Direct introduction of indoles into 2-aminopyrazine 1-oxides

Igor S. Kovalev, Dmitry N. Kozhevnikov, Vladimir L. Rusinov,* Oleg N. Chupakhin, Dmitry V. Raikov, Vladimir A. Pustovarov and Boris V. Shul'gin

Department of Organic Chemistry, Urals State Technical University, 620002 Ekaterinburg, Russian Federation. Fax: +7 3432 74 0458; e-mail: rusinov@htf.ustu.ru

10.1070/MC2000v010n06ABEH001373

The synthesis of indolyl derivatives of 2-aminopyrazine, analogues of the bioluminescent natural product Cypridina etioluciferamine, with enhanced photoluminescent properties, is reported.

Indolyl derivatives of aminopyrazine are of interest as analogues of the bioluminescent natural product Cypridina etioluciferamine, 2-amino-3-aminopropyl-5-indolylpyrazine.[1] It is well known from the chemistry of pyridine, quinoline[2,3] and 1,2,4-triazine[4,5] *N*-oxides that indolyl residues can be conveniently introduced into aza aromatics by a one-step procedure of nucleophilic substitution of hydrogen (S_N^H).[6,7] Acylating agents are often used to activate substrates through the formation of *O*-acyl azinium salts or/and to facilitate the aromatization of intermediate ^{H}-adducts.

We found that this methodology can be successfully applied to the chemistry of pyrazine *N*-oxides, allowing an easy access to indolyl derivatives of 2-aminopyrazine. Thus, the reaction of 5-R-2-amino-3-ethoxycarbonylpyrazine 1-oxides **1a–c** with indole, 1-methylindole or 2-methylindole in the presence of acetic anhydride or benzoyl chloride afforded 5-R-2-acylamino-6-(indol-3-yl)-3-ethoxycarbonylpyrazines **2a–c**,† **3a–c**,‡ **4a–c**§ (Scheme 1).¶ The reaction proceeds *via* deoxidative nucleophilic substitution of hydrogen. At the first step, O-acylation occurs to form a reactive 1-acyloxypyrazinium salt. The nucleophilic attack by indole at the position 6 gives an intermediate ^{H}-adduct. Deprotonation with simultaneous deoxygenation leads to aromatization of the 6-substituted product.

In a similar manner, aminopyrazine 1-oxide **1a** reacts with other heteroaromatic C-nucleophiles, such as pyrrole and *N*-methylpyrrole. The most reactive nucleophilic centres in pyrroles and indoles are -carbon and -carbon atoms, respectively. Indeed, as it has been expected, the reactions of pyrazine 1-oxide **1a** with pyrroles in the presence of benzoyl chloride lead to 6-(pyrrol-2-yl-) and 6-(1-methylpyrrol-2-yl)-2-benzoylamino-3-ethoxycarbonyl-5-methylpyrazines **5** and **6** in good yields.¶,††

Table 1 Photoluminescence maxima (λ_{max}) of compounds **2–8**.

Compound	λ_{max}/nm
2b	515
2c	510
3b	480
3c	520
4b	475
4c	500
5	560
6	540
8	530

† All of the compounds gave satisfactory analytical data (to within 0.20% for C, 0.15% for H and 0.27% for N). The ^{1}H NMR spectra were measured on a Bruker WM-250 spectrometer at 250.137 MHz. The mass spectra (electron ionization) were measured on a Varian MAT-311 spectrometer. The photoluminescence spectra were measured in a cryostat on irradiation with monochromated UV light (310 nm) using another monochromator equipped with a photomultiplier tube (voltage of 1050 V) and a detector (an electronic automatic potentiometer) at room temperature.

For **2a**: yield 79%, mp 185 °C. ^{1}H NMR ([$^2H_6$]DMSO/CCl_4) δ: 1.36 (t, 3H, *Me*CH_2), 2.17 (s, 3H, MeCO), 2.60 (s, 3H, Me), 4.28 (q, 2H, MeC*H*$_2$), 7.14 (m, 2H), 7.45 (m, 1H), 7.94 (d, 1H), 8.50 (m, 1H), 10.51 (s, 1H, N*H*COMe), 11.61 (s, 1H, NH). MS, *m*/*z* (%): 338 (73) M^+.

For **2b**: yield 88%, mp 211–212 °C. ^{1}H NMR ([$^2H_6$]DMSO/CCl_4) δ: 1.31 (t, 3H, *Me*CH_2), 2.19 (s, 3H, MeCO), 4.29 (q, 2H, MeC*H*$_2$), 6.83 (d, 1H), 7.32 (m, 2H), 7.42 (m, 6H), 8.35 (m, 1H), 10.71 (br. s, 1H, N*H*COMe), 11.30 (s, 1H, NH). MS, *m*/*z* (%): 400 (100) M^+.

For **2c**: yield 80%, mp 249–250 °C. ^{1}H NMR ([$^2H_6$]DMSO/CCl_4) δ: 1.29 (t, 3H, *Me*CH_2), 4.31 (q, 2H, MeC*H*$_2$), 6.95 (d, 1H), 7.45 (m, 2H), 7.56 (m, 1H), 7.59 (d, 2H), 7.62 (m, 5H), 8.09 (d, 2H), 8.53 (m, 1H), 11.38 (br. s, 2H, 2NH). MS, *m*/*z* (%): 498 (27) and 496 (72) M^+.

‡ For **3a**: yield 82%, mp 185 °C. ^{1}H NMR ([$^2H_6$]DMSO/CCl_4) δ: 1.36 (t, 3H, *Me*CH_2), 2.17 (s, 3H, MeCO), 2.75 (s, 3H, Me), 3.92 (s, 3H, NMe), 4.29 (q, 2H, MeC*H*$_2$), 7.20 (m, 2H), 7.42 (m, 1H), 7.99 (s, 1H), 8.48 (m, 1H), 10.51 (s, 1H, N*H*COMe). MS, *m*/*z* (%): 352 (100) M^+.

For **3b**: yield 80%, mp 204 °C. ^{1}H NMR ($CDCl_3$) δ: 1.45 (t, 3H, *Me*CH_2), 2.43 (s, 3H, COMe), 3.58 (s, 3H, NMe), 4.48 (q, 2H, MeC*H*$_2$), 6.71 (s, 1H), 7.40 (m, 8H), 8.65 (m, 1H), 10.82 (s, 1H, NH). MS, *m*/*z* (%): 414 (100) M^+.

For **3c**: yield 85%, mp 233–234 °C. ^{1}H NMR ([$^2H_6$]DMSO/CCl_4) δ: 1.29 (t, 3H, *Me*CH_2), 3.71 (s, 3H, NMe), 4.31 (q, 2H, MeC*H*$_2$), 6.95 (s, 1H), 7.18 (m, 2H), 7.40 (m, 3H), 7.58 (m, 5H), 8.05 (d, 2H), 8.46 (m, 1H), 11.38 (s, 1H, N*H*COPh). MS, *m*/*z* (%): 512 (25) and 510 (70) M^+.

§ For **4a**: yield 71%, mp 198 °C. ^{1}H NMR ([$^2H_6$]DMSO/CCl_4) δ: 1.36 (t, 3H, *Me*CH_2), 2.12 (s, 3H, MeCO), 2.43 (s, 3H, Me), 2.44 (s, 3H, Me), 4.30 (q, 2H, MeC*H*$_2$), 7.02 (m, 2H), 7.32 (m, 2H), 10.57 (s, 1H, N*H*COMe), 11.26 (s, 1H, NH). MS, *m*/*z* (%): 352 (100) M^+.

For **4b**: yield 72%, mp 244–245 °C. ^{1}H NMR ($CDCl_3$) δ: 1.48 (t, 3H, *Me*CH_2), 1.97 (s, 3H, Me), 2.43 (s, 3H, NHCO*Me*), 4.51 (q, 2H, MeC*H*$_2$), 7.25 (m, 9H), 8.35 (br. s, 1H, NH), 10.62 (s, 1H, N*H*COMe). MS, *m*/*z* (%): 414 (100) M^+.

For **4c**: yield 76%, mp 219–220 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.18 (t, 3H, *Me*CH_2), 2.13 (s, 3H, Me), 4.26 (q, 2H, MeC*H*$_2$), 6.95 (m, 2H), 7.37 (m, 4H), 7.57 (m, 5H), 8.06 (d, 2H), 11.36 (br. s, 2H, 2NH). MS, *m*/*z* (%): 512 (23) and 510 (60) M^+.

¶ *General procedure for the synthesis of 6-(indol-3-yl)pyrazines* **2–4**. A mixture of 2-aminopyrazine 1-oxide **1a–c** (2 mmol), a corresponding indole (2 mmol) and acetic anhydride (0.9 ml, 10 mmol) or benzoyl chloride (1.2 ml, 10 mmol) in 5 ml DMF was heated at 100 °C for 2 h and left to stand overnight at room temperature. The solvents were removed *in vacuo*, the residue was treated with ethanol and recrystallised from hexane–toluene (1:1).

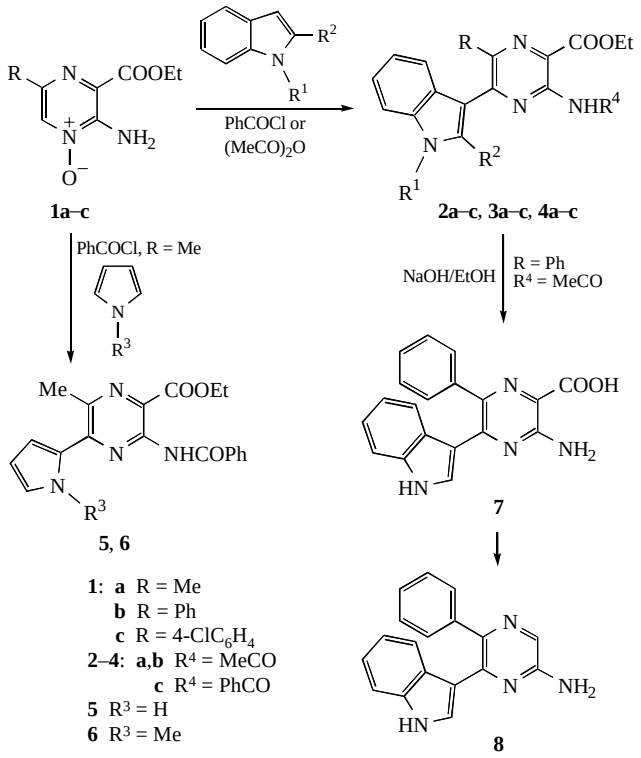
General procedure for the synthesis of 6-(1-methylpyrrol-2-yl)-2-benzylamino-5-methyl-3-ethoxycarbonylpyrazines **5** and **6**. A mixture containing pyrazine 1-oxide **1a** (2 mmol), pyrrole or 1-methylpyrrole (2 mmol) and 1.16 ml (10 mmol) of benzoyl chloride in 10 ml of CCl_4 was refluxed for 0.5–1 h. The solution was filtered, and the solvent was removed *in vacuo*. The residue was successively treated with a 10% aqueous Na_2CO_3 solution and ethanol. The crystals were collected by filtration and recrystallised from ethanol.

Hydrolysis of pyrazine **2a**. Pyrazine **2a** (0.80 g, 2 mmol) with a mixture of 20 ml of 95% ethanol and sodium (0.23 g, 10 mmol) was refluxed for 2 h. The solvent was removed *in vacuo*; the residue was treated with 80 ml of water and diluted with hydrochloric acid to adjust pH 3–4. The crystals were filtered off and washed with water.

2-Amino-6-(indol-3-yl)-5-phenylpyrazine **8**. 2-Amino-5-phenyl-6-(indol-3-yl)pyrazine-3-carboxylic acid **7** (0.66 g, 2 mmol) was heated at 210–220 °C for 1 h. The reaction mixture was refluxed with a 5% KOH solution in ethanol for 10 min. Clear solution was decanted from the resin and cooled. The crystals formed were filtered off, washed with water and recrystallised from toluene–hexane (1:1).

†† For **5**: yield 47%, mp 169–170 °C. ^{1}H NMR ([$^2H_6$]DMSO/CCl_4) δ: 1.27 (t, 3H, *Me*CH_2), 2.74 (s, 3H, Me), 4.28 (q, 2H, MeC*H*$_2$), 6.26 (m, 1H), 6.84 (m, 1H), 7.08 (m, 1H), 7.53 (m, 3H), 8.02 (m, 2H), 10.97 (br. s, 2H, 2NH). MS, *m*/*z* (%): 350 (54) M^+.

For **6**: yield 20%, mp 130 °C. ^{1}H NMR ([$^2H_6$]DMSO/CCl_4) δ: 1.31 (t, 3H, *Me*CH_2), 2.71 (s, 3H, Me), 3.96 (s, 3H, NMe), 4.31 (q, 2H, MeC*H*$_2$), 6.14 (dd, 1H), 6.65 (dd, 1H), 6.94 (dd, 1H), 7.55 (m, 3H), 8.01 (m, 2H), 11.19 (br. s, 1H, N*H*COPh). MS, *m*/*z* (%): 364 (94) M^+.



Scheme 1

3-Ethoxycarbonylpyrazine **2b** undergoes hydrolysis of the ester group under basic conditions yielding 2-amino-6-(indol-3-yl)-5-phenylpyrazine-3-carboxylic acid **7**. The heating of **7** at 210 °C causes decarboxylation and affords 2-amino-6-(indol-3-yl)-5-phenylpyrazine **8**,¶,‡‡ a structural analogue of etioluciferamine.[1]

‡‡ For **7**: yield 53%, mp 160 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.71 (d, 1H), 7.06 (m, 2H), 7.23 (br. s, 2H, NH_2), 7.30–7.49 (m, 6H), 8.32 (m, 1H), 11.19 (s, 1H, NH). MS, *m*/*z* (%): 330 (100) M^+, 286 (100) $[M - CO_2]^+$.

For **8**: yield 45%, mp 120 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.07 (br. s, 2H, NH_2), 6.79 (d, 1H), 6.90–7.39 (m, 8H), 7.62 (s, 1H, 3-H), 7.88 (m, 1H), 10.95 (s, 1H, NH).

The compounds obtained exhibit luminescent properties. The photoluminescence spectra of compounds **2b**,**c**, **3b**,**c**, **4b**,**c**, **5**, **6** and **8** excited by UV light (310 nm) have maxima at 475–560 nm (Table 1). A similar photoluminescence was observed on the initiation with X-rays and electron and ion beams. The luminescent properties of indolylpyrazines **2**–**8** are observed in the green–yel low spectral region, which is close to the spectral threshold of human eye (525 nm). Thus, the above compounds seem to be useful for the detection of UV light and particle beams. Note that these compounds exhibit rather strong luminescence comparable to the light output of stilbenes.

This work was supported by the U.S. Civilian Research and Development Foundation for the Independent States of the Former Soviet Union (SRDF) (project no. REC-005).

References

1 T. P. Karpetsky and E. H. White, *Tetrahedron*, 1973, **29**, 3761.
2 M. Hamana and I. Kumadaki, *Chem. Pharm. Bull.*, 1967, **15**, 363.
3 M. Hamana and I. Kumadaki, *Chem. Pharm. Bull.*, 1970, **18**, 1742.
4 V. L. Rusinov, D. N. Kozhevnikov, I. S. Kovalev, O. N. Chupakhin and G. G. Aleksandrov, *Zh. Org. Khim.*, 2000, **36**, 1081 (in Russian).
5 V. L. Rusinov, D. N. Kozhevnikov, E. N. Ulomsky, O. N. Chupakhin, G. G. Aleksandrov and H. Neunhoeffer, *Zh. Org. Khim.*, 1998, **34**, 429 (*Russ. J. Org. Chem.*, 1998, **34**, 400).
6 O. N. Chupakhin, V. N. Charushin and H. van der Plas, *Nucleophilic Aromatic Substitution of Hydrogen*, Academic Press, New York, 1994, p. 367.
7 N. Sato, in *Comprehensive Heterocyclic Chemistry II*, eds. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon, Oxford, 1996, vol. 6, p. 249.

Received: 8th September 2000; Com. 00/1699