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Synthesis of novel substituted isoquinolones

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Abstract—A series of novel substituted isoquinolones have been synthesised. This has been achieved by two routes, either Curtius rearrangment of cinnamic acids or via an isoquinoline *N*-oxide. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

For many years isoquinolones have been an interesting structural class of compounds, which have found many uses in the fields of medicinal and synthetic chemistry.

Recently the isoquinolone unit has formed an integral part of many new biologically active compounds targeted towards various therapeutic endpoints. A few of these are shown in Scheme 1. Compound **1**, a substituted isoquinolone,[1] has been found to be a novel orally effective 5-HT_3 antagonist (ID_{50} 0.36 μg/kg iv) and to be more potent than Odansetron (Glaxo's effective 5-HT_3 antagonist). 5-HT_3 Antagonists have demonstrated high efficacy in the control of cancer chemotherapy-induced models as well as in animal models of anxiety and schizophrenia. Compound **2**, a deaza analogue[2] of N^{10}-propargyl-5,8-dideazafolic acid, has been found to be a thymidylate synthase (TS) inhibitor (IC_{50} 0.74 μM). Since thymidylate synthase (TS) is thought to be involved in the biological pathway of tumour growth, TS inhibitors could play a role as potential anticancer agents.[3,4] The dimethoxy substituted isoquinolone[5] **3** has recently been found to be an inhibitor (IC_{50} 33 μM) of human Tumor Necrosis Factor (TNF) production in peripheral blood monocytes. Inhibition of TNF is an important strategy for pharmacological intervention in a variety of inflammatory states, such as arthritis,[6] psoriasis[7] and cystic fibrosis.[8]

Another key area of isoquinolone use is as replacements for natural bases in nucleosides.[9] Whether it be for enhanced potency or increased stability, isoquinolone and related systems are used as bases in a variety of different systems.

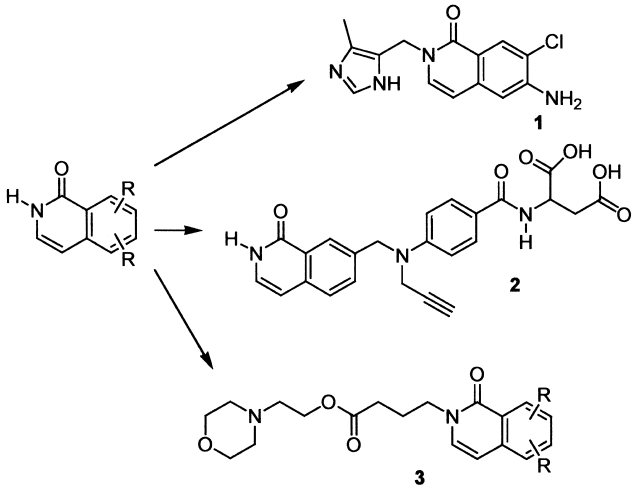
There are a variety of methodologies[10,11,12] available which could give access to a series of differentially substituted isoquinolones, however to date none have been used to systematically gain access to a wide variety of different isoquinolones.

In this article we disclose the results of a detailed study demonstrating the use of the Curtius rearrangement[13] to gain access to a large number of differentially substituted novel isoquinolones from the precursor cinnamic acids. In some cases, either when the cinnamic acids were not available, or when the cyclisation went poorly, (generally when the cinnamic acid had electron withdrawing groups attached), the desired isoquinolone was obtained from the isoquinoline.

2. Results and discussion

2.1. Isoquinolones via Curtius rearrangement

Initially we intended to use the Curtius rearrangement as a



Scheme 1.

Keywords: substituted isoquinolones; curtius rearrangement; isoquinoline *N*-oxide rearrangement.

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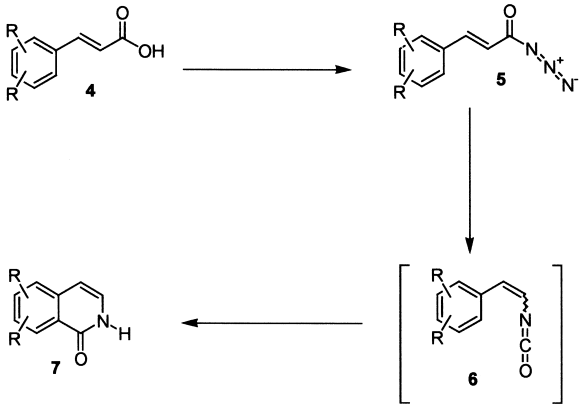


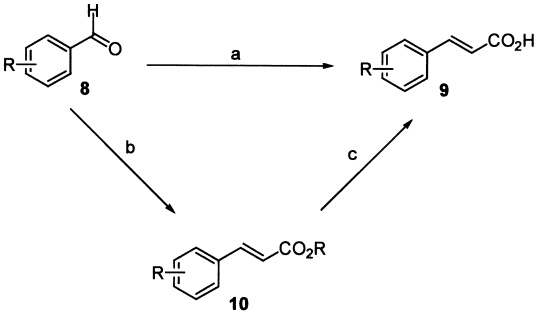
Scheme 2.

universal route towards isoquinolone analogues as there were already a few isolated cases[14,15] of this rearrangement being utilized for this purpose (Scheme 2). The cinnamic acid **4** was converted first to the acyl azide **5**, followed by thermal rearrangement to the intermediate isocyanate **6**, which may then be quenched by a variety of nucleophiles. To form the isoquinolone **7** the reactive intermediate **6** is quenched by intramolecular nucleophilic attack of the aromatic ring.

This approach was found to be applicable for the majority of cinnamic acids, giving the desired products in moderate yields, and gaining access to a wide variety of substituents. In the cases where the cinnamic acids were not available they were synthesised by elaboration of the substituted aldehyde **8** (Scheme 3), by either direct condensation[16] with malonic acid, or by Wittig reaction[17] to yield the ester **10** followed by saponification. In both routes only the *E*-regioisomer was observed.

We found the Curtius rearrangement to be useful in the majority of cases as shown in Table 1.

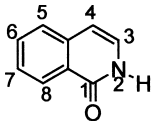
However two key points were noted. Firstly, when the rearrangement was attempted on cinnamoyl azides with rings bearing electron withdrawing substituents, the yields of isoquinolones for the Curtius rearrangement were either reduced or no desired product was obtained. It may be that the isocyanate was formed via the Curtius rearrangement, but that the aromatic rings were deactivated by the electron



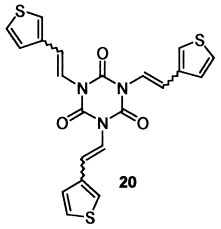
a $CH_2(CO_2H)_2$, Pyridine, b $(Ph)_3P{=}CHCO_2Me$, Toluene, c LiOH, H_2O, THF.

Scheme 3.

Table 1. Isoquinolones via the Curtius rearrangement

Product	Substitution	Yield (%)
		
11	3-Methyl	37
12	6-Methyl	30
13	6-Fluoro	4
14	7-Fluoro	44
15	7-Chloro	30
16	7-Thiomethyl	41
17a	6,7-Dimethyl	54
18	5,7-Difluoro	1
19	6,7-Difluoro	21

withdrawing groups such that they were rendered unreactive to cyclisation onto the isocyanate.

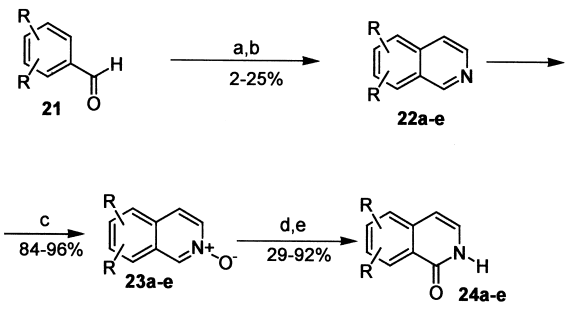


There is one isolated example in the literature[18] of a trimer **20** that was formed in a Curtius rearrangement, but we have found no evidence to suggest that we were forming compounds of this type in our Curtius rearrangements.

2.2. Isoquinolones from isoquinolines

The second key point was that we were unable to get access to 8-substituted isoquinolone analogues via the Curtius rearrangement as the 3-substituted cinnamic acid cyclised preferentially to give the 6-substituted analogue. It was thought that this was mainly due to steric interactions.

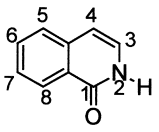
We overcame the problems of electron withdrawing groups or 8-substitution by preparing isoquinolone analogues via rearrangement of the isoquinolone *N*-oxide. Various novel substituted isoquinolones were synthesised by a route based on the published[19] route to the 8-methyl substituent (Scheme 4). Starting from commercially available



a $(MeO)_2CHCH_2NH_2$, Toluene, Reflux b H_2SO_4, 140°C c *m*CPBA, DCM d Ac_2O, Reflux, e NaOH, H_2O

Scheme 4.

Table 2. Isoquinolones via the isoquinoline-*N*-oxide rearrangement

Product	Substitution	Combined yields for reaction d+e (%)
		
24a	6,7-Dichloro	92
24b	7,8-Dichloro	78
24c	8-Fluoro	40
24d	8-Bromo	76
24e	7,8-Difluoro	29

substituted aldehydes **21**, elaboration to the dimethyl acetal was performed using dimethoxyethylamine. Refluxing in concentrated sulphuric acid followed by basic workup yielded the isoquinoline **22**, which was transformed to the isoquinoline-*N*-oxide **23** in the presence of *meta*-chloroperoxybenzoic acid. Finally isoquinolone **24** was yielded by refluxing the isoquinoline-*N*-oxide in acetic anhydride, followed by basic sodium hydroxide cleavage.

By using this method we were able to gain access to a further selection of novel substituted isoquinolones that we had been unable to prepare via the Curtius rearrangement (Table 2).

By utilizing both the above routes we were able to gain access to a wide variety of differentially substituted isoquinolones which in the majority of cases were novel, or in the few cases where the compound had been made before, by a far more convienient route.

3. Conclusions

A number of novel substituted isoquinolones have been synthesised and characterised. The Curtius rearrangement was utilized for the majority of these analogues and its generality explored. In doing so we have illustrated the limitations of the Curtius rearrangement. Isoquinolones bearing substituents in the 8-position or bearing electron withdrawing groups were synthesised via isoquinolines. In conclusion no systematic mapping of isoquinolone substitution has been previously reported. We have achieved this using two synthetic routes.

4. Experimental

4.1. General

All reactions were conducted under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. All reagents were used as received from their respective suppliers. Flash chromatography was performed using silica gel 230–400 mesh, 40–63 μm (Fluorochem Ltd). NMR ^{1}H and ^{13}C spectra were recorded on either a Bruker 300 MHz or Bruker 400 MHz spectrometer. When $CDCl_3$ was used as a NMR solvent, tetramethylsilane was used as the internal solvent, however in the case of DMSO, residual non deuterated solvent was the internal standard. LCMS spectra were recorded on a Finnigan LCQ LC-MS System, with an API ElectroSpray Source and HP1100 HPLC System with DAD. The HPLC system employed a Phenomenex Luna 2 C18, 100×4.6 mm 5 μm column. The graded mobile phase consisted of solvent A (0.08% aqueous formic acid) and solvent B (acetonitrile and 1% formic acid). The graded system was 0 min (95% A/5% B) to 6.5 min (5% A/95% B), followed by 1.5 min at (5% A/95% B) before returning to (95% A/5% B) over 2 min. Total run time 10 min.

4.2. General Curtius rearrangement procedure

4.2.1. 3-Methyl-2*H*-isoquinoline-1-one (11). α-Methyl cinnamic acid (10 g, 0.062 mol) was dissolved in acetone (80 mL) and triethylamine (17.3 mL, 0.124 mol) added. The reaction was cooled to 0°C and ethylchloroformate (6.6 mL, 0.093 mol) was added dropwise. After 1 h at 0°C, aqueous sodium azide (6.4 g, 0.1 mol, in 10 mL water) was added and the reaction stirred for 16 h at rt. Water (100 mL) was added and the acetone was removed in vacuo. The resulting slurry was extracted with toluene (3×50 mL) and dried over magnesium sulphate. This solution was added dropwise to a heated solution (190°C) of diphenylmethane (50 mL) and tributylamine (29.5 mL, 0.124 mol). The toluene was distilled off as added and after complete addition the reaction temperature was raised to 210°C for 2 h. After cooling the precipitated product was collected by filtration, washed with hexane (2×50 mL), and dried to yield an off white solid. (3.6 g, 37%) δ ^{1}H (300 MHz, $CDCl_3$) 9.12 (1H, brs, N*H*), 8.35 (1H, d, *J*=7.0 Hz, CC*H*CH), 7.62 (1H, t, *J*=7.0 Hz, CCHC*H*), 7.49–7.40 (2H, m, CC*H*C*H*), 6.39 (1H, s, C*H*CCH$_3$), 2.32 (3H, s, C*H*$_3$); R_t=3.21 min; mass spectrum *m*/*z* 160 (M+1, 98%).

The following compounds were all prepared in a similar manner.

4.2.2. 6-Methyl-2*H*-isoquinoline-1-one (12). Starting from 3-methylcinnamic acid (9.04 g, 0.056 mol), the title compound was yielded as a pale yellow solid. (2.9 g, 30%); δ ^{1}H (300 MHz, d_6-DMSO) 11.20 (1H, brs, N*H*), 8.12 (1H, d, *J*=7.5 Hz, NHC*H*CH), 7.50 (1H, s, CC*H*CCH$_3$), 7.38 (1H, d, *J*=6.5 Hz, CHC*H*CCH$_3$), 7.20 (1H, d, *J*=6.5 Hz, C*H*CHCCH$_3$), 6.52 (1H, d, *J*=7.5 Hz, NHCHC*H*), 2.53 (3H, s, C*H*$_3$); δ ^{13}C (100 MHz, d_6-DMSO) 161.8, 142.3, 138.0, 128.9, 127.7, 126.6, 125.7, 123.9, 104.4, 21.2; R_t=3.37 min; mass spectrum 160 (M+1, 100%).

4.2.3. 6-Fluoro-2*H*-isoquinoline-1-one (13). Starting from 3-fluorocinnamic acid (9.63 g, 0.058 mol), with purification by flash chromatography (eluent 2% methanol/dichloromethane) the title compound was yielded as a white solid (0.35 g, 4%); TLC R_f 0.35 (6% methanol/dichloromethane); δ ^{1}H (300 MHz, d_6-DMSO) 11.35 (1H, brs, N*H*), 8.23 (1H, dd, *J*=8.5, 6.0 Hz, CHC*H*CF), 7.54 (1H, d, *J*=8.5 Hz, C*H*CHCF), 7.35 (1H, d, *J*=6.0 Hz, CC*H*CF), 7.22 (1H, d, *J*=7.5 Hz, NHC*H*CH), 6.58 (1H, d, *J*=7.5 Hz, NHCHC*H*); R_t=3.32 min; mass spectrum *m*/*z* 164 (M+1, 100%).

4.2.4. 7-Fluoro-2*H*-isoquinoline-1-one (14). Starting from 4-fluorocinnamic acid (10.3 g, 0.061 mol), the title compound was yielded as a pale yellow solid (4.42 g, 44%). TLC R_f 0.62 (ethyl acetate); δ ^{1}H (300 MHz, d_6-DMSO)

11.62 (1H, brs, NH), 8.05 (1H, dd, J=8.5, 2.5 Hz, CCHCHCF), 7.96 (1H, d, J=4.5 Hz, CCHCF), 7.80 (1H, ddd, J=8.5, 4.5, 2.5 Hz, CCHCHCF), 7.38 (1H, d, J=7.0 Hz, NHCHCH), 6.80 (1H, d, J=7.0 Hz, NHCHCH); δ ^{13}C (100 MHz, d_6-DMSO) 161.1 (d, J=4.0 Hz), 160.4 (d, J=24 Hz), 134.7 (d, J=2 Hz), 129.1 (d, J=8 Hz), 128.2 (d, J=2 Hz), 127.5 (d, J=8 Hz) 121.0 (d, J=24 Hz), 111.2 (d, J=22 Hz), 104.2; R_t=3.27 min; mass spectrum m/z 164 (M+1, 100%).

4.2.5. 7-Chloro-2*H*-isoquinoline-1-one (15). Starting from 4-chlorocinnamic acid (10.0 g, 0.055 mol), the title compound was yielded as a pale yellow solid (2.95 g, 30%). δ ^{1}H (300 MHz, d_6-DMSO) 11.05 (1H, brs, NH), 8.21 (1H, s, CCHCCl), 7.85 (1H, d, J=8.0 Hz, NHCHCH), 7.54 (1H, d, J=6.5 Hz, CClCHCH), 7.32 (1H, d, J=6.5 Hz, CClCHCH), 6.68 (1H, d, J=8.0 Hz, NHCHCH); R_t= 3.28 min; mass spectrum m/z 180 (M+1, 100%).

4.2.6. 7-Methylsulfanyl-2*H*-isoquinoline-1-one (16). Starting from 4-(methylthio)-cinnamic acid (6.50 g, 0.034 mol), the title compound was yielded as a pale yellow solid (3.05 g, 41%). TLC R_f 0.15 (50% ethylacetate/hexane); δ ^{1}H (300 MHz, d_6-DMSO) 11.40 (1H, brs, NH), 8.02 (1H, s, CCHCSCH$_3$), 7.72–7.65 (2H, m, CHCHCSCH$_3$), 7.20 (1H, d, J=9.0 Hz, NHCHCH), 6.62 (1H, d, J=9.0 Hz, NHCHCH), 2.65 (3H, s, SCH$_3$); δ ^{13}C (100 MHz, d_6-DMSO) 161.2, 136.7, 134.9, 130.5, 128.1, 126.8, 126.5, 122.0, 104.4, 14.5; R_t=2.49 min; mass spectrum m/z 191 (M+1, 100%).

4.2.7. (*E*)-3-(3,4-Dimethyl-phenyl)-acrylic acid (17). To a stirred solution of 3,4-dimethylbenzaldehyde (10.15 g, 0.076 mol) in toluene (60 mL) was added methyl(triphenylphosphoranylidine)acetate (25.3 g, 0.076 mol) and the reaction heated at reflux for 7 h. On cooling the toluene was removed in vacuo, and the resulting slurry taken up in tetrahydrofuran (100 mL), methanol (40 mL) and water (40 mL). Lithium hydroxide (9.51 g, 0.102 mol) was added and the reaction stirred for 16 h at rt. The volatiles were removed in vacuo, and the resulting slurry diluted with water (100 mL). The mixture was extracted with dichloromethane (3×20 mL), before being acidified to pH 3 using aqueous hydrochloric acid (6 M). The resultant precipitate was collected by filtration, washing with water (3×20 mL), and dried in a vacuum oven for 16 h to yield the title compound as a off white solid (10.68 g, 82%). TLC R_f 0.50 (40% ethylacetate/hexane); δ ^{1}H (300 MHz, d_6-DMSO) 12.12 (1H, brs, OH), 7.48 (1H, d, J=17.0 Hz, COCHCH), 7.38 (1H, s, CCHCH$_3$), 7.21 (1H, d, J= 9.0 Hz, CHCHCH$_3$), 7.02 (1H, d, J=9.0 Hz, CHCHCH$_3$) 6.26 (1H, d, J=17.0 Hz, COCHCH), 2.08 (6H, s, 2×CH$_3$); δ ^{13}C (100 MHz, d_6-DMSO) 167.6, 144.0, 138.9, 136.8, 132.4, 130.2, 129.1, 126.0, 117.8, 19.3, 19.2; R_t= 1.53 min; mass spectrum m/z 177 (M+1, 100%).

The following compounds were prepared in a similar manner to, example, **11**.

4.2.8. 6,7-Dimethyl-2*H*-isoquinoline-1-one (17a). Starting from (*E*)-3-(3,4-dimethyl-phenyl)-acrylic acid (10.68 g, 0.060 mol), the title compound was yielded as a pale yellow solid (5.25 g, 54%). δ ^{1}H (300 MHz, d_6-DMSO) 11.05 (1H, brs, NH), 7.95 (1H, s, CHCCH), 7.42 (1H, s, COCCH), 7.05 (1H, d, J=8.0 Hz, NHCHCH), 6.45 (1H, d, J=8.0 Hz, NHCHCH), 2.35 (6H, s, 2×CH$_3$); δ ^{13}C (100 MHz, d_6-DMSO) 161.6, 141.7, 136.0, 135.2, 127.9, 126.6, 126.2, 124.1, 104.2, 19.7, 19.4; R_t=3.73 min; mass spectrum m/z 174 (M+1, 100%).

4.2.9. 5,7-Difluoro-2*H*-isoquinolin-1-one (18). Starting from 2,4-difluorocinnamic acid (11.38 g, 0.060 mol) with purification by flash chromatography (eluent 30–50% ethylacetate/hexane) the title compound was yielded as a pale yellow solid (0.40 g, 1%). TLC R_f 0.35 (50% ethylacetate/hexane); δ ^{1}H (300 MHz, d_6-DMSO) 11.50 (1H, brs, NH), 7.65 (2H, m, CFCHCFCH), 7.15 (1H, d, J=8.0 Hz, NHCHCH), 6.54 (1H, d, J=8.0 Hz, NHCHCH); R_t= 3.56 min; mass spectrum m/z 182 (M+1, 87%).

4.2.10. 6,7-Difluoro-2*H*-isoquinolin-1-one (19). Starting from 3,4-difluorocinnamic acid (10.0 g, 0.055 mol) with purification by flash chromatography (eluent 5:4:1 hexane/ethylacetate/methanol) the title compound was yielded as a pale yellow solid (2.13 g, 21%). TLC R_f 0.31 (40% ethylacetate/hexane); δ ^{1}H (300 MHz, d_6-DMSO) 11.50 (1H, brs, NH), 8.19 (1H, dd, J=10.0, 8.0 Hz, CHCFCFCH), 7.85 (1H, dd, J=10.0, 8.0 Hz, CHCFCFCH), 7.30 (1H, d, J=7.0 Hz, NHCHCH); 6.68 (1H, d, J=7.0 Hz, NHCHCH); δ ^{13}C (100 MHz, d_6-DMSO) 160.5, 152.4 (dd, J=250.0 10.0 Hz), 148.5 (dd, J=250.0, 10.0 Hz), 136.1 (d, J=10.0 Hz), 129.6 (d, J= 3.0 Hz), 123.2 (d, J=6.0 Hz), 114.8 (d, J=18 Hz), 114.2 (d, J=18 Hz), 103.7; R_t=3.48 min; mass spectrum m/z 182 (M+1, 93%).

4.2.11. 6,7-Dichloroisoquinoline (22a). 3,4-Dichlorobenzaldehyde (23.9 g, 0.13 mol) and aminoacetaldehyde dimethyl acetal (14.4 g, 0.16 mol) were heated in toluene (250 mL) under nitrogen with a Dean–Stark trap at reflux for 30 min. The mixture was concentrated to give 4-(dichlorobenzylidene)(2,2-dimethoxyethyl)amine as an orange-brown oil (36 g, quantitative); δ ^{1}H (300 MHz, $CDCl_3$) 8.22 (1H, s, NCHC), 7.88 (1H, d, J=8.5 Hz, CHCHCCl), 7.56 (1H, d, J=8.5 Hz, CHCHCCl), 7.48 (1H, s, CCHCCl), 4.68 (1H, t, J=5.0 Hz, CH$_2$CH), 3.78 (2H, d, J=5.0 Hz, CH$_2$CH) and 3.44 (6H, s, 2×OCH$_3$). 3,4-(Dichlorobenzylidene)(2,2-dimethoxyethyl)amine (36 g, 0.16 mol) and cold concentrated sulfuric acid (60 mL) were added separately, dropwise, over a period of 20 min to concentrated sulfuric acid (180 mL) at 140°C. The mixture was stirred at 130–140°C for 30 min, allowed to cool, and carefully poured onto ice (1 kg). Solid material was removed by filtration, and the mixture extracted with dichloromethane (2×200 mL). The mixture was cautiously basified with 10 M sodium hydroxide and, after allowing to cool, extracted with diethyl ether (2×300 mL). These diethyl ether extracts were combined, dried and concentrated to give a mixture of the title compound and isomeric 5,6-dichloroisoquinoline as a beige solid (5.58 g, 21%). Chromatography (20–50% ethylacetate/hexane) followed by recrystallisation from heptane/ethyl acetate (9:1) gave the title compound as a beige solid (1.3 g, 5%); TLC R_f 0.55 (ethylacetate); δ ^{1}H (300 MHz, $CDCl_3$) 9.20 (1H, s, NCHC), 8.58 (1H, d, J=6.5 Hz, NCHCH), 8.14 (1H, s, CHCCl), 7.98 (1H, s, CHCCl); 7.58 (1H, d, J=6.5 Hz, NCHCH).

The following compounds were prepared in a similar manner.

4.2.12. 7,8-Dichloroisoquinoline (22b). From 2,3-dichlorobenzaldehyde (30 g, 0.17 mol) and aminoacetaldehyde dimethyl acetal (18 g, 0.20 mol), (2,3-dichlorobenzylidene)(2,2-dimethoxyethyl)amine was yielded as a pale orange-brown oil (45 g, quantitative); δ ^{1}H (300 MHz, $CDCl_3$) 8.74 (1H, s, NC*H*C), 7.96 (1H, dd, *J*=7.5, 8.0 Hz, CC*H*), 7.54 (1H, dd, *J*=8.5, 7.5 Hz CFC*H*), 7.24 (1H, t, *J*=7.5 Hz, CFCHC*H*), 4.72 (1H, t, *J*=4.0 Hz, CH_2CH), 3.84 (2H, d, *J*=4.0 Hz, CH_2CH) and 3.44 (6H, s, 2×OCH_3). (2,3-Dichlorobenzylidene)(2,2-dimethoxyethyl)-amine (45 g, 0.17 mol) was reacted with concentrated sulfuric acid, to give the title compound as a brown solid (12.5 g, 49%); TLC R_f 0.6 (ethylacetate). δ ^{1}H (300 MHz, $CDCl_3$) 9.70 (1H, s, NC*H*C), 8.65 (1H, d, *J*=6.0 Hz, NC*H*CH), 7.72 (2H, s, C*H*C*H*CCl), 7.66 (1H, d, *J*=6.0 Hz, NCHC*H*).

4.2.13. 8-Fluoroisoquinoline (22c). From 2-fluorobenzaldehyde (20.8 g, 0.17 mol) and aminoacetaldehyde dimethyl acetal (17.6 g, 0.19 mol), (2-fluorobenzylidene)(2,2-dimethoxyethyl)amine was yielded as a pale orange-brown oil (35 g, quantitative); δ ^{1}H (300 MHz, $CDCl_3$) 8.60 (1H, s, NC*H*C), 8.00 (1H, dd, *J*=8.0, 7.5 Hz, CC*H*), 7.41–7.38 (1H, m, CFC*H*), 7.18 (1H, t, *J*=8.0 Hz, CCHC*H*), 7.08 (1H, t, *J*=8.0 Hz, CFCHC*H*), 4.70 (1H, t, *J*=4.5 Hz, CH_2CH), 3.82 (1H, t, *J*=4.5 Hz, CH_2CH) and 3.42 (6H, s, 2×OCH_3). (2-Fluorobenzylidene)(2,2-dimethoxyethyl)amine (35 g, 0.17 mol) was reacted with concentrated sulfuric acid to yield the title compound as a pale yellow solid (0.7 g, 3%); TLC R_f 0.45 (50% ethylacetate/hexane); δ ^{1}H (300 MHz, $CDCl_3$) 9.60 (1H, s, NC*H*C), 8.62 (1H, d, *J*=7.0 Hz, NC*H*CH), 7.68–7.60 (2H, m, C*H*CC*H*), 7.26–7.20 (1H, m, CFC*H*).

4.2.14. 8-Bromoisoquinoline (22d). From 2-bromobenzaldehyde (10 g, 54 mmol) and aminoacetaldehyde dimethyl acetal (5.89 mL, 54 mmol), (2-bromobenzylidene)(2,2-dimethoxyethyl)amine was yielded as a pale orange-brown oil (15 g, quantitative); δ ^{1}H (300 MHz, $CDCl_3$) 8.60 (1H, s, NC*H*C), 8.00 (1H, d, *J*=9.0 Hz, CC*H*), 7.52 (1H, d, *J*=8.0 Hz, CBrC*H*), 7.38–7.12 (2H, m, CHC*H*C*H*CH), 4.70 (1H, t, *J*=4.5 Hz, CH_2CH), 3.82 (2H, d, *J*=4.5 Hz, CH_2CH) and 3.42 (6H, s, 2×OCH_3). R_t=2.56 min; mass spectrum *m*/*z* 273 (M+1, 100%). (2-Bromobenzylidene)(2,2-dimethoxyethyl)amine (15 g, 54 mmol) was reacted with concentrated sulfuric acid and purified by flash chromatography (eluent 40% hexane/ethylacetate) to give the title compound as a beige yellow solid (0.19 g, 1.8%); TLC R_f 0.45 (50% ethylacetate/hexane), δ ^{1}H (300 MHz, $CDCl_3$) 9.68 (1H, s, NC*H*C), 8.64 (1H, d, *J*=7.0 Hz, NC*H*CH), 7.88 (1H, d, *J*=8.5 Hz, CBrC*H*), 7.80 (1H, d, *J*=8.5 Hz, CBrCHCHC*H*), 7.62 (1H, d, *J*=7.0 Hz, NCHC*H*), 7.52 (1H, t, *J*=8.54 Hz, CBrCHC*H*); R_t=2.92 min; mass spectrum *m*/*z* 208 (M^+, 100%), 129 (15).

4.2.15. 7,8-Difluoroisoquinoline (22e). From 2, 3-difluorobenzaldehyde (9.7 g, 68 mmol) and aminoacetaldehyde dimethyl acetal (7.17 g, 68 mmol), to give (2,3-dfluorobenzylidene)(2,2-dimethoxyethyl)amine as a pale orange-brown oil (11 g, quantitative); δ ^{1}H (300 MHz, $CDCl_3$) 8.60 (1H, s, NC*H*C), 8.00 (1H, d, *J*=8.0 Hz, CFCHCHC*H*), 7.44–7.41 (1H, m, CFC*H*), 7.18 (1H, dd, *J*=8.0, 7.0 Hz, CFCHC*H*), 4.70 (1H, t, *J*=4.0 Hz, CH_2CH), 3.82 (2H, d, *J*=4.0 Hz, CH_2CH) and 3.42 (6H, s, 2×OCH_3). R_t= 2.84 min; mass spectrum *m*/*z* 273 (M+1, 100%). 2,3-Difluorobenzylidene)(2,2-dimethoxyethyl)amine (11 g, 68 mmol) was reacted with concentrated sulfuric acid to yield the title compound as a orange solid (2.80 g, 25%); TLC R_f 0.45 (50% ethylacetate/hexane); δ ^{1}H (300 MHz, $CDCl_3$) 9.58 (1H, s, NC*H*C), 8.62 (1H, d, *J*=7.5 Hz, NC*H*CH), 7.52–7.70 (3H, m, NCHC*H*, C*H*C*H*CF); R_t= 3.23 min; mass spectrum *m*/*z* 166 (M+1, 100%).

4.2.16. 6,7-Dichloroisoquinoline 2-oxide (23a). 3-Chloroperoxybenzoic acid (57–86%, 0.716 g) was added to a solution of 6,7-dichloroisoquinoline (0.343 g, 1.73 mmol) in dichloromethane (10 mL) at rt, and the mixture stirred for 2 h. The mixture was diluted with dichloromethane (50 mL) and methanol (5 mL), and washed with sodium hydroxide solution (2 M, 60 mL). The aqueous phase was extracted with dichloromethane (2×20 mL), and the combined organic phases dried ($MgSO_4$) and concentrated. The residue was chromatographed (eluent, 5–10% methanol/ethylacetate) to give the title compound as a white solid (0.323 g, 87%); TLC R_f 0.26 (5% methanol/ethylacetate); δ ^{1}H (300 MHz, $CDCl_3$) 8.76 (1H, s, NC*H*C), 8.14 (1H, d, *J*= 7.5 Hz, NC*H*CH), 7.92 (1H, s, C*H*CCl), 7.83 (1H, s, C*H*CCl), 7.58 (1H, d, *J*=7.5 Hz, NCHC*H*); R_t=2.87 min; mass spectrum *m*/*z* 166 (M+1, 80%).

4.2.17. 7,8-Dichloroisoquinoline 2-oxide (23b). From 7,8-dichloroisoquinoline (2.00 g, 0.20 mol) and 3-chloroperoxybenzoic acid (57–86%, 4.18 g), without chromatography, to give the title compound as a white solid (1.81 g, 84%); TLC R_f 0.19 (5% methanol/ethylacetate); δ ^{1}H (300 MHz, $CDCl_3$) 9.14 (1H, s, NC*H*C), 8.18 (1H, d, *J*=9.0 Hz, NC*H*CH), 7.71–7.58 (3H, m, NCHC*H*, C*H*C*H*CCl); R_t= 3.36 min; mass spectrum *m*/*z* 214 (M^+, 100%), 197 (30).

4.2.18. 8-Fluoroisoquinoline 2-oxide (23c). From 8-fluoroisoquinoline (0.69 g, 4.63 mmol) and 3-chloroperoxybenzoic acid (57–86%, 1.62 g), without chromatography, to give the title compound as a pale beige solid (0.73 g, 95%); TLC R_f 0.05 (ethylacetate). δ ^{1}H (300 MHz, $CDCl_3$) 8.96 (1H, s, NC*H*C), 8.16 (1H, d, *J*=7.5 Hz, NC*H*CH), 7.70 (1H, d, *J*=7.5 Hz, NCHC*H*), 7.64–7.50 (2H, m, CFC*H*CHC*H*), 7.34–7.26 (1H, m, CFCHC*H*).

4.2.19. 8-Bromoisoquinoline 2-oxide (23d). From 8-bromoisoquinoline (0.19 g, 0.89 mmol) and 3-chloroperoxybenzoic acid (28%, 0.26 mL), without chromatography, to give the title compound as a pale beige solid (0.16 g, 84%); TLC R_f 0.25 (10% methanol/ethylacetate). δ ^{1}H (300 MHz, $CDCl_3$) 9.16 (1H, s, NC*H*C), 8.18 (1H, d, *J*=9.0 Hz, NC*H*CH), 7.88 (1H, d, *J*=8.0 Hz, CBrC*H*), 7.74 (1H, d, *J*=8.0 Hz, CBrCHCHC*H*), 7.64 (1H, d, *J*= 9.0 Hz, NCHC*H*), 7.44 (1H, t, *J*=8.0 Hz, CBrCHC*H*CH); R_t=2.93 min; mass spectrum *m*/*z* 225 (M+1, 100%).

4.2.20. 7,8-Difluoroisoquinoline 2-oxide (23e). From 7,8-difluoroisoquinoline (0.80 g, 4.85 mmol) and 3-chloroperoxybenzoic acid (57–86%, 1.00 g), without chromatography, to give the title compound as a white solid

(0.76 g, 87%); TLC R_f 0.19 (5% methanol/ethylacetate); δ ^{1}H (300 MHz, $CDCl_3$) 8.92 (1H, s, NC*H*C), 8.12 (1H, d, *J*=7.0 Hz, NC*H*CH), 7.67 (1H, d, *J*=7.0 Hz, NC*H*CH), 7.58 (1H, dd, *J*=7.0, 4.5 Hz, C*H*CHCF), 7.42 (1H, dd, 9.5, *J*=7.0 Hz, CHC*H*CF).

4.2.21. 6,7-Dichloro-2*H*-isoquinolin-1-one (24a). 6,7-Dichloroisoquinoline 2-oxide (0.323 g, 1.5 mmol) was dissolved in acetic anhydride (5 mL), and the mixture heated under reflux for 3 h. The mixture was concentrated under reduced pressure, and the residue heated in aqueous sodium hydroxide (2 M, 10 mL) for 1 h. The mixture was acidified to pH 6 with citric acid (5% in water), and extracted with dichloromethane (2×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to give the title compound as a pale brown solid (0.299 g, 92%); TLC R_f 0.5 (ethylacetate); δ ^{1}H (300 MHz, $CDCl_3$) 10.45 (1H, brs, N*H*), 8.45 (1H, s, C*H*CCl), 7.70 (1H, s, C*H*CCl), 7.16 (1H, d, *J*=8.0 Hz, NHC*H*CH), 6.48 (1H, d, *J*=8.0 Hz, NHCHC*H*); δ ^{13}C (100 MHz, d_6-DMSO) 160.3, 137.7, 135.3, 130.9, 128.7, 128.1, 127.9, 125.7, 103.2; R_t= 4.41 min; mass spectrum *m*/*z* 214 (M^+, 58%).

Prepared in a similar manner.

4.2.22. 7,8-Dichloro-2*H*-isoquinolin-1-one (24b). From 7,8-dichloroisoquinoline 2-oxide (0.914 g, 4.3 mmol), the title compound was yielded as a pale brown solid (0.713 g, 78%); TLC R_f 0.63 (5% methanol/ethylacetate), δ ^{1}H (300 MHz, $CDCl_3$) 9.97 (1H, brs, N*H*), 7.70 (1H, d, *J*=8.5 Hz, C*H*CHCCl), 7.39 (1H, d, *J*=8.5 Hz, CHC*H*CCl), 7.13 (1H, d, *J*=8.0 Hz, NHC*H*CH) 6.47 (1H, d, *J*=8.0 Hz, NHCHC*H*); δ ^{13}C (100 MHz, d_6-DMSO) 159.5, 139.7, 133.2, 131.1, 130.9, 130.6, 126.6, 123.5, 104.1; R_t= 4.04 min; mass spectrum *m*/*z* 214 (M^+, 100%).

4.2.23. 8-Fluoro-2*H*-isoquinolin-1-one (24c). From 8-fluoroisoquinoline 2-oxide (0.72 g, 4.39 mmol), with purification by flash chromatography (eluent 40% *ethylacetate/hexane–5% methanol/ethylacetate) yielded the title compound as a pale beige solid (0.287 g, 40%); TLC R_f 0.5 (ethylacetate). δ ^{1}H (300 MHz, d_6-DMSO) 11.16 (1H, brs, N*H*), 7.54–7.63 (1H, m, CHC*H*CH), 7.38 (1H, d, *J*=7.5 Hz, NHC*H*CH), 7.04–7.16 (2H, m, C*H*CHC*H*), 6.47 (1H, d, *J*=7.5 Hz, NHCHC*H*); R_t=2.83 min; mass spectrum *m*/*z* 164 (M+1, 97%).

4.2.24. 8-Bromo-2*H*-isoquinolin-1-one (24d). From 8-bromoisoquinoline 2-oxide (0.16 g, 0.74 mmol), the title compound was yielded as a pale beige solid (0.126 g, 76%); TLC R_f 0.7 (ethylacetate). δ ^{1}H (300 MHz, $CDCl_3$) 9.84 (1H, brs, N*H*), 7.75 (1H, d, *J*=7.5 Hz, C*H*CHCH), 7.48 (1H, d, *J*=7.5 Hz, CHCHC*H*), 7.40 (1H, t, *J*=7.5 Hz, CHC*H*CH), 7.10 (1H, d, *J*=7.0 Hz, NHC*H*CH), 6.48 (1H, d, *J*=7.0 Hz, NHCHC*H*); δ ^{13}C (100 MHz, d_6-DMSO) 160.1, 141.0, 132.9, 132.6, 129.8, 126.4, 122.9, 121.3, 104.6; R_t=3.60 min; mass spectrum *m*/*z* 224 (M+1, 100%).

4.2.25. 7,8-Difluoro-2*H*-isoquinolin-1-one (24e). From 7,8-difluoroisoquinoline 2-oxide (0.76 g, 4.19 mmol), with purification by flash chromatography (eluent 50% ethylacetate/hexane–10% methanol/ethylacetate) yielded the title compound as a pale beige solid (0.220 g, 29%); TLC R_f 0.45 (ethylacetate) δ ^{1}H (300 MHz, d_6-DMSO) 11.12 (1H, brs, N*H*), 7.58 (1H, dd, *J*=7.5, 3.0 Hz, CFC*H*), 7.28 (1H, dd, *J*=7.5, 1.5 Hz, CFCHC*H*), 6.94 (1H, d, *J*=5.5 Hz, NHC*H*CH), 6.34 (1H, d, *J*=5.5 Hz, NHCHC*H*); δ ^{13}C (100 MHz, d_6-DMSO) 158.9, 148.7 (dd, *J*=260.5, 11.5 Hz), 146.6 (dd, *J*=243.0, 11.0 Hz) 136.0, 129.2, 122.6, 122.1 (d, *J*=18.5 Hz), 116.1, 103.7; R_t=3.01 min; mass spectrum *m*/*z* 182 (M+1, 95%).

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