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A new approach towards the synthesis of pyrrolo[2,1-*a*]isoquinolines

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ABSTRACT

Reaction of 5-bromo-2-methyl-8-nitro-1,2,3,4-tetrahydroisoquinoline with activated alkynes affords stable tetrahydropyrrolo[2,1-*a*]isoquinolin-4-ium ylides. Further reactions of ylide **2** gives access to substituted dihydropyrrolo[2,1-*a*]isoquinolines in good yields.

Pyrrolo[2,1-*a*]isoquinolones have attracted considerable interest because they possess antidepressant,[1] muscarinic agonist, cardiotonic[2] and anticancer activity. Moreover, they can be used as PET (positron emission tomography) radiotracers for imaging serotonin uptake sites.[3] The importance of these nitrogen heterocycles is further enhanced by their utility as advanced intermediates for the synthesis of alkaloids.[4]

Pyrrolo[2,1-*a*]isoquinoline is the core skeleton of a number of antitumour alkaloids such as lamellarins[5] and crysrine.[6]

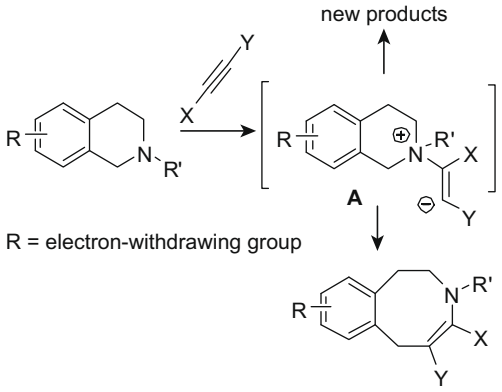
The reported pathways towards this scaffold include (but are not limited to) *N*-acyliminium Pictet-Spengler cyclizations,[7,8] Bischler–Napieralski reaction[9] or annelation of pyrrole to isoquinolines.[10,11]

However, to prepare libraries of biologically active analogues of such natural products for lead discovery and/or optimization in medicinal chemistry, it is essential to have versatile synthetic methods in hand. Thus we turned our attention towards developing a novel synthetic approach towards this heterocyclic system based on the reaction of readily available tetrahydroisoquinolines with electron-poor acetylenes.

Previously, we reported on tandem transformations of tetrahydroisoquinolines with electron-donating groups on the benzene fragment under the action of activated alkynes.[12] This reaction allowed us to obtain substituted benzoazocines in one step. However, the reactivity of tetrahydroisoquinolines possessing electron-withdrawing groups with activated alkynes has not been studied. Since it is known that the reaction proceeds via intermediate zwitterion **A**, the result of Michael addition of the tertiary N-atom of the tetrahydropyridine ring to the activated alkyne, we wondered if the presence of electron-withdrawing groups would affect the nature of intermediate **A** thus leading to new products, or, whether the reaction does not depend on the effects of the substituents on the benzene ring (Scheme 1).

The starting 5-bromo-2-methyl-8-nitro-1,2,3,4-tetrahydroisoquinoline (**1**) required for the present study was obtained according to the previously described method.[13] The reaction of isoquinoline **1** with methyl propiolate in methanol proceeded smoothly at room temperature. The only product isolated from the reaction in good yield (70%) was a stable pyrrolo[2,1-*a*]isoquinolinium ylide **2**[14] (Scheme 2). The reaction of isoquinoline **1** with DMAD required excess alkyne and a lower temperature (−5 °C), however it failed to go to completion and ylide **3**[15] was obtained in a moderate yield of 30%.

We presume that the formation of the ylides **2** and **3** proceeds via zwitterion **A**, the anionic part of which deprotonates a molecule of methanol thus producing a highly basic methoxide anion. The latter catalyzes the formation of **B**. Intramolecular nucleophilic attack of the anionic centre in ylide **B** on the ester group leads to elimination of methanol to form pyrroloisoquinolinium ylides **2** or **3** (Scheme 2). The intramolecular S_N reaction in this case is probably facilitated by methanol.



Scheme 1.

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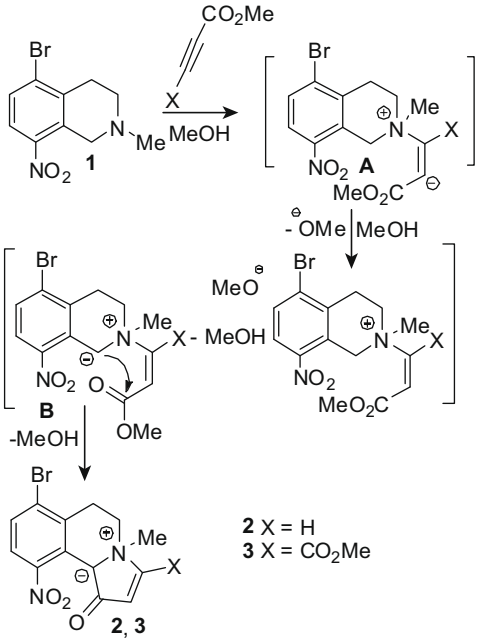


Scheme 2.

The structure of ylide **2** was unambiguously assigned by X-ray analysis. A suitable crystal was obtained by slow evaporation of a methanolic solution of compound **2**. The refined X-ray structure[16] of ylide **2** is shown in Figure 1.

We found that the solvent used in the reaction of isoquinoline **1** with methyl propiolate defines the reaction pathway. Thus, in the case of acetonitrile, the only product isolated from the reaction was 1-vinyl substituted isoquinoline **4**.[17] We presume that in the case of an aprotic solvent, zwitterion **A** rearranges to ylide **B** and the latter undergoes a Stevens rearrangement leading to compound **4** (Scheme 3).

Recently we demonstrated that stable benzo[*b*]pyrrolo[2,1-*f*][1,6]naphthyridin-4-ium ylides underwent O-acylation under the action of acetic anhydride.[18] We carried out analogous reactions of ylide **2** with 2-phenylethanoyl chloride, 4-fluoro-1-benzene- and 2-naphthalenesulfonyl chloride. The reactions did not require any special conditions and proceeded smoothly at room temperature in 1-2 hours. In all cases the O-acylation was accompanied by elimination of a methyl group and subsequent aromatization of the pyrrole fragment giving pyrroloisoquinolines **5**–**7**[19–21] in good preparative yields (Scheme 4).

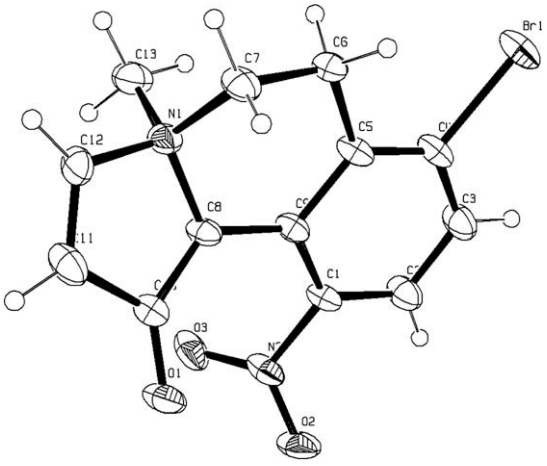
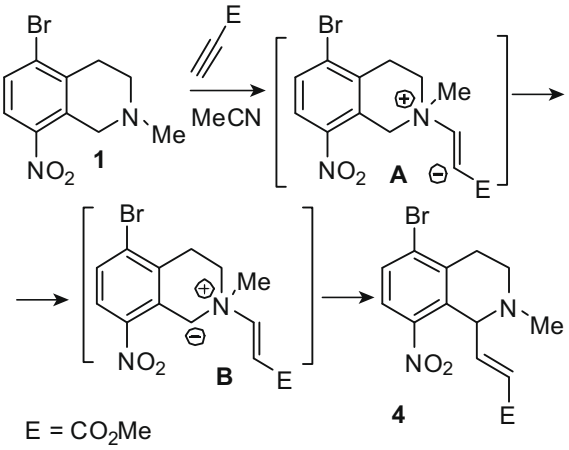
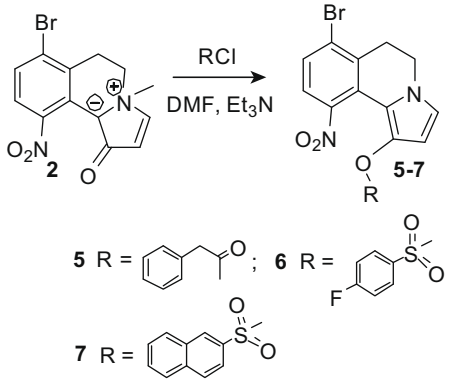


Figure 1. ORTEP structure of **2**.



Scheme 3.



Scheme 4.

In conclusion, we have demonstrated the synthesis of the pyrrolo[2,1-*a*]isoquinoline core via a new tandem Michael addition–intramolecular nucleophilic substitution reaction of easily available tetrahydroisoquinolines with electron-poor alkynes. The reaction results in the formation of unusually stable ammonium ylides **2** and **3**, which can be further modified, thus providing access to polysubstituted pyrrolo[2,1-*a*]isoquinoline frameworks. Work aimed at exploring other tetrahydroisoquinolines bearing electron-withdrawing groups as well as other alkynes in this transformation is underway and will be reported in due course.

Acknowledgement

The financial support of the Russian Foundation for Basic Research (Grant 08-03-00226-a) is gratefully acknowledged.

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14. *7-Bromo-4-methyl-10-nitro-1-oxo-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-4-ium ylide* (**2**): To a solution of 2-methyl-5-bromo-8-nitro-1,2,3,4-tetrahydroisoquinoline (**1**) (275 mg, 1 mmol) in MeOH (15 mL) was added methyl propiolate (0.11 mL, 1.2 mmol). The reaction mixture was stirred at room temperature (TLC monitoring). After completion of the reaction, the wine-red precipitate formed was collected by filtration and dried in air. The yield of ylide **2** was 250 mg (77%); mp 280–282 °C (dec) (MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.88 (dt, J = 6.7, J = 11.9 Hz, 1H, 6-CH$_2$), 3.18 (s, 3 H, N-CH$_3$), 3.23–3.30 (m, 2H, 6-CH$_2$ and 5-CH$_2$), 4.23 (dd, J = 6.0, J = 11.2 Hz, 1H, 5-CH$_2$), 6.57 (d, J = 3.4 Hz, 1H, 2-H), 7.19 (d, J = 8.7 Hz, 1H, 8-H), 7.54 (d, J = 8.7 Hz, 1H, 9-H), 7.62 (d, J = 3.4 Hz, 1H, 3-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.6, 48.7, 57.2, 107.6, 122.8, 124.6, 124.8, 125.1, 127.1, 131.2, 140.7, 145.4, 166.0 ppm. IR (KBr): ν 1618, 1558 cm^{-1}. EI MS: m/z (%) 324 (98), 322 (94) [M$^+$], 314 (14), 308 (53), 306 (52), 305 (31), 294 (11), 293 (21), 292 (12), 291 (15), 281 (11), 280 (27), 278 (23), 277 (21), 265 (23), 256 (27), 254 (25), 252 (31), 251 (17), 225 (16), 223 (19), 213 (43), 211 (41), 210 (14), 196 (11), 185 (17), 169 (13), 143 (11), 141 (12), 129 (11), 115 (12), 104 (16), 102 (14), 96 (33), 94 (30), 81 (52), 79 (25), 77 (18), 65 (11), 63 (13), 57 (13), 52 (12), 51 (11), 43 (45). Calcd for $C_{13}H_{11}BrN_2O_3$ (323.14): C, 48.32; H, 3.43; N, 8.67. Found: C, 48.59, H 3.61, N 8.43.
15. *7-Bromo-3-(methoxycarbonyl)-4-methyl-10-nitro-1-oxo-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-4-ium ylide* (**3**): To an ice-cold solution of 2-methyl-5-bromo-8-nitro-1,2,3,4-tetrahydroisoquinoline (**1**) (100 mg, 0.34 mmol) in MeOH (5 mL) was added DMAD (0.3 mL, 2.38 mmol). The reaction mixture was kept at −5 °C (TLC monitoring). The wine-red precipitate formed was collected by filtration and dried in air. The yield of ylide **3** was 42 mg (30%); mp 288–290 °C (dec) (MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.11 (ddd, J = 6.0, J = 12.4, J = 18.2 Hz, 1H, 6-CH$_2$), 3.29–3.31 (m, 2H, 6-CH$_2$ and 5-CH$_2$), 3.35 (s, 3H, N-CH$_3$), 3.86 (s, 3H, CO$_2$CH$_3$), 4.51–4.54 (m, 1H, 5-CH$_2$), 7.35 (d, J = 5.5 Hz, 1H, 8-H), 7.47 (s, 1H, 2-H), 7.57 (d, J = 5.5 Hz, 1H, 9-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.8, 41.6, 51.7, 53.8, 98.7, 114.3, 117.5, 118.2, 118.7, 124.9, 132.5, 139.4, 150.1, 165.7, 169.9 IR (KBr): ν 1714, 1629, 1521 cm^{-1}. EI MS: m/z (%) 382 (33), 380 (37) [M$^+$], 337 (11), 276 (10), 264 (13), 263 (17), 255 (32), 254 (63), 242 (23), 209 (10), 197 (11), 182 (16), 171 (17), 170 (24), 169 (27), 168 (33), 166 (41), 165 (37), 164 (29), 140 (14), 139 (26), 129 (18), 128 (35), 127 (37), 126 (26), 118 (12), 117 (35), 116 (46), 115 (63), 113 (100), 114 (57), 112 (45), 103 (16), 101 (26), 89 (14), 81 (29), 76 (22), 77 (17), 69 (15), 63 (23), 59 (44), 45 (33), 43 (58). Calcd for $C_{15}H_{13}BrN_2O_3$ (381.18): C, 47.26; H, 3.44; N, 7.35. Found: C, 47.42; H, 3.51; N, 7.47.
16. CCDC 737829 (for **2**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Canbridge CB1 1 EZ, UK; Fax +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk.
17. *Methyl (2E)-3-(5-bromo-2-methyl-8-nitro-1,2,3,4-tetrahydroisoquinolin-1-yl)-acrylate* (**4**): To a solution of 5-bromo-2-methyl-1,2,3,4-tetrahydro-8-nitroisoquinoline (**1**) (275 mg, 1 mmol) in MeCN (15 mL) was added methyl propiolate (0.11 mL, 1.2 mmol). The reaction mixture was stirred at room temperature (TLC monitoring). After completion of the reaction, the solvent was evaporated under reduced pressure and the resulting residue was purified by column chromatography with hexane/EtOAc (1:15) as eluent to give isoquinoline **4** (179 mg, 50%) as a greenish oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.51 (s, 3H, N-CH$_3$), 2.77–2.88 (m, 2H, 4-CH$_2$), 2.93–3.08 (m, 2H, 3-CH$_2$), 3.71 (s, 3H, OCH$_3$), 5.12 (d, J = 6.5 Hz, 1H, =*CH*–COCH$_3$), 5.62 (d, J = 16.0 Hz, 1H, 1-H), 6.96 (dd, J = 6.6, J = 16.0 Hz, 1H, =CH), 7.26–7.27 (m, 2H, CH-Ar) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 28.1, 41.5, 44.4, 51.6, 58.7, 123.8, 123.9, 130.6, 130.7, 132.0, 136.9, 144.5, 148.2, 165.3 ppm. IR (KBr): ν 1725, 1654 cm^{-1}. EI MS: m/z (%) 356 (5), 354 (5) [M$^+$], 339 (19), 337 (18), 280 (95), 278 (100), 270 (45), 262 (53), 248 (35), 225 (43), 223 (47), 168 (11), 144 (23), 115 (11), 42 (13). Calcd for $C_{14}H_{15}BrN_2O_3$ (355.18): C, 47.34; H, 4.26; N, 7.86. Found: C, 47.53; H, 4.43; N, 7.65.
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19. *7-Bromo-10-nitro-5,6-dihydropyrrolo[2,1-a]isoquinolin-1-yl 2-phenylacetate* (**5**): Yield (65%) yellow crystals mp 210–212 °C (hexane/EtOAc). ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.17 (t, J = 6.3 Hz, 2H, 5-CH$_2$), 3.80 (s, 2H, CO*CH*$_2$Ph), 4.12 (t, J = 6.3 Hz, 2H, 6-CH$_2$), 6.28 (d, J = 3.0 Hz, 1H, 3-H), 6.67 (d, J = 3.0 Hz, 1H, 2-H), 7.24–7.26 (m, 1H, CH-Ph), 7.30–7.33 (m, 2H, 2CH-Ph), 7.35–7.36 (m, 2H, 2CH-Ph), 7.46 (d, J = 8.7 Hz, 1H, 8-CH), 7.55 (d, J = 8.7 Hz, 1H, 9-CH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 30.7, 39.6, 42.7, 102.1, 110.9, 121.1, 122.8, 124.6, 126.9, 127.6, 128.3 (2C), 129.4 (2C), 129.6, 133.6, 135.3, 136.0, 144.7, 168.3 ppm. IR (KBr): ν 1751, 1527 cm^{-1}. EI MS: m/z (%) 428 (11), 426 (13) [M$^+$], 312 (7), 311 (23), 310 (95), 308 (100), 293 (32), 291 (34), 277 (27), 263 (11), 253 (23), 223 (13), 212 (21), 198 (13), 185 (53), 173 (15), 162 (12), 156 (19), 155 (32), 145 (27), 133 (29), 119 (23), 105 (35), 92 (10), 91 (82), 85 (67), 81 (85), 65 (43), 59 (31), 55 (83), 45 (16), 43 (76). Calcd for $C_{20}H_{15}BrN_2O_4$ (427.25): C, 56.22; H, 3.54; N, 6.56. Found: C, 56.51; H, 3.32; N, 7.69.
20. *7-Bromo-1-(4-fluorophenylsulfonyloxy)-10-nitro-5,6-dihydropyrrolo[2,1-a]isoquinoline* (**6**): Yield (72%) yellow crystals mp 212–213 °C (hexane/EtOAc). ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.94-2.96 (m, 2H, 5-CH$_2$), 4.02 (t, J = 6.3 Hz, 2H, 6-CH$_2$), 6.21 (d, J = 3.0 Hz, 1H, 3-H), 6.67 (d, J = 3.0 Hz, 1H, 2-H), 6.86–6.89 (m, 2H, CH-Ar), 7.41 (m, 2H, 8-H and 9-H), 7.61–7.64 (m, 2H, 2CH-Ar) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 30.4, 42.7, 103.4, 113.7, 115.7 (d, 2C, $^2J_{C,F}$ = 23 Hz), 121.3, 121.5, 124.4, 127.0, 127.9, 128.0, 131.0 (d, 2C, $^3J_{C,F}$ = 10 Hz), 133.3, 135.5, 144.7, 165.6 (d, $^1J_{C,F}$ = 255 Hz) ppm. IR (KBr): ν 1592, 1527 cm^{-1}. EI MS: m/z (%) 468 (11), 466 (12) [M$^+$], 307 (37), 291 (11), 280 (25), 279 (100), 277 (94), 261 (13), 251 (11), 250 (33), 233 (7), 228 (23), 198 (29), 184 (10), 182 (24), 170 (13), 169 (16), 155 (22), 154 (28), 144 (12), 143 (23), 129 (23), 127 (26), 126 (27), 116 (26), 115 (50), 102 (24), 95 (31), 89 (17), 82 (12), 81 (60), 75 (27), 69 (26), 55 (18), 53 (26), 51 (42), 44 (14), 43 (26). Calcd for $C_{18}H_{12}BrFN_2O_5S$ (467.27): C, 46.27; H, 2.59; N, 6.00. Found: C, 46.61; H, 2.37; N, 5.91.
21. *7-Bromo-1-(2-naphthylsulfonyloxy)-10-nitro-5,6-dihydropyrrolo[2,1-a]isoquinoline* (**7**): Yield (68%) yellow crystals mp 208–209 °C (hexane/EtOAc). ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.28–3.33 (m, 2H, 5-CH$_2$), 3.95 (t, J = 6.6 Hz, 2H, 6-CH$_2$), 6.22 (d, J = 3.0 Hz, 1H, 3-H), 6.97 (d, J = 8.7 Hz, 1H, 8-H), 7.04 (d, J = 3.0 Hz, 1H, 2-H), 7.24 (d, J = 8.7 Hz, 1H, 9-H), 7.27 (dd, J = 2.1, J = 8.7 Hz, 1H, CH-Ar), 7.59–7.63 (m, 1H, CH-Ar), 7.69–7.71 (m, 1H, CH-Ar), 7.72–7.74 (m, 1H, CH-Ar), 7.85 (d, J = 9.1 Hz, 1H, CH-Ar), 7.96 (dd, J = 0.8, J = 8.5 Hz, 1H, CH-Ar), 8.04 (d, J = 2.6 Hz, 1H, CH-Ar) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 30.2, 42.7, 103.6, 113.8, 121.2 (2C), 122.1, 123.8, 126.6, 127.6, 127.7, 128.3, 128.8, 129.3, 129.6, 129.9 (2C), 130.7, 133.5, 134.8, 135.0, 144.4 ppm. IR (KBr): ν 1524 cm^{-1}. EI MS: m/z (%) 500 (45), 499 (10), 498 (46) [M$^+$], 310 (34), 309 (100), 307 (94), 293 (12), 291 (19), 280 (63), 279 (81), 277 (79), 262 (12), 251 (13), 250 (34), 212 (17), 208 (22), 198 (16), 191 (17), 175 (26), 170 (29), 160 (18), 129 (23), 128 (62), 127 (89), 115 (78), 102 (13), 101 (17), 89 (16), 81 (82), 64 (24), 55 (27), 44 (12), 43 (66). Calcd for $C_{22}H_{15}BrN_2O_5S$ (499.33): C, 52.92; H, 3.03; N, 5.61. Found: C, 53.12; H, 2.87; N, 5.75.