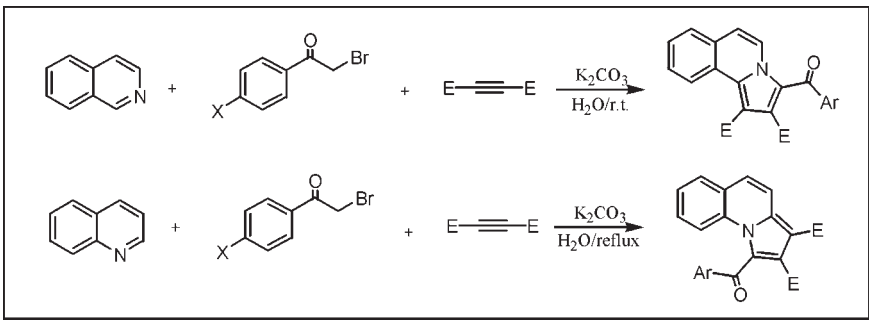
Efficient Synthesis of Pyrrolo[2,1-*a*]isoquinoline and Pyrrolo[1,2-*a*]quinoline Derivatives in Aqueous Media

Ebrahim Kianmehr,* Hamid Estiri, and Azadeh Bahreman

School of Chemistry, College of Science, University of Tehran, Tehran, Iran
*E-mail: kianmehr@khayam.ut.ac.ir

Received April 4, 2009
DOI 10.1002/jhet.205
Published online 5 November 2009 in Wiley InterScience (www.interscience.wiley.com).



A one-pot procedure for the synthesis of pyrrolo[2,1-*a*]isoquinolines and pyrrolo[1,2-*a*]quinolines in good to excellent yields has been reported, using quinoline or isoquinoline, phenacylbromide derivatives and activated alkynes in aqueous medium.

J. Heterocyclic Chem., **46**, 1203 (2009).

INTRODUCTION

The synthesis of indolizines, and their derivatives with additional rings fused like pyrrolo[2,1-*a*]isoquinolines and pyrrolo[1,2-*a*]quinolines, has puzzled scientists for decades. The interest in these compounds is largely owing to their properties. Synthetic indolizines are used as potential central nervous system depressants [1], calcium entry blockers [2], testosterone 5α-reductase inhibitors [3], cardiovascular agents [4], spectral sensitizers [5], and novel dyes [6]. Pyrrolo[2,1-*a*]isoquinoline derivatives [7] have attracted considerable interest, because they possess antidepressant [8], muscarinic agonist [9], antiplatelet [10], and anticancer activity [11]. Moreover, they can be used as Positron emission tomography (PET) radiotracers for imaging serotinine uptake sites [12]. The importance of these nitrogen heterocycles is further enhanced by their utility as advanced intermediates for the synthesis of alkaloids [13]. Acetoxy substituted 5,6-dihydro[2,1-*a*]isoquinolines (**1** in Fig. 1) exhibit strong binding affinities for the estrogen receptor of MDA-MB 231 and MCF-7 mammary tumor cell lines [14].

The parent framework of **1** (**2** in Fig. 1) is an α_2-adrenoreceptor antagonist[15] and its 5-phenyl derivatives exhibit antidepressant-like activity.[16] 1-benzoyl-3-cyano-pyrrolo[1,2-a]quinolines (**3** in Fig. 1) have been shown to be activators of caspases and inducers of apoptosis and also are used as therapeutically effective anticancer agents [17]. As a result, development of new methods to synthesize these classes of compounds is of considerable importance, and a number of general synthetic methods for their preparation have been reported [7,18].

The increasing environmental consciousness of the chemical community has led to the search for more efficient and environmentally friendly methods for chemical syntheses [19]. Because of the environmental acceptability, abundance, and low cost of water, organic reactions in water have received increased attention [20]. Many reactions that are traditionally carried out in organic solvent can be carried out in water with additional interesting features [21]. Thus, the development of efficient procedures for useful chemical transformations in water is highly appreciated.

RESULTS AND DISCUSSION

As part of our current studies on the development of ylide reactions in aqueous media [22], we report herein an efficient synthesis of pyrrolo[2,1-*a*]isoquinolines and pyrrolo[1,2-*a*]quinolines via a one-pot three component reaction of isoquinoline or quinoline with phenacylbromide derivatives and activated alkynes.

We began our study by investigating the reactivity of preformed salts, such as **4** or **5** as nitrogen ylide precursors (Scheme 1).

Treatment of salt **4** or **5** with activated acetylenes in water, in the presence of a base, formed compounds **6**, **7**, respectively, in good to excellent yields. The temperature was of crucial importance. No reaction was observed at room temperature with quinoline ylides and

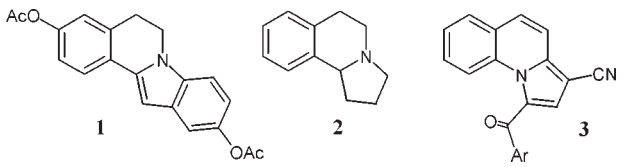


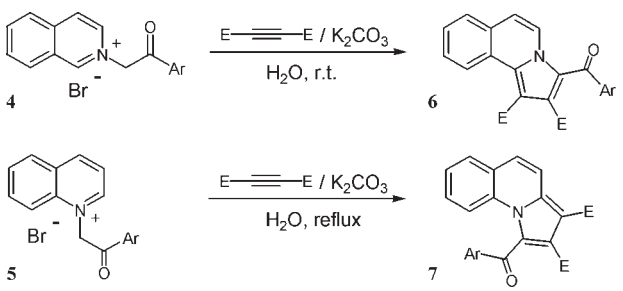
Figure 1. Chemical structures of **1**, **2**, and **3**.

all of the reactions were carried out at reflux. However, isoquinoline ylides produced the corresponding products in good to excellent yields at room temperature. To increase the efficiency of this process, we investigated the development of a one-pot reaction in which the salt and the ylide could be generated *in situ*, in water, from readily available starting materials. Accordingly, phenacylbromide derivative was added to isoquioline or quinoline in water, and after a while, activated alkyne and base were added to the reaction mixture, and the reaction continued at room temperature or at reflux (Scheme 2).

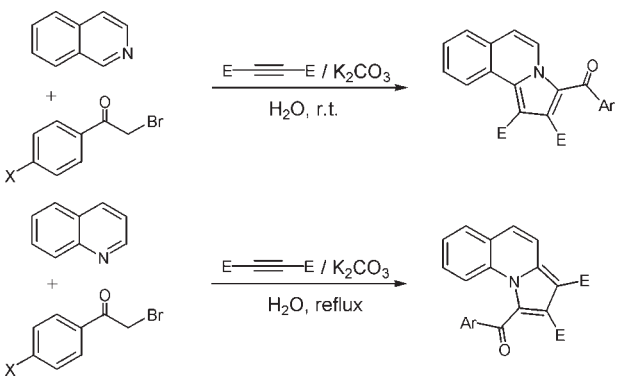
The use of optimal conditions to the reaction of quinoline and isoquinoline with different phenacylbromide derivatives and activated acetylenes afforded good to excellent yields of pyrrolo[2,1-*a*]isoquinolines and pyrrolo[1,2-*a*]quinolines. The results of this study are summarized in Tables 1 and 2.

The structures of all the synthesized compounds were established on the basis of their spectroscopic data. The ^{1}H NMR spectrum of **6d** exhibited two coupled pairs of triplet and quarted signals for ethoxy groups, centered at $\delta = 1.02$, 1.43 ppm and $\delta = 3.83$, 4.48 ppm, respectively. Methoxy group resonated at $\delta = 3.91$ ppm as a single sharp line. The peaks corresponding to aromatic protons of methoxyphenyl moiety and protons of nitrogen containing ring of isoquinoline were seen as two coupled pairs of doublet signals at $\delta = 6.98$, 7.86 ppm ($J = 8.7$ Hz) and $\delta = 7.12$, 8.66 ppm ($J = 7.5$ Hz), respectively. Other aromatic protons gave rise to characteristic signals in the aromatic region of the spectrum. The proton decoupled ^{13}C NMR spectrum of **6d** showed 24 distinct resonances in agreement with the proposed structure. ^{1}H NMR spectrum of **7c** exhibited three sharp

Scheme 1



Scheme 2



singlet signals readily recognized as arising from methoxy protons. ($\delta = 3.55$, 3.90 and 3.93 ppm) Signals due to aromatic protons of methoxyphenyl moiety and protons of nitrogen containing ring of quinoline were discernible as two coupled pairs of doublet signals at $\delta = 6.98$, 7.98 ppm ($J = 8.7$ Hz) and $\delta = 7.55$, 8.22 ppm ($J = 9.4$ Hz). Other aromatic protons gave rise to characteristic signals in the aromatic region of the spectrum. The proton decoupled ^{13}C NMR spectrum of **7c** showed 22 distinct resonances in agreement with the proposed structure.

Mechanistically, it is conceivable that the reaction involves the initial formation of ylide A by the reaction of isoquinoline (or quinoline) and phenacylbromide derivative followed by deprotonation in the presence of K_2CO_3 as the base. This ylide intermediate then undergoes reaction with activated alkynes to produce B, which leads to C by oxidation (Scheme 3).

In summary, a one-pot procedure for the synthesis of pyrrolo[2,1-*a*]isoquinolines and pyrrolo[1,2-*a*]quinolines via *in situ* formation of quinoline or isoquinoline ylides and reaction of with activated alkynes in aqueous media has been reported. The notable advantages offered by this method are simple operation, mild and environment friendly reaction conditions, high yields of products, and costeffectiveness. Most significantly, this demonstrates

Table 1

Reaction of isoquinoline with phenacylbromide derivatives and activated alkynes in H_2O.

6	X	E	Time (h)	Yield (%)
a	H	CO_2Me	6	90
b	H	CO_2Et	6	85
c	4-OMe	CO_2Me	6	94
d	4-OMe	CO_2Et	6	93
e	4-Br	CO_2Me	6	87
f	4-Br	CO_2Et	7	83
g	4-Ph	CO_2Me	7	80
h	4-Ph	CO_2Et	7	80

Table 2

Reaction of quinoline with phenacylbromide derivatives and activated alkynes in H_2O.

7	X	E	Time (h)	Yield (%)
a	H	CO_2Me	14	77
b	H	CO_2Et	15	78
c	4-OMe	CO_2Me	12	82
d	4-OMe	CO_2Et	12	85
e	4-Br	CO_2Me	14	69
f	4-Br	CO_2Et	13	71
g	4-Ph	CO_2Me	14	86
h	4-Ph	CO_2Et	11	84

the potential of water as an efficient promoter and provides much promise for the use of water in other chemical transformations.

EXPERIMENTAL

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker DRX-500 NMR spectrometer using TMS as an internal standard. Mass spectrometry (MS) spectra were carried out on HP 5973 GC-MS instrument. Infrared (IR) spectra were measured using a Shimadzu FTIR-4300. Chemicals were purchased from Merck and were used as received. Column chromatography was performed on silica gel (0.063-0.200 mm; Merck).

General procedure for the preparation of compound 6a. Isoquinoline (0.19 g, 1.5 mmol) and phenacylbromide (0.3 g, 1.5 mmol) were taken in water (10 mL), and the mixture was stirred at room temperature for 2 h. To this mixture, dimethyl acetylenedicarboxylate (0.14 g, 1.0 mmol) and K_2CO_3 (0.28 g, 2.0 mmol) were added, and it was allowed to stir at room temperature for 4 h. The reaction mixture was filtered and purified by column chromatography on silica gel with eluent 10%EtOAc in hexane to afford **6a** as yellow solid.

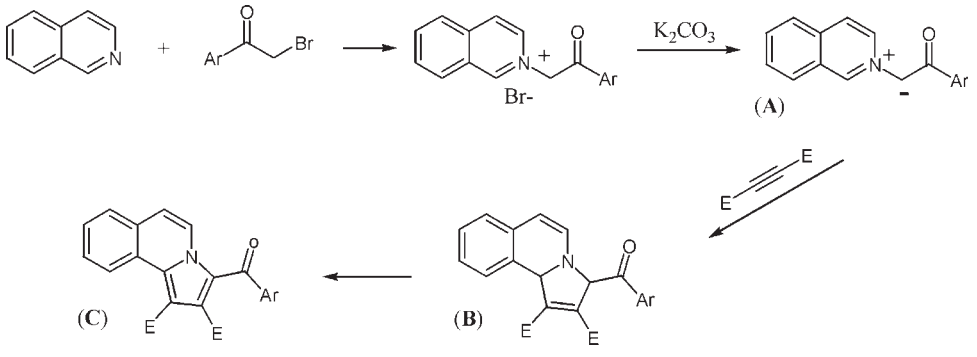
Compound (6a). Yellow solid; mp 154–155°C. IR (KBr) υ/cm^{-1}: 2951, 1749, 1709, 1624, 1518, 1492, 1475, 1398, 1363, 1269, 1225, 1201, 1101, 897, 866, 787 cm^{-1}. ^{1}H NMR: δ (ppm) 3.29 (s, 3H), 4.0 (s, 3H), 7.22 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.62 (m, 1H), 7.65 (m, 2H), 7.77 (m, 1H), 7.82 (dd, J = 7.1Hz, J = 1.3Hz, 2H), 8.91 (m, 1H), 8.94 (d, J = 7.5 Hz, 1H). ^{13}C NMR: δ (ppm) 52.3, 52.9, 110.0, 116.3, 123.4, 124.1, 124.7, 126.1, 127.6, 128.7, 128.8, 129.3, 129.5, 130.0, 132.8, 133.1, 140.2, 165.1, 166.4, 187.7. MS (EI, 70 eV) *m*/*z* (%) 387 (M$^+$, 100), 356 (57), 324 (58), 310 (20), 298 (11), 284 (22), 269 (16), 252 (10), 240 (21), 193 (10), 164 (14), 139 (10), 105 (19).

Compound (6b). Yellow solid; mp 115–117°C. IR (KBr) υ/cm^{-1}: 2991, 2876, 1728, 1622, 1527, 1500, 1404, 1354, 1227, 1198, 1101, 1020, 966, 919, 800 cm^{-1}. ^{1}H NMR: δ (ppm) 1.0 (t, J = 7.2 Hz, 3H), 1.39 (t, J = 7.2 Hz, 3H), 3.67 (q, J = 7.2 Hz, 2H), 4.46 (q, J = 7.2 Hz, 2H), 7.19 (d, J = 7.5 Hz, 1H), 7.49 (t, J = 7.53,2H), 7.59 (m, 1H), 7.63 (m, 2H), 7.74 (m, 1H), 7.84 (dd, J = 8.4Hz, J = 1.3Hz, 2H), 8.89 (d, J = 7.5 Hz, 1H), 8.90 (m, 1H). ^{13}C NMR: δ (ppm) 14.0, 14.4, 61.8, 62.0, 110.4, 116.2, 123.2, 124.1,124.8, 126.1, 127.6, 127.7, 128.7, 128.8, 129.4, 129.6, 130.0, 132.7, 133.2, 140.1, 164.7, 166.0, 187.6. MS (EI, 70 eV) *m*/*z* (%) 415 (M$^+$, 100), 387 (9), 370 (20), 343 (25), 324 (17), 298 (44), 279, 279 (10), 270 (19), 241 (21), 220 (12), 167 (23), 149 (53), 105 (23).

Compound (6c). Yellow solid; mp 137–138°C. IR (KBr) υ/cm^{-1}: 2953, 2841, 1734, 1708, 1620, 1600, 1572, 1504, 1396, 1362, 1313, 1259, 1222, 1201, 1101, 1026, 903, 839, 785 cm^{-1}. ^{1}H NMR: δ (ppm) 3.42 (s, 3H), 3.92 (s, 3H), 4.01 (s, 3H), 7.0 (d, J = 8.77 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 7.64 (m, 2H), 7.74 (m, 1H), 7.84 (d, J = 8.77 Hz, 2H), 8.7 (d, J = 7.5 Hz, 1H), 8.8 (m, 1H). ^{13}C NMR: δ (ppm) 52.4, 53.0, 56.0, 109.8, 114.2, 116.0, 123.9, 124.2, 124.9, 125.9, 127.6, 128.7, 129.3, 129.7, 131.9, 132.1, 132.7, 164.0, 165.1, 166.6, 186.4. MS (EI, 70 eV) *m*/*z* (%) 417 (M$^+$, 6), 387 (100), 356 (69), 324 (76), 310 (29), 298 (16), 284 (29), 269 (20), 252 (31), 240 (26), 167 (20), 149 (39), 105 (22).

Compound (6d). Yellow solid; mp 112–114°C. IR (KBr) υ/cm^{-1}: 2997, 1738, 1705, 1626, 1599, 1504, 1464, 1360, 1309, 1257, 1217, 1202, 1169, 1097, 1022,846, 796 cm^{-1}. ^{1}H NMR: δ (ppm) 1.02 (t, J = 7.16 Hz, 3H), 1.43 (t, J = 7.14 Hz, 3H), 3.84 (q, J = 7.15 Hz, 2H), 3.91 (s, 3H), 4.49 (q, J = 7.1 Hz 2H), 7.0 (d, J = 8.75 Hz,2H), 7.12 (d, J = 7.5 Hz, 1H)7.6 (m, 2H), 7.7 (m, 1H), 7.9 (d, J = 8.7 Hz, 2H), 8.66 (d, J = 7.53 Hz, 1H), 8.9 (dd, J = 7Hz, J=1.9 Hz, 1H). ^{13}C NMR: δ (ppm) 14.0, 14.4, 56.0, 61.7, 62.0, 110.2, 114.1, 115.8, 123.9, 124.0, 125.0, 125.9, 126.0, 127.6, 128.6, 129.1, 129.7, 132.0, 132.1, 132.7, 164.1, 164.7, 166.2, 186.4. MS (EI, 70 eV) *m*/*z* (%) 445 (M$^+$, 31), 415 (2), 400 (3), 328 (12), 311 (100), 266 (43), 238 (92), 211 (15), 194 (25), 167 (41), 149 (16), 139 (27), 128 (15).

Scheme 3



Compound (6e). Yellow solid; mp 142–144°C. IR (KBr) υ/ cm^{-1}: 3004, 2842, 1740, 1732, 1624, 1585, 1504, 1398, 1360, 1263, 1225, 1201, 1176, 1097, 895, 831, 797 cm^{-1}. ^1H NMR: δ (ppm) 3.39 (s, 3H), 4.0 (s, 3H), 7.23 (d, J = .5 Hz, 1H), 7.67 (m, 6H), 7.77 (m, 1H), 8.90 (m, 1H), 8.91 (d, J = 7.5 Hz, 1H). ^{13}C NMR: δ (ppm) 52.5, 53.0, 110.3, 116.5, 122.9, 124.0, 124.7, 126.2, 127.7, 128.0, 128.9, 129.6, 130.1, 130.9, 132.1, 133.0, 139.0, 164.9, 166.2, 186.4. MS (EI, 70 eV) *m/z* (%) 467 (M^+, ^{81}Br, 100), 465 (M^+, ^{79}Br, 99), 436 (27), 434 (27), 404 (22), 402 (18), 324 (33), 310 (26), 297 (13), 240 (21), 213 (21), 185 (39), 183 (39), 155 (24).

Compound (6f). Yellow solid; mp 125–126°C. IR (KBr) υ/ cm^{-1}: 2363, 1722, 1628, 1585, 1516, 1473, 1450, 1400, 1354, 1263, 1196, 1097, 1068, 1030, 960, 916, 833, 796 cm^{-1}. ^1H NMR: δ (ppm) 1.10 (t, J = 7.1 Hz, 3H), 1.42 (t, J = 7.1 Hz, 3H), 3.80 (q, J = 7.1 Hz, 2H), 4.49 (q, J = 7.1 Hz, 2H), 7.22 (d, J = 7.5 Hz, 1H), 7.66 (m, 4H), 7.72 (d, J = 8.5 Hz, 2H), 7.77 (m, 1H), 8.89 (d, J = 7.5 Hz, 1H), 8.92 (m, 1H). ^{13}C NMR: δ (ppm) 14.0, 14.4, 62.0, 62.1, 110.7, 116.4, 122.8, 124.0, 124.8, 126.2, 127.6, 127.7, 128.1, 128.8, 129.5, 130.0, 131.1, 132.1, 132.8, 139.0, 164.6, 165.9, 186.4. MS (EI, 70 eV) *m/z* (%) 495 (M^+, ^{81}Br, 100), 493 (M^+, ^{79}Br, 99), 450 (13), 448 (14), 421 (27), 376 (28), 348 (17), 297 (29), 264 (19), 238 (36), 220 (24), 199 (18), 183 (24), 164 (17), 149 (21), 139 (16), 128 (14).

Compound (6g). Yellow solid; mp 174–176°C. IR (KBr) υ/ cm^{-1}: 2945, 1727, 1720, 1637, 1603, 1502, 1479, 1358, 1273, 1230, 1201, 1176, 1101, 897, 869, 820 cm^{-1}. ^1H NMR: δ (ppm) 3.35 (s, 3H), 4.01 (s, 3H), 7.22 (d, J = 7.5 Hz, 1H), 7.46 (m, 1H), 7.53 (t, J = 7.3 Hz, 2H), 7.66 (m, 2H), 7.69 (d, J = 7.3Hz,2H), 7.76 (m, 3H), 7.91 (d, J = 8.2 Hz, 2H), 8.8 (m, 1H), 8.90 (m, 1H), 8.91 (d, J = 7.5 Hz, 1H). ^{13}C NMR: δ (ppm) 52.4, 53.0, 110.1, 116.3, 123.6, 124.1, 124.8, 126.1, 127.3, 127.4, 127.6, 127.7, 128.7,128.8, 129.4, 129.5, 130.0, 130.1, 132.7, 138.9, 140.2, 145.9, 165.1, 166.4, 187.2. MS (EI, 70 eV) *m/z* (%) 463(M^+, 100), 432 (22), 400 (45), 387 (13.4), 374 (7.1), 360 (13), 345 (8), 310 (18), 252 (7), 218 (8), 194 (10), 181 (18), 152 (35).

Compound (6h). Yellow solid; mp 149–150°C. IR (KBr) υ/ cm^{-1}: 2956, 2854, 1736, 1711, 1624, 1604, 1524, 1501, 1470, 1371, 1352, 1221, 1097, 1020, 920, 800 cm^{-1}. ^1H NMR: δ (ppm) 1.01 (t, J = 7.1 Hz, 3H), 1.43 (t, J = 7.1 Hz, 3H), 3.77 (q, J = 7.1 Hz, 2H), 4.49 (q, J = 7.1 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.46 (m, 1H), 7.53 (m, 2H), 7.67 (m, 4H), 7.74 (d, J = 8.2 Hz, 2H), 7.77 (m, 1H), 7.95 (d, J = 8.2 Hz, 2H), 8.89 (d, J = 7.5 Hz, 1H), 8.91 (m, 1H) ppm. ^{13}C NMR: δ (ppm) 14.0, 14.4, 61.9, 62.0, 110.6, 116.2, 123.4, 124.1, 124.9, 126.1, 127.3, 127.4, 127.6, 127.7, 128.71, 128.73, 129.36, 129.44, 129.9, 130.3, 132.5, 138.9, 140.2, 146.0, 164.7, 166.1, 187.2 ppm. MS (EI, 70 eV) *m/z* (%) 491 (M^+, 52), 463 (9), 400 (13), 374 (16), 279 (11), 198 (17), 181 (46), 167 (29), 149 (60), 125 (28), 111 (44), 97 (61), 83 (59), 71 (76).

Compound (7a). Yellow solid; mp 158–160°C. IR (KBr) υ/ cm^{-1}: 2993, 2360, 1730, 1697, 1633, 1612, 1550, 1491, 1450, 1418, 1362, 1323, 1259, 1219, 1171, 1093, 877, cm^{-1}. ^1H NMR: δ (ppm) 3.48 (s, 3H), 3.95 (s, 3H), 7.47 (m, 2H), 7.54 (t, J = 7.59 Hz, 2H), 7.68 (m, 3H), 7.83 (m, 1H), 8.01 (d, J = 7.6 Hz, 2H), 8.30 (d, J = 9.43 Hz, 1H) ppm. ^{13}C NMR: δ (ppm) 52.1, 52.6, 106.0, 118.4, 119.5, 125.7, 126.1, 126.9, 128.4, 129.1, 129.4, 129.5, 129.6, 130.3, 132.9, 134.3, 137.6, 138.1, 164.1, 165.5, 188.2. MS (EI, 70 eV) *m/z* (%) 387 (M^+, 34), 356 (10), 330 (75), 298 (61), 283 (96), 252 (100), 241 (17), 222 (34), 194 (18), 166 (35), 139 (14), 128 (13), 105 (60), 77 (41).

Compound (7b). Yellow solid; mp 154–156°C. IR (KBr) υ/ cm^{-1}: 2975, 1730, 1697, 1634, 1612, 1556, 1494, 1437, 1392, 1323, 1237, 1213, 1167, 1095, 874 cm^{-1}. ^1H NMR: δ (ppm) 1.11 (t, J = 7.2 Hz, 3H), 1.41 (t, J = 7.2 Hz, 3H), 3.90 (q, J = 7.2 Hz, 2H), 4.41 (q, J = 7.2 Hz, 2H), 7.4 (m, 2H), 7.46 (t, J = 7.7 Hz, 2H), 7.62 (d, J = 9.4 Hz, 1H),7.67 (m, 2H), 7.8 (m, 1H), 8.03 (d, J = 7.3 Hz, 2H), 8.30 (d, J = 9.4 Hz, 1H). ^{13}C NMR: δ (ppm) 14.1, 14.7, 60.9, 62.0, 106.2, 118.3, 119.4, 125.7, 126.0, 128.3, 128.6, 129.1, 129.3, 129.6, 130.5, 132.9, 134.3, 137.6, 138.1, 163.7, 165.2, 188.1. MS (EI, 70 eV) *m/z* (%) 415 (M^+, 100), 387 (5), 370 (30), 343 (19), 324 (14), 312 (16), 298 (59), 270 (35), 241 (35), 220 (26), 194 (12), 164 (15), 128 (113), 105 (50), 77 (50).

Compound (7c). Yellow solid; mp 169–172°C. IR (KBr) υ/ cm^{-1}: 2949, 1724, 1710, 1649, 1597, 1573, 1508, 1448, 1421, 1323, 1259, 1213, 1174, 1091, 889cm^{-1}. ^1H NMR: δ (ppm) 3.55 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 6.98 (d, J = 8.8 Hz, 2H), 7.41 (m, 2H), 7.55 (d, J = 9.4 Hz, 1H), 7.68 (m, 1H), 7.75 (m,1H), 7.98 (d, J = 8.7 Hz, 2H), 8.22 (d, J = 9.4 Hz, 1H) ppm. ^{13}C NMR: δ (ppm) 52.1, 52.7, 56.0, 105.8, 114.4, 118.3, 119.2, 125.6, 126.0, 126.9, 127.1, 127.8, 129.3, 129.6, 130.9, 132.8, 132.9, 137.0, 164.2, 164.8, 165.6, 187.2. MS (EI, 70 eV) *m/z* (%) 417 (M^+, 65), 386 (11), 354 (25), 328 (18), 298 (13), 287 (24), 179 (14), 252 (18), 228 (13), 167 (36), 149 (92), 135 (85), 111 (27),97 (40), 83 (48).

Compound (7d). Yellow solid; mp 166–168°C. IR (KBr) υ/ cm^{-1}: 2980, 1716, 1702, 1643, 1597, 1577, 1508, 1441, 1257, 1217, 1173, 1093, 877 cm^{-1}. ^1H NMR: δ (ppm)1.13 (t, J = 7.2Hz, 3H), 1.4 (t, J = 7.2 Hz, 3H), 3.99 (q, J = 7.2 Hz, 2H), 4.41 (q, J = 7.2 Hz, 2H), 7.0 (d, J = 8.8 Hz, 2H), 7.44 (m, 2H), 7.58 (d, J = 9.4 Hz, 1H), 7.70 (m, 1H), 7.79 (m, 1H), 8.0 (d, J = 8.7 Hz, 2H), 8.29 (d, J = 9.4 Hz, 2H). ^{13}C NMR: δ (ppm) 14.1, 14.7, 56.0, 60.9, 62.0, 106.0, 114.4, 118.4, 119.2, 125.7, 125.9, 126.8, 127.2, 127.7, 129.3, 129.6, 131.0, 132.9, 137.1, 163.8, 164.8, 165.2, 187.2. MS (EI, 70 eV) *m/z* (%) 445 (M^+, 100), 400 (19), 354 (13), 328 (21), 300 (17), 266 (15), 238 (16), 220 (14), 167 (16), 149 (37), 135 (62), 107 (12), 97 (12),77 (17).

Compound (7e). Yellow solid; mp 194–195°C. IR (KBr) υ/ cm^{-1}: 2852, 1742, 1693, 1651, 1583, 1543, 1477, 1446, 1392, 1267, 1207, 1102, 1095, 885, 810 cm^{-1}. ^1H NMR: δ (ppm) 3.55 (s, 3H), 3.95 (s, 3H), 7.48 (m, 2H), 7.64 (m, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.82 (m, 1H), 7.87 (d, J = 8.4 Hz, 2H), 8.28 (d, J = 9.4 Hz, 1H). ^{13}C NMR: δ (ppm) 52.2, 52.8, 106.1, 118.3, 119.3, 125.7, 126.2, 126.3, 128.60, 128.62, 129.5, 129.6, 129.7, 131.7, 132.4, 132.8, 136.9, 137.7, 164.0, 165.5, 187.0. MS (EI, 70 eV) *m/z* (%) 467 (M^+, ^{81}Br, 100), 465 (M^+, ^{79}Br, 99), 434 (21), 406 (18), 347 (8), 324 (18), 310 (47), 252 (22), 239 (19), 193 (14), 183 (20), 167 (21), 149 (42), 97 (21), 83 (23), 71 (34).

Compound (7f). Yellow solid; mp 150–152°C. IR (KBr) υ/ cm^{-1}: 2937, 1716, 1695, 1645, 1581, 1544, 1483, 1434, 1400, 1342, 1300, 1257, 1225, 1093, 889cm^{-1}. ^1H NMR: δ (ppm) 1.15 (t, J = 7.2 Hz, 3H), 1.4 (t, J = 7.2Hz, 3H), 3.97 (q, J = 7.2 Hz, 2H), 4.42 (q, J = 7.2 Hz, 2H), 7.49 (m,2H), 7.63 (m, 2H), 7.68 (d, J = 8.5 Hz, 2H), 7.84 (m, 1H), 7.90 (d, J = 8.5 Hz, 2H), 8.32 (d, J = 9.4 Hz, 1H). ^{13}C NMR: δ (ppm) 14.1, 14.7, 61.0, 62.1, 106.3, 118.3, 119.3, 125.7, 126.0, 126.2,

128.5, 128.9, 129.4, 129.6, 129.7, 131.8, 132.4, 132.8, 136.9, 137.7, 163.5, 165.1, 186.9. MS (EI, 70 eV) *m*/*z* (%) 495 (M^+, ^{81}Br, 100), 493 (M^+, ^{79}Br, 96), 450 (13), 422 (13), 376 (22), 348 (16), 297 (17), 266 (28), 238 (44), 220 (25), 183 (25), 166 (14), 155 (18), 128 (16), 97 (15).

Compound (7g). Yellow solid; mp 164–165°C. IR (KBr) υ/cm^{-1}: 2954, 1745, 1707, 1637, 1604, 1554, 1477, 1444, 1361, 1325, 1259, 1213, 1095, 883, 744 cm^{-1}. ^1H NMR: δ (ppm) 3.53 (s, 3H), 3.97 (s, 3H), 7.47 (m, 3H), 7.53 (m, 2H), 7.65 (d, J = 9.4 Hz, 1H), 7.70 (d, J = 7.4 Hz, 2H), 7.75 (m, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.83 (m, 1H), 8.10 (d, J = 8.3 Hz, 2H), 8.30 (d, J = 9.4 Hz, 1H). ^{13}C NMR: δ (ppm) 52.2, 52.7, 106.0, 118.4, 119.5, 125.7, 126.1, 127.0, 127.70, 127.74, 128.1, 128.3, 128.9, 129.5, 129.7, 131.0, 133.0, 136.8, 137.5, 140.0, 147.0, 164.1, 165.6, 187.8. MS (EI, 70 eV) *m*/*z* (%) 463 (M^+, 53), 432 (6), 400 (8), 283 (86), 252 (92), 222 (27), 181 (17), 167 (30), 149 (69), 135 (46), 125 (24), 111 (39), 97 (59), 83 (58), 71 (72), 57 (100).

Compound (7h). Yellow solid; mp 139–142°C. IR (KBr) υ/cm^{-1}: 2902, 1725, 1703, 1639, 1600, 1547, 1483, 1435, 1301, 1342, 1255, 1220, 1184, 1110, 1056, 976,891, 852cm^{-1}. ^1H NMR: δ (ppm)1.12 (t, J = 7.2 Hz, 3H), 1.4 (t, J = 7.2Hz, 3H), 4.0 (q, J = 7.2 Hz, 2H), 4.4 (q, J = 7.2 Hz, 2H), 7.46 (m, 3H), 7.53 (t, J = 7.5Hz, 2H), 7.64 (d, J = 9.4 Hz, 1H), 7.68 (d, J = 7.4 Hz, 2H), 7.73 (m, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.83 (m, 2H), 8.11 (d, J = 8.2 Hz, 2H), 8.33 (d, J = 9.4 Hz, 1H). ^{13}C NMR: δ (ppm) 14.1, 14.7, 60.9, 62.0, 106.2, 118.4, 119.4, 125.7, 126.0, 126.7, 127.68, 127.72, 128.1, 128.3, 128.9, 129.4, 129.5,129.6, 131, 133.0, 136.9, 137.5, 140.1, 147.0,163.7, 165.2, 187.8. MS (EI, 70 eV) *m*/*z* (%) 491 (M^+, 100), 463 (2), 446 (15), 400 (13), 374 (20), 346 (17), 311 (31), 259 (28), 238 (42), 220 (17), 181 (34), 166 (16), 152 (49), 139 (113), 97 (17), 83 (20).

Acknowledgments. Financial support by the research council of the University of Tehran is gratefully acknowledged. We thank Dr. Karol Gajewski for helpful comments on this work.

REFERENCES AND NOTES

[1] Harrell, W. B.; Doerge, R. F. J Pharm Sci 1967, 56, 225.

[2] Gubin, J.; Vogelaer, H.; Inion, H.; C. Houben, J. Lucchetti, J.;Mahaux, G.; Rosseels, M.; Peiren, M.;.Clinet, P.; Polster; Chatelain, P. J. Med Chem 1993, 36, 1425.

[3] Okada, S.; Sawada, K.; Kuroda, S.; Watanabe; Tanaka, H.; Eur. Pat. Appl. EP 519 353, 1992; Okada, S.; Sawada, K.; Kuroda, S.; Watanabe; Tanaka, H. Chem Abstr 1993, 118, 212886y.

[4] Gubin, J.; Descamps, M.; Chatelain, P.; Nisato, D. Eur. Pat. Appl. EP 235 111, 1987; Gubin, J.; Descamps, M.; Chatelain, P.; Nisato, D. Chem Abstr 1988, 109, 6405b.

[5] Wheeler, J. W.; Eur Pat Appl EP 161 789, 1985; Chem Abstr 1985, 104, 170108z.

[6] Weidner, C. H.; Wadsworth, D. H.; Bender, S. L.; Beltman, D. J. J Org Chem 1989, 54, 3660.

[7] For a general review on properties, synthesis, and reactivity of pyrrolo[2,1-a]isoquinolines, see: Mikhailovskii, A. G.; Shklyaev, V. S. Chem Heterocycl Comp 1997, 33, 243.

[8] (a) Elwan, N. M.; Abelhadi, H. A.; Abdallah, T. A.; Hassaneen, H. M. Tetrahedron 1996, 52, 3451; (b) McComsey D. F.; Maryanoff, B. E. J Org Chem 2000, 65, 4938.

[9] Loesel, W.; Roos, O.; Schnorrenberger, G. U. S. Patent 4694085, 1987; Chem Abstr 1988, 108, 204513.

[10] Kuo, R.-Y.; Wu, C.-C.; Chang, F.-R.; Yeh, J.-L.; Chen, I.-J.; Wu, Y.-C. Bioorg Med Chem Lett 2003, 13, 821.

[11] Anderson, W. K.; Heider, A. R.; Raju, N.; Yucht, J. A. J Med Chem 1988, 31, 2097.

[12] Suehiro, M.; Greenberg, J. H.; Shine, C. Y.; González, C.; Dembowski, B.; Reivich, M. Nucl Med Biol 1996, 44, 407 and references therein.

[13] (a) Gill, C.; Greenhalgh, D. A.; Simpkins, N. S. Tetrahedron Lett 2003, 44, 7803; (b) Ploypradith, P.; Jinaglueng, W.; Pavaro, C.; Ruchirawat, S. Tetrahedron Lett 2003, 44, 1363; (c) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. Org Lett 2002, 4, 885; (d) Bentley, K. Nat Prod Rep 2003, 20, 342.

[14] Ambros, R.; Schneider, M. R.; von Angerer, S. J Med Chem 1990, 33, 153.

[15] Chung, S.-H.; Yook, J.; Min, B. J.; Lee, J. Y.; Lee, Y. S.; Jin, C. Arch Pharm Res 2000, 23, 353.

[16] Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Costanzo, M. J.; Nortey, S. O.; Schneider, C. R.; Setler, P. E. J Med Chem 1987, 30, 1433.

[17] Cai, S. X.; Drewe, J. A.; Jiang, S.; Kasibhatla, S.; Kuemmerle, J. D.; Sirisoma, N. S.; Zhang, H.-Z.US Pat.7, 135, 480, B2, 2006.

[18] (a) Orito, K.; Harada, R.; Uchiito, S.; Tokuda, M. Org Lett 2000, 2, 1799; (b) Chavdarian, C. G.; Seeman, J. I.; Wooten, J. B. J Org Chem 1983, 48, 492; (c) Haldar, P.; Kar, G. K.; Ray, J. K. Tetrahedron Lett 2003, 44, 7433; (d) Knölker, H. J.; Agarwal, S. Tetrahedron Lett 2005, 46, 1173; (e) de Koning, C. B.; Michael, J. P.; Pathak, R.; van Otterlo, W. A. L. Tetrahedron Lett 2004, 45, 1117.

[19] Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice; Oxford University Press, Oxford, 1998.

[20] (a) Li, C. J.; Chang, T. H. In Organic Reactions in Aqueous Media; Wiley: New York, 1997; (b) Organic Synthesis in Water; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998.

[21] (a) Li, C. J.; Chan, T. H. Tetrahedron 1999, 55, 11149; (b) Li, C. J.; Chem Rev 1993, 93, 2023; (c) Yao, X.; Li, C. J. Org Lett 2005, 7, 4395; (d) Li, C. J. Chem Rev 2005, 105, 3095; (e) Lindström, U. M. Chem Rev, 2002, 102, 2751.

[22] Kianmehr, E.; Faramarzy, R.; Estiri, H. Heterocycles 2008, 78, 415.