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# Experimental and computational evidences for KO*t*-Bu-promoted synthesis of oxopyrazino[1,2-*a*]indoles

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A novel series of oxopyrazino[1,2-*a*]indole derivatives were prepared *via* two-step synthetic procedure including Ugi-four-component reaction followed by the transition metal-free intramolecular hydroamination of Ugi adducts in the presence of KO*t*-Bu in DMF at room temperature. Density functional theory (DFT) calculations were also performed to elucidate the mechanistic aspects of the reaction.

## 1. Introduction

Natural and non-natural *N*-heterocyclic compounds constitute the most important part of biologically active structures having crucial roles in medicinal chemistry. Among the vast heterocyclic structural space, indole moieties have occupied a position of major importance and known as anti-inflammatory,[1] antibacterial,[2] antidepressants,[3] and analgesics.[4] Structurally remarkable alkaloids possessing significant biological properties[5] such as anti-tumor,[6] anti-depression,[7] cytotoxic and anti-microbial[8] activities consist of indole skeleton. At this juncture, fused indole derivatives have attracted significant interest over the past decades owing to a wide variety of pharmacological properties.[9] Among various fused indole, pyrazino[1,2-*a*]indole scaffold absorbed our attention since they act as melatoninergic ligands,[10] histamine H3 receptor,[11] inhibitors of geranylgeranyltransferase I,[12] selective imidazoline $I_2$ receptor ligands,[13] 5-$HT_{2C}$ and dual 5-$HT_{2C}$/5-$HT_6$ receptor agonists.[14,15] Also they have depicted antifungal,[16] antiproliferative,[17] antibacterial,[18] and anticancer[19] activities. In spite of the efficacy of pyrazino[1,2-*a*]indoles, literature lacks adequate reports for their synthesis.[20-24] Hence, development of novel, efficient, easy, and rapid synthetic approaches is still a common research area. Intramolecular cyclization of several 2-carbonyl-1-propargylindoles in the presence of ammonia was developed by Abbiati et al.[20] The reaction was investigated in various heating conditions in the presence of different metal catalysts. Also, in the study reported by Laliberté et al.[21] pyrazino[1,2-*a*]indole derivatives were prepared through palladium-catalyzed double allylic alkylation of indole-2-hydroxamates. Katritzky et al.[24] studied three-step synthesis of 10-methyl-1,2,3,4-tetrahydropyrazino-[1,2-*a*]indoles starting from 2-(3-methyl-1*H*-indol-1-yl)ethylamine. It reacted with 2-chloroethan-1-amine, and then benzotriazole/formaldehyde. Finally, the corresponding derivatives were obtained *via* various nucleophilic substitutions using allylsilanes, silyl enol ether, and Grignard reagents.

The intramolecular and intermolecular addition of an amine to an unsaturated carbon-carbon bond known as hydroamination reaction, has been powerful and versatile tool for the direct formation of C-N bond affording N-containing heterocycles.[25-27] Comprehensive literature review related to hydroamination reactions showed that they usually need to be catalyzed by metals.[25-27] Consequently, developing an efficient protocol in the absence of complex and transition metal-free catalysts would be worthwhile from the synthetic organic point of view.

In view of our interest in the synthesis of novel heterocyclic compounds[28] using isocyanide-based multicomponent reactions (IMCRs) as well as hydroamination reaction, we have developed an efficient, simple, and rapid synthesis of oxopyrazino[1,2-*a*]indole derivatives **2** (Scheme 1).

## 2. Experimental

### 2.1. Reagents

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on Bruker FT-500 and 400 using TMS as an internal standard. The IR spectra were obtained on a Nicolet Magna FTIR 550 spectrophotometer (in KBr). Mass spectra were documented on an Agilent Technology (HP) mass spectrometer operating at an

ionization potential of 70 eV. The elemental analysis was performed on an Elementar Analysensystem. GmbH Vario EL CHNS mode.

## 2.2. Synthesis of Ugi adduct 1; General Procedure

A mixture of indole-2-carboxylic acid **3** (1 mmol), aromatic aldehyde **4** (1 mmol), propargylamine **5** (1 mmol), and isocyanide **6** (1.2 mmol) were dissolved in methanol (10 mL) and stirred at room temperature for 8 h. After completion of reaction, the precipitated Ugi product **1** was filtered off, washed with aqueous methanolic solution (20%), dried, and used for further reactions.

***N*-(2-(Cyclohexylamino)-2-oxo-1-phenylethyl)-*N*-(prop-2-yn-1-yl)-1*H*-indole-2-carboxamide (1a)**

Yield: 94%; colourless crystals; mp 202-204 °C; IR (KBr): 3288, 3420, 3280, 2150, 1675, 1655 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta_H$ = 1.16-1.94 (m, 10H, Cyclohexyl), 2.19 (s, 1H, ≡CH), 3.86-3.90 (m, 1H, NCH), 4.38-4.54 (m, 2H, $CH_2$), 6.12-6.13 (m, 2H, CH, $H_3$), 7.13 (td, $J$ = 8.0, 1.0 Hz, 1H, $H_6$), 7.29 (td, $J$ = 8.0, 1.0 Hz, 1H, $H_5$), 7.38-7.44 (m, 7H, Ph, $H_4$, $H_7$), 7.67 (d, $J$ = 8.0 Hz, 1H, NH), 9.48 (s, 1H, NH). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta_C$ = 24.8, 25.5, 32.8, 38.2, 48.8, 64.8, 72.8, 79.3, 106.6, 111.7, 120.7, 122.4, 125.1, 127.1, 128.8, 128.9, 129.8, 130.3, 134.3, 136.0, 163.9, 168.3. Anal. Calcd for $C_{26}H_{27}N_3O_2$: C, 75.52; H, 6.58; N, 10.16; Found: C, 75.41; H, 6.71; N, 10.29.

***N*-(2-(Cyclohexylamino)-2-oxo-1-(*p*-tolyl)ethyl)-*N*-(prop-2-yn-1-yl)-1*H*-indole-2-carboxamide (1b)**

Yield: 90%; colourless crystals; mp 222-224 °C; IR (KBr): 3423, 3275, 2145, 1670, 1648 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta_H$ = 1.08-1.95 (m, 10H, Cyclohexyl), 2.17 (s, 1H, ≡CH), 2.36 (s, 3H, $CH_3$), 3.87-3.90 (m, 1H, NCH), 4.30-4.54 (m, 2H, $CH_2$), 6.14-6.17 (m, 2H, CH, $H_3$), 7.13 (t, $J$ = 8.0 Hz, 1H, $H_6$), 7.19 (d, $J$ = 8.0 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.22-7.32 (m, 3H, $H_4$, $H_5$, $H_7$), 7.40 (d, $J$ = 8.0 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.67 (d, $J$ = 8.0 Hz, 1H, NH), 9.52 (s, 1H, NH). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta_C$ = 21.1, 24.8, 25.5, 32.8, 38.2, 48.7, 64.1, 72.8, 80.0, 106.5, 111.7, 120.6, 122.4, 125.0, 127.8, 128.6, 129.6, 129.7, 131.2, 136.0, 138.7, 163.9, 168.5. Anal. Calcd for $C_{27}H_{29}N_3O_2$: C, 75.85; H, 6.48; N, 9.83; Found: C, 76.04; H, 6.62; N, 9.98.

***N*-(2-(Cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl)-*N*-(prop-2-yn-1-yl)-1*H*-indole-2-carboxamide (1c)**

Yield: 88%; colourless crystals; mp 215-216 °C; IR (KBr): 3470, 3275, 2150, 1680, 1655 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta_H$ = 1.11-1.98 (m, 10H, Cyclohexyl), 2.18 (t, $J$ = 2.5 Hz, 1H, ≡CH), 3.82 (s, 3H, $OCH_3$), 3.84-3.89 (m, 1H, NCH), 4.36-4.50 (m, 2H, $CH_2$), 6.08-6.11 (m, 2H, CH, $H_3$), 6.91 (d, $J$ = 8.0 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.13 (t, $J$ = 8.0 Hz, 1H, $H_6$), 7.30 (td, $J$ = 8.0, 1.0 Hz, 1H, $H_5$), 7.437 (m, 3H, $H_4$, $H_{2'}$, $H_{6'}$), 7.41 (d, $J$ = 8.0 Hz, 1H, $H_7$), 7.67 (d, $J$ = 8.0 Hz, 1H, NH), 9.35 (s, 1H, NH). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta_C$ = 24.8, 25.5, 32.9, 38.2, 48.7, 55.3, 62.1, 72.7, 80.0, 106.5, 111.7, 114.3, 120.7, 122.5, 125.0, 126.2, 127.9, 128.1, 131.3, 136.0, 160.0, 163.9, 168.6. Anal. Calcd for $C_{27}H_{29}N_3O_3$: C, 73.11; H, 6.59; N, 9.47; Found: C, 73.28; H, 6.78; N, 9.67.

***N*-(1-(2-Chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl)-*N*-(prop-2-yn-1-yl)-1*H*-indole-2-carboxamide (1d)**

Yield: 90%; colourless crystals; mp 160-162 °C; IR (KBr): 3450, 3285, 2142, 1675, 1657 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta_H$ = 1.10-1.98 (m, 10H, Cyclohexyl), 2.09 (s, 1H, ≡CH), 3.89-3.92 (m, 1H, NCH), 4.52-4.56 (m, 2H, $CH_2$), 6.00 (s, 1H, CH), 6.46 (s, 1H, $H_3$), 7.13 (td, $J$ = 8.0, 1.0 Hz, 1H, $H_6$), 7.28 (td, $J$ = 8.0, 1.0 Hz, 1H, $H_5$), 7.33-7.35 (m, 3H, $H_{4'}$, $H_{5'}$, $H_{6'}$), 7.40-7.43 (m, 2H, $H_3$, $H_4$), 7.56 (d, $J$ = 7.5 Hz, 1H, $H_{3'}$), 7.67 (d, $J$ = 8.0 Hz, 1H, NH), 9.39 (s, 1H, NH). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta_C$ = 24.7, 24.8, 25.4, 32.8, 32.9, 38.2, 48.9, 61.5, 72.3, 79.3, 106.4, 111.7, 120.7, 122.5, 125.0, 127.2, 127.8, 128.4, 129.8, 130.0, 130.4, 131.0, 132.4, 136.0, 163.1, 168.1. Anal. Calcd for $C_{26}H_{26}ClN_3O_2$: C, 69.71; H, 5.85; N, 9.38; Found: C, 69.84; H, 5.68; N, 9.21.

***N*-(2-(Cyclohexylamino)-1-(4-(dimethylamino)phenyl)-2-oxoethyl)-*N*-(prop-2-yn-1-yl)-1*H*-indole-2-carboxamide (1e)**

Yield: 88%; colourless crystals; mp 190-192 °C; IR (KBr): 3425, 3275, 2151, 1670, 1650 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta_H$ = 1.06-1.96 (m, 10H, Cyclohexyl), 2.19 (t, $J$ = 2.0 Hz, 1H, ≡CH), 2.95 (s, 6H, 2 × $CH_3$), 3.88-3.91 (m, 1H, NCH), 4.38-4.46 (m, 2H, $CH_2$), 6.00-6.07 (m, 2H, CH, $H_3$), 6.70 (d, $J$ = 9.0 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.13 (td, $J$ = 8.0, 1.0 Hz, 1H, $H_6$), 7.26-7.31 (m, 4H, $H_4$, $H_5$, $H_{2'}$, $H_{6'}$), 7.41 (d, $J$ = 8.0 Hz, 1H, $H_7$), 7.67 (d, $J$ = 8.0 Hz, 1H, NH), 9.25 (s, 1H, NH). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta_C$ = 24.7, 24.8, 25.5, 32.9, 33.0, 38.1, 40.3, 48.7, 63.0, 72.4, 80.3, 106.4, 111.6, 112.4, 120.6, 121.5, 122.5, 124.0, 124.9, 127.8, 129.0, 130.9, 150.0, 163.2, 169.0. Anal. Calcd for $C_{28}H_{32}N_4O_2$: C, 73.66; H, 7.06; N, 12.27; Found: C, 73.82; H, 7.22; N, 12.41.

***N*-(2-(*tert*-Butylamino)-2-oxo-1-(*p*-tolyl)ethyl)-*N*-(prop-2-yn-1-yl)-1*H*-indole-2-carboxamide (1f)**

Yield: 90%; colourless crystals; mp 185-187 °C; IR (KBr): 3425, 3280, 2150, 1675, 1644 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta_H$ = 1.37 (s, 9H, *tert*-Butyl), 2.15 (s, 1H, ≡CH), 2.37 (s, 3H, $CH_3$), 4.48-4.53 (m, 2H, $CH_2$), 5.95-6.03 (m, 2H, CH, $H_3$), 7.13 (td, $J$ = 8.0, 1.0 Hz, 1H, $H_6$), 7.20 (d, $J$ = 8.0 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.28-7.37 (m, 4H, $H_4$, $H_5$, $H_{2'}$, $H_{6'}$), 7.42 (d, $J$ = 8.0 Hz, 1H, $H_7$), 7.67 (d, $J$ = 8.0 Hz, 1H, NH), 9.37 (s, 1H, NH). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta_C$ = 21.2, 28.7, 38.1, 52.0, 65.1, 72.6, 80.0, 106.5, 111.6, 120.6, 122.5, 125.0, 127.9, 128.6, 129.6, 129.8, 131.3, 135.9, 138.7, 163.8, 168.7. Anal. Calcd for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47; Found: C, 74.88; H, 6.60; N, 10.38.

***N*-(2-(*tert*-Butylamino)-1-(4-methoxyphenyl)-2-oxoethyl)-*N*-(prop-2-yn-1-yl)-1*H*-indole-2-carboxamide (1g)**

Yield: 85%; colourless crystals; mp 192-194 °C; IR (KBr): 3420, 3325, 2148, 1680, 1660 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta_H$ = 1.37 (s, 9H, *tert*-Butyl), 2.15 (s, 1H, ≡CH), 3.82 (s, 3H, $OCH_3$), 4.38-4.52 (m, 2H, $CH_2$), 5.95-6.04 (m, 2H, CH, $H_3$), 6.92 (d, $J$ = 8.0 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.13 (t, $J$ = 8.0 Hz, 1H, $H_6$), 7.27-7.30 (m, 2H, $H_4$, $H_5$), 7.37 (d, $J$ = 8.0 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.42 (d, $J$ = 8.0 Hz, 1H, $H_7$), 7.67 (d, $J$ = 8.0 Hz, 1H, NH), 9.45 (s, 1H, NH). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta_C$ = 28.6, 38.2, 51.9, 55.3, 65.1, 72.6, 80.1, 106.4, 111.7, 114.3, 120.6, 122.4, 125.0, 126.4, 127.8, 131.3, 135.8, 136.0, 160.0, 163.8, 168.8. Anal. Calcd for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06; Found: C, 71.83; H, 6.41; N, 10.27.

***N*-(2-(*tert*-Butylamino)-1-(2-fluorophenyl)-2-oxoethyl)-*N*-(prop-2-yn-1-yl)-1*H*-indole-2-carboxamide (1h)**

Yield: 85%; colourless crystals; mp 170-172 °C; IR (KBr): 3420, 3325, 2150, 1682, 1652 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta_H$ = 1.40 (s, 9H, *tert*-Butyl), 2.10 (s, 1H, ≡CH), 4.49-4.52 (m, 2H, $CH_2$), 5.90 (s, 1H, CH), 6.32 (s, 1H, $H_3$), 7.08 (t, $J$ = 9.0 Hz, 1H, $H_{5'}$), 7.14 (t, $J$ = 8.0 Hz, 1H, $H_6$), 7.20-7.23 (m, 2H, $H_{4'}$, $H_{6'}$), 7.30 (t, $J$ = 8.0 Hz, 1H, $H_5$), 7.38-7.43 (m, 2H, $H_4$, $H_7$), 7.53-7.55 (m, 1H, $H_{3'}$), 7.67 (d, $J$ = 8.0 Hz, 1H, NH), 9.32 (s, 1H, NH). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta_C$ = 28.6, 38.2, 52.1, 65.1, 72.4, 79.5, 106.4, 111.7, 115.7 (d, $J_{C\text{-}F}$ = 21.2 Hz), 120.7, 122.1 (d, $J_{C\text{-}F}$ = 12.5 Hz), 122.4, 124.5, 125.0, 128.4, 128.5, 131.0, 136.0, 136.5, 162.1 (d, $J_{C\text{-}F}$ = 245.0 Hz), 164.0, 168.0. Anal. Calcd for $C_{24}H_{24}FN_3O_2$: C, 71.09; H, 5.97; N, 10.36; Found: C, 71.18; H, 6.22; N, 10.50.

***N*-(2-(tert-Butylamino)-1-(2-chlorophenyl)-2-oxoethyl)-*N*-(prop-2-yn-1-yl)-1*H*-indole-2-carboxamide (1i)**

Yield: 90%; colourless crystals; mp 122-124 °C; IR (KBr): 3425, 3324, 2148, 16875, 1651 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta_H$ = 1.41 (s, 9H, *tert*-Butyl), 2.15 (s, 1H, ≡CH), 4.49-4.53 (m, 2H, $CH_2$), 5.85 (s, 1H, CH), 6.35 (s, 1H, $H_3$), 7.13 (t, $J$ = 8.0 Hz, 1H, $H_6$), 7.29 (t, $J$ = 8.0 Hz, 1H, $H_5$), 7.20-7.23 (m, 3H, $H_{4'}$, $H_{5'}$, $H_{6'}$), 7.32-7.43 (m, 2H, $H_4$, $H_7$), 7.59 (d, $J$ = 7.5 Hz, 1H, $H_{3'}$), 7.67 (d, $J$ = 8.0 Hz, 1H, NH), 9.25 (s, 1H, NH). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta_C$ = 28.7, 38.1, 52.0, 65.1, 72.2, 80.0, 106.4, 111.6,

120.7, 122.5, 125.0, 127.3, 128.0, 130.0, 130.3, 130.9, 131.4, 132.5, 136.1, 136.4, 163.1, 168.5. Anal. Calcd for $C_{24}H_{24}ClN_3O_2$: C, 68.32; H, 5.73; N, 9.96; Found: C, 68.51; H, 5.60; N, 10.17.

## 2.3. Synthesis of oxopyrazino[1,2-*a*]indole derivatives 2; General Procedure

A mixture of Ugi product **1** (1 mmol) and potassium *tert*-butoxide (0.5 mmol) in dry DMF (7 mL) was stirred at room temperature for 5-15 min. After completion of reaction (checked by TLC), water (20 mL) was added to the reaction mixture and it was extracted with ethyl acetate (3 × 20 mL). The organic phase was dried over $Na_2SO_4$, the solvent was removed under reduced pressure, and the resulting residue was purified by column chromatography using ethyl acetate/petroleum ether = 1/3 as eluent and silica gel as stationary phase.

***N*-Cyclohexyl-2-(4-methyl-1-oxopyrazino[1,2-*a*]indol-2(1*H*)-yl)-2-phenylacetamide (2a)**

Yield: 75%; colourless crystals; mp 219-220 °C; IR (KBr): 3288, 3079, 2926, 2851, 1684, 1622, 1577 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 1.10-1.32 (m, 5H, Cyclohexyl), 1.53-1.83 (m, 5H, Cyclohexyl), 2.62 (s, 3H, $CH_3$), 3.64-3.66 (m, 1H, CH), 6.25 (s, 1H, CH), 6.69 (s, 1H, $H_3$), 7.28-7.46 (m, 8H, Ph, $H_7$, $H_8$, $H_{10}$), 7.85 (d, $J$ = 8.0 Hz, 1H, $H_9$), 8.09 (d, $J$ = 8.0 Hz, 1H, $H_6$), 8.51 (d, $J$ = 7.6 Hz, 1H, NH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta_C$ = 18.2, 24.8, 24.9, 25.6, 32.5, 32.6, 48.5, 58.5, 104.2, 111.6, 114.9, 117.4, 122.5, 122.7, 124.5, 128.3, 128.5, 128.8, 129.0, 129.4, 133.6, 136.7, 156.0, 167.1. MS: $m/z$ = 413 $[M]^{+\cdot}$. Anal. Calcd for $C_{26}H_{27}N_3O_2$: C, 75.52; H, 6.58; N, 10.16; Found: C, 75.76; H, 6.72; N, 10.28.

***N*-Cyclohexyl-2-(4-methyl-1-oxopyrazino[1,2-*a*]indol-2(1*H*)-yl)-2-(*p*-tolyl)acetamide (2b)**

Yield: 77%; colourless crystals; mp 225-227 °C; IR (KBr): 3285, 3088, 2926, 2851, 1689, 1645, 1560 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 1.12-1.30 (m, 5H, Cyclohexyl), 1.52-1.81 (m, 5H, Cyclohexyl), 2.31 (s, 3H, $CH_3$), 2.62 (s, 3H, $CH_3$), 3.62-3.64 (m, 1H, CH), 6.21 (s, 1H, CH), 6.63 (s, 1H, $H_3$), 7.20 (d, $J$ = 8.4 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.26 (d, $J$ = 8.4 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.29 (t, $J$ = 8.0 Hz, 1H, $H_8$), 7.35 (td, $J$ = 8.0, 1.6 Hz, 1H, $H_7$), 7.41 (s, 1H, $H_{10}$), 7.85 (d, $J$ = 8.0 Hz, 1H, $H_9$), 8.09 (d, $J$ = 8.0 Hz, 1H, $H_6$), 8.51 (d, $J$ = 7.6 Hz, 1H, NH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta_C$ = 18.2, 21.1, 24.8, 24.9, 25.6, 32.5, 32.6, 48.4, 58.3, 104.1, 111.6, 114.9, 117.3, 122.5, 122.7, 124.4, 128.3, 128.6, 129.0, 130.0, 133.5, 133.6, 138.2, 156.0, 167.3. MS: $m/z$ = 427 $[M]^{+\cdot}$. Anal. Calcd for $C_{27}H_{29}N_3O_2$: C, 75.85; H, 6.48; N, 9.83; Found: C, 75.70; H, 6.31; N, 9.68.

***N*-Cyclohexyl-2-(4-methoxyphenyl)-2-(4-methyl-1-oxopyrazino[1,2-*a*]indol-2(1*H*)-yl)acetamide (2c)**

Yield: 75%; colourless crystals; mp 233-235 °C; IR (KBr): 3287, 2928, 2852, 1681, 1616, 1550 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 1.09-1.30 (m, 7H, Cyclohexyl), 1.53-1.81 (m, 3H, Cyclohexyl), 2.63 (s, 3H, $CH_3$), 3.59-3.63 (m, 1H, CH), 3.77 (s, 3H, $OCH_3$), 6.20 (s, 1H, CH), 6.59 (s, 1H, $H_3$), 6.99 (d, $J$ = 8.8 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.25 (d, $J$ = 8.8 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.30 (t, $J$ = 8.0 Hz, 1H, $H_8$), 7.37 (td, $J$ = 8.0, 1.6 Hz, 1H, $H_7$), 7.40 (s, 1H, $H_{10}$), 7.85 (d, $J$ = 8.0 Hz, 1H, $H_9$), 8.09 (d, $J$ = 8.0 Hz, 1H, $H_6$), 8.51 (d, $J$ = 7.6 Hz, 1H, NH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta_C$ = 18.2, 24.8, 24.9, 25.6, 32.5, 32.6, 48.4, 55.6, 58.2, 104.1, 111.6, 114.8, 114.9, 117.2, 122.5, 122.7, 124.4, 128.2, 128.3, 128.6, 130.5, 133.6, 156.0, 159.6, 167.4. MS: $m/z$ = 443 $[M]^{+\cdot}$. Anal. Calcd for $C_{27}H_{29}N_3O_3$: C, 73.11; H, 6.59; N, 9.47; Found: C, 72.96; H, 6.37; N, 9.26.

**2-(2-Chlorophenyl)-*N*-cyclohexyl-2-(4-methyl-1-oxopyrazino[1,2-*a*]indol-2(1*H*)-yl)acetamide (2d)**

Yield: 70%; colourless crystals; mp 228-230 °C; IR (KBr): 3292, 3068, 2926, 2853, 1684, 1660, 1546 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 1.11-1.32 (m, 6H, Cyclohexyl), 1.52-1.83 (m, 4H, Cyclohexyl), 2.62 (s, 3H, $CH_3$), 3.61-3.63 (m, 1H, CH), 5.93 (s, 1H, CH), 6.59 (s, 1H, $H_3$), 7.30 (t, $J$ = 7.5 Hz, 1H, $H_8$), 7.37 (td, $J$ = 7.5, 1.2 Hz, 1H, $H_7$), 7.41 (s, 1H, $H_{10}$), 7.44-7.47 (m, 3H, $H_{4'}$, $H_{5'}$, $H_{6'}$), 7.53 (dd, $J$ = 7.0, 1.5 Hz, 1H, $H_{3'}$), 7.85 (d, $J$ = 7.5 Hz, 1H, $H_9$), 8.10 (d, $J$ = 7.5 Hz, 1H, $H_6$), 8.59 (d, $J$ = 7.6 Hz, 1H, NH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta_C$ = 18.2, 24.8, 24.9, 25.6, 32.4, 32.5, 48.6, 57.8, 104.2, 111.0, 115.0, 117.7, 122.5, 122.7, 124.5, 128.2, 128.3, 128.5, 130.5, 130.9, 131.0, 133.6, 134.0, 134.5, 155.7, 166.7. MS: $m/z$ (%) = 449 $[M+2]^{+\cdot}$ (1), 447 $[M]^{+\cdot}$ (3), 202 (42), 143 (87), 115 (34), 43 (100). Anal. Calcd for $C_{26}H_{26}ClN_3O_2$: C, 69.71; H, 5.85; N, 9.38; Found: C, 69.58; H, 5.67; N, 9.60.

***N*-Cyclohexyl-2-(4-(dimethylamino)phenyl)-2-(4-methyl-1-oxopyrazino[1,2-*a*]indol-2(1*H*)-yl)acetamide (2e)**

Yield: 75%; colourless crystals; mp 215-217 °C; IR (KBr): 3286, 229, 2852, 1679, 1619, 1552 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 1.01-1.28 (m, 6H, Cyclohexyl), 1.49-1.76 (m, 4H, Cyclohexyl), 2.62 (s, 3H, $CH_3$), 2.91 (s, 6H, 2 × $CH_3$), 3.60-3.62 (m, 1H, CH), 6.20 (s, 1H, CH), 6.52 (s, 1H, $H_3$), 6.74 (d, $J$ = 9.0 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.14 (d, $J$ = 9.0 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.29 (t, $J$ = 8.0 Hz, 1H, $H_8$), 7.36 (td, $J$ = 8.0, 1.6 Hz, 1H, $H_7$), 7.38 (s, 1H, $H_{10}$), 7.84 (d, $J$ = 8.0 Hz, 1H, $H_9$), 8.09 (d, $J$ = 8.0 Hz, 1H, $H_6$), 8.2 (s, 1H, NH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta_C$ = 18.3, 24.9, 25.0, 25.6, 32.6, 32.7, 48.0, 48.4, 58.6, 60.2, 103.8, 111.8, 112.8, 114.9, 117.0, 122.4, 122.7, 123.0, 124.3, 128.3, 128.7, 130.0, 133.5, 156.0, 155.9, 167.7. MS: $m/z$ = 456 $[M]^{+\cdot}$. Anal. Calcd for $C_{28}H_{32}N_4O_2$: C, 73.66; H, 7.06; N, 12.27; Found: C, 73.42; H, 6.87; N, 12.42.

***N*-(tert-Butyl)-2-(4-methyl-1-oxopyrazino[1,2-*a*]indol-2(1*H*)-yl)-2-(p-tolyl)acetamide (2f)**

Yield: 80%; colourless crystals; mp 231-233 °C; IR (KBr): 3296, 3067, 2962, 2920, 1683, 1616, 1550 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 1.30 (s, 9H, 3 × $CH_3$), 2.32 (s, 3H, $CH_3$), 2.62 (s, 3H, $CH_3$), 6.19 (s, 1H, CH), 6.65 (s, 1H, $H_3$), 7.21 (d, $J$ = 8.4 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.24 (d, $J$ = 8.4 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.29 (t, $J$ = 7.5 Hz, 1H, $H_8$), 7.35 (td, $J$ = 7.5, 1.2 Hz, 1H, $H_7$), 7.41 (s, 1H, $H_{10}$), 7.84 (d, $J$ = 7.5 Hz, 1H, $H_9$), 8.09 (d, $J$ = 7.5 Hz, 1H, $H_6$), 8.24 (s, 1H, NH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta_C$ = 18.2, 21.1, 28.8, 51.5, 58.3, 104.1, 111.9, 114.9, 117.1, 122.5, 122.7, 124.4, 128.3, 128.6, 129.0, 130.0, 133.6, 133.9, 138.1, 156.0, 167.7. MS: $m/z$ (%) = 401 $[M]^{+\cdot}$ (34), 301 (56), 197 (22), 154 (15), 115 (16), 57 (100), 41 (35). Anal. Calcd for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47; Found: C, 74.58; H, 6.92; N, 10.63.

***N*-(tert-Butyl)-2-(4-methoxyphenyl)-2-(4-methyl-1-oxopyrazino[1,2-*a*]indol-2(1*H*)-yl)acetamide (2g)**

Yield: 77%; colourless crystals; mp 276-277 °C; IR (KBr): 3275, 2925, 2850, 1683, 1621, 1555 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 1.30 (s, 9H, 3 × $CH_3$), 2.62 (s, 3H, $CH_3$), 3.77 (s, 3H, $OCH_3$), 6.17 (s, 1H, CH), 6.61 (s, 1H, $H_3$), 7.21 (d, $J$ = 8.4 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.24 (d, $J$ = 8.4 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.29 (t, $J$ = 7.5 Hz, 1H, $H_8$), 7.35 (td, $J$ = 7.5, 1.6 Hz, 1H, $H_7$), 7.42 (s, 1H, $H_{10}$), 7.85 (d, $J$ = 7.5 Hz, 1H, $H_9$), 8.10 (d, $J$ = 7.5 Hz, 1H, $H_6$), 8.24 (s, 1H, NH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta_C$ = 18.2, 28.8, 51.1, 55.6, 58.2, 104.0, 111.8, 114.8, 114.9, 117.1, 122.5, 122.7, 124.4, 128.3, 128.5, 128.6, 130.5, 133.6, 156.0, 159.6, 168.0. MS: $m/z$ = 417 $[M]^{+\cdot}$. Anal. Calcd for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06; Found: C, 72.14; H, 6.70; N, 9.87.

***N*-(tert-Butyl)-2-(2-fluorophenyl)-2-(4-methyl-1-oxopyrazino[1,2-*a*]indol-2(1*H*)-yl)acetamide (2h)**

Yield: 78%; colourless crystals; mp 235-236 °C; IR (KBr): 3313, 3092, 2973, 2923, 1658, 1637, 1588, 1559 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 1.31 (s, 9H, 3 × $CH_3$), 2.65 (s, 3H, $CH_3$), 6.26 (s, 1H, CH), 6.70 (s, 1H, $H_3$), 7.19 (d, $J$ = 8.0 Hz, 1H, $H_{6'}$), 7.26 (td, $J$ = 8.0, 2.0 Hz, 2H, $H_{4'}$, $H_{5'}$), 7.31 (t, $J$ = 7.5 Hz, 1H, $H_8$), 7.35 (td, $J$ = 7.5, 1.5 Hz, 1H, $H_7$), 7.49 (ddd, $J$ = 15.2, 8.0, 2.0 Hz, 1H, $H_{3'}$), 7.43 (s, 1H, $H_{10}$), 7.85 (d, $J$ = 7.5 Hz, 1H, $H_9$), 8.10 (d, $J$ = 7.5 Hz, 1H, $H_6$), 8.38 (s, 1H, NH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta_C$ = 18.1, 28.7 (d, $J_{C-F}$ = 5.3 Hz), 51.3, 58.1, 104.3, 111.6, 114.9, 115.6 (d, $J_{C-F}$ = 5.3 Hz), 115.8 (d, $J_{C-F}$ = 6.7

Hz), 117.5, 122.5, 122.7, 124.5, 125.1 (d, $J_{C-F}$ = 2.6 Hz), 128.3, 128.5, 131.4 (d, $J_{C-F}$ = 8.4 Hz), 133.7, 139.6 (d, $J_{C-F}$ = 7.3 Hz), 156.0, 162.7 (d, $J_{C-F}$ = 243.1 Hz), 167.1. MS: *m/z* (%) = 405 $[M]^{+\cdot}$ (98), 333 (20), 306 (55), 197 (47), 183 (14), 162 (17), 144 (37), 115 (18), 89 (27), 57 (100), 41 (54). Anal. Calcd for $C_{24}H_{24}FN_3O_2$: C, 71.09; H, 5.97; N, 10.36; Found: C, 70.86; H, 6.21; N, 10.17.

***N*-(tert-Butyl)-2-(2-chlorophenyl)-2-(4-methyl-1-oxopyrazino[1,2-*a*]indol-2(1*H*)-yl)acetamide (2i)**

Yield: 75%; colourless crystals; mp 248-250 °C; IR (KBr): 3336, 3056, 2956, 2927, 1681, 1624, 1548 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 1.30 (s, 9H, 3 × $CH_3$), 2.61 (s, 3H, $CH_3$), 5.91 (s, 1H, CH), 6.71 (s, 1H, $H_3$), 7.30 (t, *J* = 8.0 Hz, 1H, $H_8$), 7.35 (td, *J* = 8.0, 1.5 Hz, 1H, $H_7$), 7.43-7.55 (m, 4H, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$), 7.41 (s, 1H, $H_{10}$), 7.85 (d, *J* = 8.0 Hz, 1H, $H_9$), 8.10 (d, *J* = 8.0 Hz, 1H, $H_6$), 8.42 (s, 1H, NH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta_C$ = 18.1, 28.8, 51.3, 57.9, 104.1, 111.2, 114.9, 117.5, 122.5, 122.7, 124.5, 128.1, 128.3, 128.5, 130.6, 130.8, 130.9, 133.6, 134.2, 134.7, 155.6, 167.2. MS: *m/z* = 423 $[M+2]^{+\cdot}$, 421 $[M]^{+\cdot}$. Anal. Calcd for $C_{24}H_{24}ClN_3O_2$: C, 68.32; H, 5.73; N, 9.96; Found: C, 68.18; H, 5.84; N, 10.14.

**Computational Study**

Gaussian 09[31] was used to fully optimize all the structures involved in this study at the B3LYP level of density functional theory (DFT)[32] in DMF using the CPCM solvation model.[33] The 6-31G(d) basis set was used for all atoms.[34] Frequency analyses were performed at the same level of theory to ensure that a minimum or transition state was achieved. Transition structures were located using the Berny algorithm and intrinsic reaction coordinate (IRC)[35] calculations were used to confirm the connectivity between transition structures and minima. To further refine the energies obtained from the B3LYP/6-31G(d) calculations, we carried out single-point energy calculations for all of the structures with 6-311+G(2d,p) basis set in DMF using the CPCM solvation model at the M06 level. We have used the Gibbs free energies obtained from the M06/6-311+G(2d,p) //B3LYP/6-31G(d) calculations in DMF throughout the paper.

## 3. Results and discussion

After the introduction of novel multicomponent reactions (MCR),[29] the obtained products from isocyanide-based multicomponent reactions (IMCRs) attracted lots of attention as they could perform further condensation or cyclization reactions due to the presence of versatile functional groups.[28a,30] In this study, we focused on the Ugi adducts **1** obtained by the simultaneous reaction between indole-2-carboxylic acid **3** aromatic aldehydes **4**, propargylamine **5**, and isocyanides **6** (Scheme 1).

For the preparation of desirable starting materials **1**, four-component reaction of indole-2-carboxylic acid (1 mmol) **3**, various aromatic aldehydes **4** (1 mmol), propargylamine **5** (1 mmol), and isocyanides **6** (1.2 mmol) were conducted in methanol at room temperature in the absence of any catalysts or additives within 8 h (Scheme 1). Subsequently, the intramolecular hydroamination reaction for compound **1** leading to the formation of product **2** (Scheme 1) was comprehensively studied. For this purpose, *N*-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-*N*-(prop-2-yn-1-yl)-1*H*-indole-2-carboxamide (**1a**) was chosen as the test substrate. To obtain product **2a** in a rapid and efficient method, the effect of various conditions such as temperature, different solvents, and bases were investigated (Table 1).

Recently, we have described synthesis of novel benzo[6,7][1,4]oxazepino[4,5-*a*]quinazolinones *via* 7-*exo-dig* hydroamination of 3-substituted-2-[2-(prop-2-yn-1-yloxy)phenyl]-2,3-dihydroquinazolin-4(1*H*)-ones in the presence of potassium *tert*-butoxide (KO*t*-Bu) in DMF at 130 °C.[28d] It was revealed that KO*t*-Bu/DMF system could efficiently promote the corresponding hydroamination. The efficiency of KO*t*-Bu was previously confirmed by Polindara-Garcoía et al. in the hydroamination reaction of some Ugi adducts.[30b] Those results led us to examine the aforementioned model reaction under similar condition as well all conditions depicted in Table 1. As shown in Table 1, product **2a** was obtained in the presence of KO*t*-Bu in DMF at room temperature (Table 1, Entry 1), in very short reaction time and good yields. It was found that 0.5 equivalent amount of base was sufficient and higher amounts did not improve the yield of reaction. Also, we perceived that the model reaction was efficiently conducted at room temperature and higher temperature not only did not increase the yield of reaction but also decreased it (Table 1, Entry 3).

With these results in hand, various oxopyrazino[1,2-*a*]indole derivatives **2a-i** were synthesized using various Ugi adducts **1** (Table 2). All substrates possessing electron-rich as well as electron-poor substituents underwent intramolecular hydroamination reaction leading to the formation of the related products **2** in very short reaction time (5-15 min) and good yields (75-80%). All products were characterized using IR, NMR spectroscopy as well as mass spectrometry and all data confirmed the structures of the synthesized compounds.

As shown in Scheme 2, the intramolecular hydroamination reaction occurred through 6-*exo-dig* ring closure system followed by [1,3]-H shift to afford product **2**. It was clear that no product was obtained through 5-*endo-dig* ring closure which is probable as reported by Polindara-Garcoía et al.[30b] In the mentioned report, Ugi adducts were prepared by the reaction of aldehydes, isocyanides, carboxylic acids, and propargylamine. Then, KO*t*-Bu-mediated ring closure afforded 2,3-dihydropyrroles through 5-*endo* cycloisomerization of the later adducts. It is clear that presence of indole NH in our study played important role to change the mode of ring closure.

In continuation of our investigations to gain further understanding of probable mechanism of the reaction, density functional theory (DFT) calculations were performed. Two major pathways were investigated for the corresponding C-N bond formation catalyzed by KO*t*-Bu. In pathway A (Figure 1a), the reaction starts with the deprotonation of the indole N-H proton using $^-$O*t*-Bu followed by nucleophilic attack of the nitrogen anion on the internal C2 alkyne carbon to give vinyl anion intermediate **4m**.This intermediate is capable of re-deprotonating the alcohol formed *in situ* (HO*t*-Bu) to produce the alkene intermediate **5m**. Eventually, proton abstraction from **5m** by $^-$O*t*-Bu gives allyl anion intermediate **6m** and the final product **2m** is formed through a proton transfer from HO*t*-Bu to **6m**. In pathway B (Figure 1b), the C3 of **1m** is deprotonated by $^-$O*t*-Bu to yield allenyl anion **7m**. Internal proton transfer from the indole N-H to C1 atom of **7m** followed by attack of the nitrogen anion on the C2 atom of **8m** gives the allyl anion **6m** from which product **2m** is formed *via* the sequence **6m** → $\mathbf{TS_{6-2}}$ → **2m** (as discussed in pathway A). As the N-H deprotonation (the first step of pathway A) is calculated to proceed *via* a barrierless process,[36] the reaction is expected to initiate on the pathway A; the C3 deprotonation with $\Delta G^{\ddagger}$ = 5.3 kcal/mol (the first step of pathway B) is much less favorable than the indole N-H deprotonation. On the other hand, the reaction of **1m** with $^-$O*t*-Bu on pathway A is predicted to be irreversible due to the fact that the energy of all transition structures on this pathway ($\mathbf{TS_{3-4}}$, $\mathbf{TS_{4-5}}$, $\mathbf{TS_{5-6}}$, and $\mathbf{TS_{6-2}}$) lies below the energy of **1m**. All the transition structures of pathway A are calculated to be lower in

energy than the vital transition structures of pathway B (**$TS_{1-7}$** and **$TS_{7-8}$**). We have also investigated another alternative pathway for the 6-*exo*-*dig* ring closure process in which the alkyne terminal CH proton is deprotonated followed by the intramolecular deprotonation of NH indole group.[37] Although the alkyne terminal CH proton is acidic and no transition structure was found for its deprotonation, this pathway is not favorable at all because transition structure relating to the intramolecular NH deprotonation with a relative Gibbs energy of 13.9 kcal/mol lies above all the calculated transition structures. From these results, it can be concluded that pathway A is most likely operative for formation of product **2**.

On the basis of the calculations, reaction of **1m** → **2m** is exergonic by -47.2 kcal/mol and the rate determining step for this reaction is computed to be attack of the nitrogen anion on the internal C2 alkyne carbon (transformation **3m** → **4m**) with an activation energy of 20.5 kcal/mol. The detailed catalytic cycle of the $^{-}$O*t*-Bu-catalyzed intramolecular hydroamination reaction is summarized in Scheme 3. Striking features that emerge from the calculations are that, in this catalytic reaction, the $^{-}$O*t*-Bu catalyst is consumed and regenerated several times during the catalytic cycle (Scheme 3) and proton transfers are not likely to occur without the assistance of the conjugate acid-base pairs ($^{-}$O*t*-Bu/HO*t*-Bu). For example, the activation barrier for conversion of **4m** to **6m** in the absence of *t*BuO$^{-}$/ *t*BuOH is calculated to be as high as 41.5 kcal/mol while it reduces to 15.2 kcal/mol in the presence of the acid-base pairs.

We now turn our attention to address why the 5-*endo*-*dig* ring closure does not occur for these substrates (Scheme 2). The first step for this process is surmised to be deprotonation of the carbon bound to the phenyl group (Figure 2). Our calculations show that the activation energy for the deprotonation via **$TS_{1-9}$** (10.0 kcal/mol) is much higher in energy than that for the deprotonation of the indole N-H (Figure 1a).

The transformation **1m** + tBuO$^{-}$ → **9m** is about 12.0 kcal/mol less exergonic than the transformation **1m** + *t*BuO$^{-}$ → **3m**. These results suggest that the indole N-H proton is more acidic, resulting in more favorable 6-*exo*-*dig* ring closure. Indeed, the acidity of the proton being initially deprotonated mainly controls the chemoselectivity of the catalytic reaction.[38]

## 4. Conclusion

In conclusion, a two-step synthetic procedure for the synthesis of novel oxopyrazino[1,2-*a*]indole derivatives was described *via* a convenient Ugi 4-CR of indole-2-carboxylic acid, various aromatic aldehydes, propargylamine, and isocyanides, followed by the intramolecular hydroamination cyclization of indolic NH group and propargylic triple bond in the presence of KO*t*-Bu in DMF at room temperature. All products were obtained in very short reaction time (5-15 min) and good yields which make it a practical protocol for the library-based synthesis of oxopyrazino[1,2-*a*]indoles as well as investigation of miscellaneous biological activities. Also, density functional theory (DFT) calculations were applied to gain insight into the mechanism of reaction (Scheme 3). It seems that the catalytic reaction is started by the deprotonation of the indole N-H, followed by nucleophilic attack of the nitrogen anion on the internal C2 alkyne carbon to obtain a vinyl anion. This vinyl intermediate then deprotonates HO*t*-Bu to give analkene intermediate. Finally, an allyl anion formed by deprotonation of the alkene intermediate abstracts a proton from HO*t*-Bu and gives the final product.

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36 We are not able to locate any transition structure for this process due to the fact that the indole deprotonation has no enthalpic activation barrier, a result which is supported by a relaxed PES scan (Figure S1).

37 Consider pathway C, Figure S2.

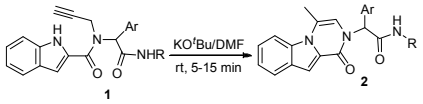
38 Although, in this system, the p$K_a$ values determine which mechanism is operative (Figure S3), it is not necessarily true to say that the reaction is always initiated from the most acidic proton. For example, if the transition structure $\mathbf{TS_{3\text{-}4}}$ was calculated to be higher in energy than transition structure $\mathbf{TS_{1\text{-}7}}$ (Figure 1), then the reaction did proceed via pathway B and not pathway A. Therefore, in order to determine which pathway is responsible for producing the final product, we have to investigate all single steps of all possible pathways.

**Table 1** Effect of various conditions on the intramolecular hydroamination reaction of **1a** for obtaining product **2a**

| Entry | Solvent | Reagent[a] | Temperature | Time | Yield[b] |
|---|---|---|---|---|---|
| 1 | DMF | KO*t*-Bu | rt | 10 min | 75 |
| 2 | DMF | KO*t*-Bu | 45 °C | 10 min | 75 |
| 3 | DMF | KO*t*-Bu | 90 °C | 10 min | 30 |
| 4 | DMSO | KO*t*-Bu | rt | 30 min | 65 |
| 5 | DMSO | KO*t*-Bu | 50 °C | 30 min | 65 |
| 6 | DMF | $K_2CO_3$ | rt | 2 h | 45 |
| 7 | DMF | $NEt_3$ | rt | 2 h | 10 |
| 8 | DMF | NaOH | rt | 1 h | 50 |
| 9 | DMF | L-proline | rt | 1 h | 15 |
| 10 | THF | KO*t*-Bu | rt | 1 h | 60 |
| 11 | 1,4-Dioxane | KO*t*-Bu | rt | 1 h | 55 |
| 12 | Toluene | KO*t*-Bu | rt | 1 h | 40 |
| 13 | $CH_2Cl_2$ | KO*t*-Bu | rt | 1 h | 35 |

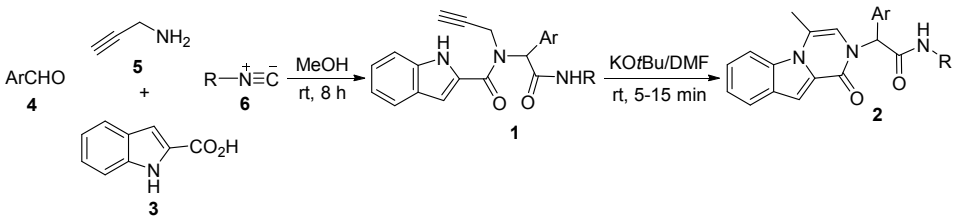
[a] All reactions were performed in the presence of 0.5 mmol of reagent.
[b] Isolated yield.

**Table 2** Synthesis of oxopyrazino[1,2-*a*]indoles **2**

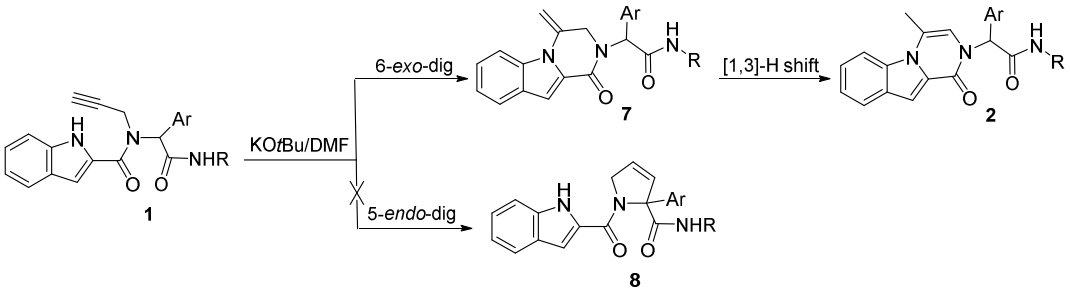



| Entry | Ar | R | Product **2** | Yield[a] |
|---|---|---|---|---|
| 1 | $C_6H_5$ | Cyclohexyl | **2a** | 75 |
| 2 | 4-Me-$C_6H_4$ | Cyclohexyl | **2b** | 77 |
| 3 | 4-MeO-$C_6H_4$ | Cyclohexyl | **2c** | 75 |
| 4 | 2-Cl-$C_6H_4$ | Cyclohexyl | **2d** | 70 |
| 5 | 4-N(Me)$_2$-$C_6H_4$ | Cyclohexyl | **2e** | 75 |
| 6 | 4-Me-$C_6H_4$ | *tetr*-Butyl | **2f** | 80 |
| 7 | 4-MeO-$C_6H_4$ | *tetr*-Butyl | **2g** | 77 |
| 8 | 2-F-$C_6H_4$ | *tetr*-Butyl | **2h** | 78 |
| 9 | 2-Cl-$C_6H_4$ | *tetr*-Butyl | **2i** | 75 |

[a] Isolated yield.




**Scheme 1** Synthesis of novel oxopyrazino[1,2-*a*]indoles **2**.




**Scheme 2** Reaction sequences for the construction of oxopyrazino[1,2-*a*]indoles **2**.

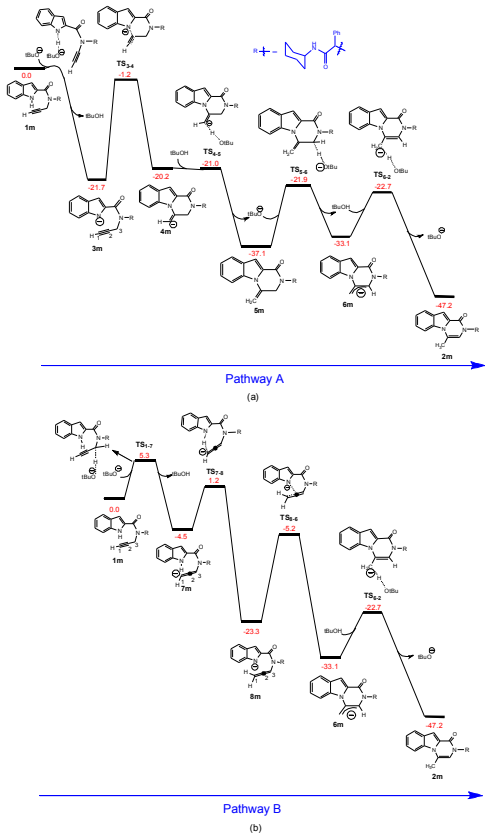



**Fig. 1** Potential energy profiles relating to formation of oxopyrazino[1,2-*a*]indoles **2m.** The relative free energies obtained from the M06/6-311+G(2d,p)//B3LYP/6-31G(d) calculations in DMF are given in kcal/mol.

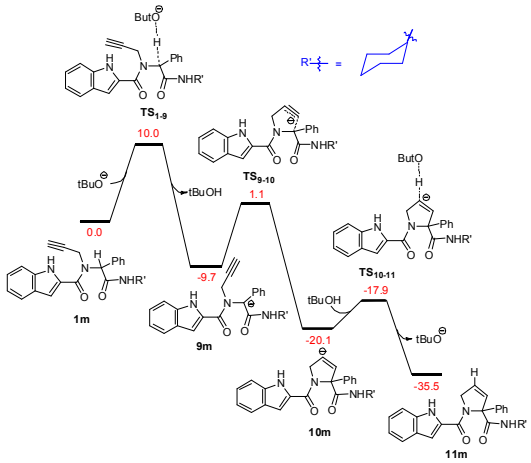
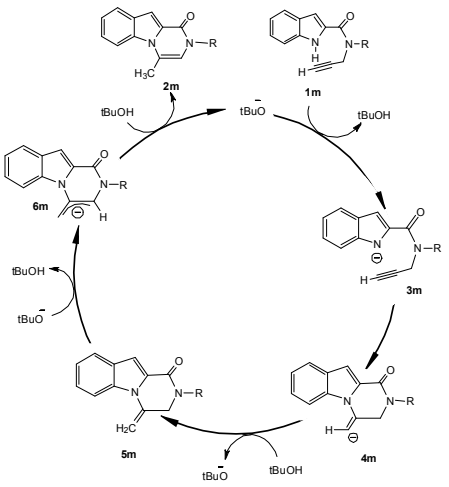



**Fig. 2** Potential energy profile for the 5-*endo-dig* ring closure process. The relative free energies obtained from the M06/6-311+G(2d,p)//B3LYP/6-31G(d) calculations in DMF are given in kcal/mol.




**Scheme 3** Intramolecular hydroamination reaction.

Graphical abstract