5.55 (s,1H, C=C–H), 6.79–6.94 (m, 4H, arom), 10.98 (s, 1H, NH exchangeable with D_2O), 11.17 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$+DMSO (3%)): δ 14.7, 59.9, 85.3, 114.7, 116.1, 122.7, 124.0, 125.5, 125.6, 144.5, 156.9, 171.0. Anal. calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06; found: C, 61.55; H, 5.40; N, 12.14%.

(Z)-tert-butyl 2-(3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidene) acetate (**3c):** Yellow powder, 0.452 g, yield 96%; m.p. 187–190 °C; IR (ν_{max}): 3434, 3257, 3162, 3044, 3008, 2969, 2923, 2880, 2785, 2736, 1683, 1643, 1625, 1480; ^{1}H NMR ($CDCl_3$): 1.58 (s, 9H, C(*CH*$_3$)$_3$), 5.82 (s, 1H, C=C–H), 7.04–7.30 (m, 4H, arom) 10.34 (s, 1H, NH exchangeable with D_2O), 11.152 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$+DMSO (5%)): 28.5, 79.7, 86.9, 114.5, 115.8, 122.2, 123.7, 125.3, 125.4, 143.7, 156.7, 170.4. Anal. calcd for $C_{14}H_{16}O_3N_2$: C, 64.60; H, 6.20; N, 10.76; found: C, 64.77; H, 6.23; N, 10.83%.

Methyl 7-amino-2-oxo-1,2-dihydroquinoline-4-carboxylate (**4a):** Yellow powder, 0.198 g, yield 90%; m.p. 201–203 °C; IR (ν_{max}): 3447, 3339, 3218, 3218, 3097, 2998, 2957, 1725, 1669, 1623, 1474; ^{1}H NMR ($CDCl_3$): 3.43 (s, 3H, OCH_3), 4.77 (s, 2H, NH_2 exchangeable with D_2O), 6.09 (s, 1H, C=C–H), 6.02–7.34 (m, ^3J=8.8, ^4J=2.0, 3H, arom), 11.08 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (DMSO): 53.5, 97.4, 107.0, 112.2, 116.9, 127.6, 141.0, 142.6, 152.5, 162.4, 167.1. Anal. calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84; found: C, 60.46; H, 4.59; N, 12.89%.

Ethyl 7-amino-2-oxo-1,2-dihydroquinoline-4-carboxylate (**4b):** Yellow powder, 0.232 g, yield 91%; m.p. 208 °C; IR (ν_{max}): 3427, 3367, 3323, 3046, 3215, 3087, 2981, 2927, 2866, 1709, 1672, 1623, 1471; ^{1}H NMR ($CDCl_3$): 1.09 (t, *J*=7.1, 3H, CH_3), 4.07 (q, *J*=7.1, 2H, O*CH*$_2$), 4.62, 6.36 (s,1H, C=C–H), 6.22–7.60 (m, ^3J=8.8,^4J=2.1, 3H, arom), δ 11.23 (s,1H, NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$): 14.8, 62.3, 97.4, 107.0, 112.2, 116.6, 127.5, 141.3, 142.6, 152.5, 162.5, 166.6. Anal. calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06; found: C, 61.96; H, 5.11; N, 12.18%.

tert-Butyl 7-amino-2-oxo-1,2-dihydroquinoline-4-carboxylate (**4c**): Yellow powder, 0.210 g, yield 86%; m.p. 202–204 °C; IR (ν_{max}): 3467, 3365, 3296, 3197, 3093, 3027, 2925, 2860, 1725, 1669, 1622, 1475; ^{1}H NMR ($CDCl_3$): 1.53 (s, 9H, C(*CH*$_3$)$_3$), 4.56 (2H, NH_2 exchangeable with D_2O), 6.30 (s, 1H, C=C–H), 6.39–7.06 (m, 3H, ^3J=8, ^4J=1.3, arom), 11.53 (s, 1H, NH exchangeable with D_2O)·^{13}C NMR (DMSO): 28.0, 80.4, 96.9, 108.4, 112.3, 116.2, 128.1, 141.1, 142.6, 152.0, 162.8, 167.9. Anal. calcd for $C_{14}H_{16}O_2N_2$: C, 64.60; H, 6.20; N, 10.76; found: C, 64.48; H, 6.11; N, 10.69%.

Methyl 6-amino-2-oxo-1,2-dihydroquinoline-4-carboxylate (**5a):** Yellow oil, (0.189 g, yield 85%; IR (ν_{max}): 3445, 3367, 3323, 3215, 3110, 3000, 2875, 1721, 1642, 1600, 1495; ^{1}H NMR ($CDCl_3$): 3.56 (s, 2H, NH_2 exchangeable with D_2O), 4.25 (s, 3H, O*CH*$_3$), 6.61–6.81 (m, 4H, ^3J=8.4 arom, C=C*H*,), 9.56 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$): 53.5 (OCH_3), 98.8 (C=C–H), δ 109.5, 115.0, 121.2, 127.6, 140.0, 141.0, 153.6, 163.4, 166.1. Anal. calcd for $C_{11}H_{10}N_2O_3$:C, 60.55; H, 4.62; N, 12.84;; found: C, 60.45; H, 4.52; N, 12.75%.

Ethyl 6-amino-2-oxo-1,2-dihydroquinoline-4-carboxylate (**5b):** Yellow oil, 0.20 g, yield 86%; IR (ν_{max}): 3432, 3383, 3351, 3215, 3087, 2957, 2925, 2860, 1725, 1669, 1623, 147; ^{1}H NMR ($CDCl_3$): 1.157 (t, *J*=7.1, 3H, CH_3), 3.65 (s, 2H, NH_2 exchangeable with D_2O), 4.16 (q, *J*=7.1, 2H, OCH_2) 6.61–6.87 (m, 4H, ^3J=8.4, arom, C=C*H*) 9.56 (s,1H, NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$): 14.7, 59.9, 98.3, 109.5,

115.0, 121.7, 127.5, 140.0, 141.00 153.0, 163.8, 166.8. Anal. calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06; found: C, 62.22; H, 5.11; N, 12.26%.

tert-Butyl 6-amino-2-oxo-1,2-dihydroquinoline-4-carboxylate **(5c):** Yellow oil, 0.21 g, yield 89%; IR (ν_{max}): 3444, 3383, 3281, 2972, 2931, 1737, 1659, 1607, 1475; ^{1}H NMR ($CDCl_3$): 1.53 (s, 9H, C)$CH_3)_3$), 3.61(s, 2H, NH_2 exchangeable with D_2O), 6.63–6.90 (m, 4H, ^3J=8.5, C=C–H, arom), 9.49 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$): δ 28.0, 80.1, 97.5, 109.3, 115.8, 121.3, 127.0, 141.0,142.6, 153.292, 164.0, 167.2. Anal. calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76; found: C, 64.74; H, 6.10; N, 10.59%.

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