SYNTHESIS OF TETRACYCLIC PYRANO[4,3-b]-6H-IMIDAZO[1,2-a] [1,5]BENZODIAZEPINES

Lamouri Hammal[1], Yamina Bentarzi[1], Bellara Nedjar-Kolli[1,*], and Pascal Hoffmann[2,*]

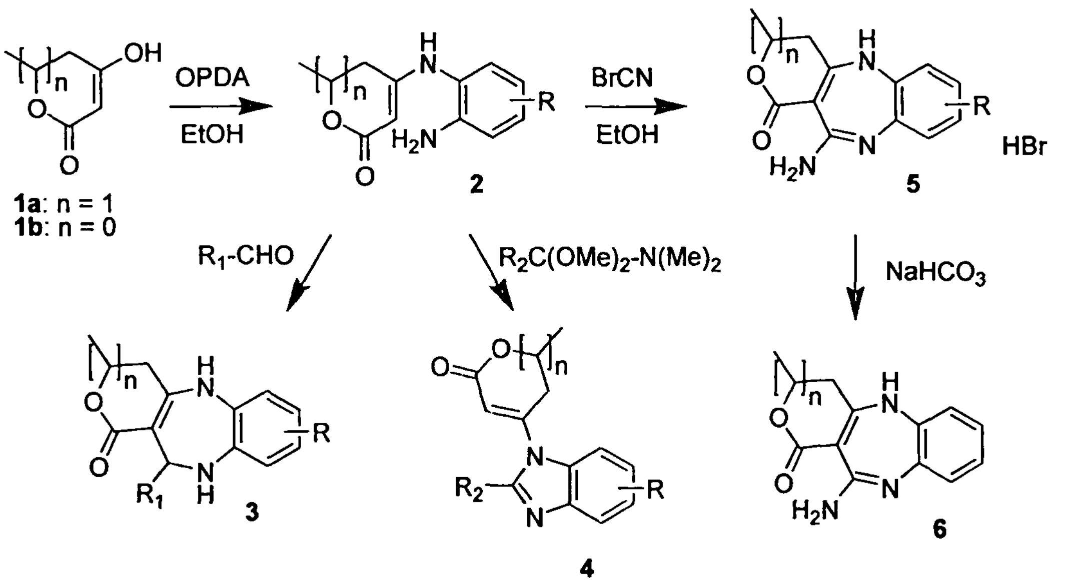
[1]Houari Boumediene University, Algiers, Algeria. E-mail: bellara_kollidz@yahoo.fr
[2]Paul Sabatier University, Toulouse, France. E-mail: hoffmann@cict.fr

Abstract

A synthetic route to tetracyclic pyrano[4,3-b]-imidazo[1,2-a][1,5]benzodiazepines is described. The key is the intramolecular cyclization using cyanogen bromide of enaminones, obtained from reaction of pyrone or tetronic acid with o-phenylenediamine derivatives, to amino-pyrano[4,3-b][1,5]benzodiazepines. Treatment of the latter with 2-chloroethanal gave the corresponding N-alkylated intermediates, which spontaneously cyclized under heating to give the tetracyclic ring.

Introduction

Interest in benzodiazepines and their derivatives is attributed to their diverse biological properties, more particularly as psychoactive drugs molecules (1). For this reason, substituted benzodiazepines and benzodiazepines fused to other heterocyclic rings, such as triazolo (2), oxazino (3), oxadiazolo (4), pyrimido (5) or furano-benzodiazepines (6), have attracted considerable synthetic attention. A number of methods were reported for the preparation of 1,5-benzodiazepines, including condensation reactions of o-phenylenediamine derivatives (OPDA) with □-□ unsaturated carbonyl (7), β-haloketones (8) or ketones under acid catalysis conditions (9). In previous studies, enaminone compounds 2 were used as starting material for the synthesis of benzodiazepines fused to pyronic moiety 3 and benzimidazoles 4 bearing a pyronyl side chain (10,11) (Scheme 1). In this work, the versatile properties of these enaminones 2 were further studied and used to develop a new synthetic method to prepare pyranobenzodiazepines fused to imidazole. Indeed, compounds 2 in the presence of cyanobromide gave tricyclic pyranobenzodiazepines 6, which then cyclized to fused tetracyclic compounds 8 under subsequent chloroethanal treatment.



Scheme 1. Versatile cyclization of enaminone compounds 2 (OPDA: o-phenylenediamines).

Experimental

General. All melting points were determined with a Büchi 512 melting point apparatus and were uncorrected. ^{1}H NMR (250 MHz) and ^{13}C-NMR spectra (63 MHz) were recorded on a Bruker AC 250 spectrometer. Chemical shifts (□) are given from TMS (0 ppm) as internal standard for ^{1}H-NMR, and $^{13}CDCl_3$ (77.0 ppm) for ^{13}C-NMR. Mass spectra were measured on a Nermag R10-10C mass spectrometer. All chemicals were obtaned from Aldrich or Acros Organics.

General procedure for the preparation of compounds 5. A solution of compound 2 (1 mmol) in ethanol (10 mL) was added dropwise to a solution of cyanogen bromide (1.2 mmol) in ethanol and the solution was stirred for 1 hour at 70 °C. The resulting precipitate was then collected by filtration, and washed with ethanol. Recrystallization from a mixture of ethanol and methanol (1:1) gave the desired compounds **5a-f.**

11-Imino-3-methyl-4,5,10,11-tetrahydropyrano[4,3-b][1,5]benzodiazepin-1(3H)-one hydrobromide (5a). Yield: 40 %, mp 215-217 °C. ^{1}H NMR ($CDCl_3$/ CF_3COOH) δ (ppm): 1.47 (d, J = 6 Hz, 3H, CH_3CHCH_2), 2.80 (dd, J = 16 and 11 Hz, 1H, $CHCH_2$), 3.08 (dd, J = 16 and 4 Hz, 1H, $CHCH_2$), 4.60 (m, 1H, CH_3CH), 6.90-7.3 (m, 4H, ArH), 8.15 (s, 1H, N-H), 9.04 (s, 1H, N-H), 9.50 (s, 1H, N^+-H), 9.94 (s, 1H, N^+-H). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.3, 38.6, 71.2, 122.1, 123.1, 129.1, 129.7, 130.0, 134.0, 136.0, 138.1, 163.4, 169.4. MS (70 eV, electron impact) m/z: 244 (MH^+, 35 %), 200 (28 %), 144 (40 %), 44 (100 %). Anal.calcd for $C_{13}H_{13}N_3O_2$.HBr: C, 48.17; H, 4.35; N, 12.96. Found: C, 47.96; H, 4.22; N, 12.76.

11-Ammonio-3,8-dimethyl-4,5,10,11-tetrahydropyrano[4,3-b][1,5]benzodiazepin-1(3H)-one hydrobromide (5b). Yield: 42 %. mp 220-222 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.30 (d, J = 6 Hz, 3H, CH_3CHCH_2), 2.19 (s, 3H, CH_3), 2.76 (dd, J = 16 and 11 Hz, 1H, $CHCH_2$), 3.02 (dd, J = 11 and 4 Hz, 1H, $CHCH_2$), 4.46 (m, 1H, CH_3CH), 6.72-7.01 (m, 3H, Ar-H), 8.54, 8.62 (s, 1H, N-H); 9.00 (s, 1H, N-H), 9.95 (s, 1H, N^+-H), 10.70 (s, 1H, N^+-H). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.9, 20.6, 38.0, 69.9, 122.2, 122.3, 127.1, 129.0, 130.3, 134.2, 136.0, 138.2, 164.0, 170.0. MS (70 eV, electron impact) m/z: 258 (MH^+ , 20 %), 214 (16 %), 158 (30 %), 44 (100 %). Anal.calcd for $C_{14}H_{15}N_3O_2$.HBr: C, 49.72; H, 4.77; N, 12.42. Found: C, 49.65; H, 4.69; N, 12.51.

11-Ammonio-8-chloro-3-methyl-4,5,10,11-tetrahydropyrano[4,3-b][1,5]benzodiazepin-1(3H)-one hydrobromide (5c). Yield: 35 %. mp 235-237 °C. ^1H NMR (DMSO-d_6) δ (ppm): 1.40 (d, J = 6 Hz, 3H, CH_3CHCH_2), 2.75 (dd, J =16 and 11 Hz, 1H, $CHCH_2$), 2.95 (dd, J = 11 and 4 Hz, 1H, $CHCH_2$), 4.50 (m, 1H, CH_3CH), 6.90-7.30 (m, 3H, Ar-H), 8.8 (s, 1H, N-H), 9.67 (s, 1H, N-H), 10.30 (s, 1H, N^+-H), 10.75 (s, 1H, N^+-H). ^{13}C NMR (DMSO-d_6) δ (ppm): 19.9, 38.0, 69.9, 121.6, 122.3, 127.0, 129.2, 131.1, 133.9, 136.2, 138.0, 163.4, 170.4. MS (70 eV, electron impact) m/z: 278 (MH^+, 37 %), 234 (20 %), 178 (42 %), 44 (100 %). Anal. calcd for $C_{13}H_{12}ClN_3O_2$.HBr: C, 43.54; H, 3.65; N, 11.72. Found: C, 43.51; H, 3.59; N, 11.68.

10-Imino-3,4,9,10-tetrahydro-1H-furo[3,4-b][1,5]benzodiazepin-1-one hydrobromide (5d). Yield: 60 %. mp 265-267 °C. ^1H NMR (DMSO-d_6) δ (ppm): 5.10 (s, 2H, OCH_2), 6.80-7.50 (m, 4H, Ar-H), 8.5 (s, 1H, N-H), 8.80 (s, 1H, N-H), 10.04 (s, 1H, N^+-H), 11.00 (s, 1H, N^+-H). ^{13}C NMR (DMSO-d_6) δ (ppm): 67.2, 122.7, 122.9, 127.2, 128.2, 128.5, 129.1, 135.0, 138.1, 157.7, 170.3. MS (70 eV) m/z: 216 (MH^+, 40 %), 159 (20 %), 146 (45 %), 44 (100 %). Anal. calcd for $C_{11}H_9N_3O_2$.HBr: C, 44.62; H, 3.40; N, 14.19. Found: C, 44.57; H, 3.33; N, 14.15.

10-Imino-7-methyl-3,4,9,10-tetrahydro-1H-furo[3,4-b][1,5]benzodiazepin-1-one hydrobromide (5e). Yield: 55 %. mp 280-282 °C. ^1H NMR (DMSO-d_6) δ (ppm): 2.10 (s, 3H, CH_3); 4.91 (s, 2H, OCH_2); 6.50-7.50 (m, 3H, Ar-H), 8.53 (s, 1H, N-H), 8.82 (s, 1H, N-H), 10.00 (s, 1H, N^+-H), 11.10 (s, 1H, N^+-H). ^{13}C NMR (DMSO-d_6) δ (ppm): 20.5, 68.4, 122.7, 122.2, 122.9, 126.2, 128.0, 129.1, 134.8, 138.1, 157.7, 171.1. MS (70 eV, electron impact) m/z: 230 (MH^+, 34 %), 173 (25 %), 160 (41 %), 44 (100 %). Anal. calcd for $C_{13}H_{11}N_3O_2$.HBr: C, 46.47; H, 3.90; N, 13.55. Found: C, 46.39; H, 3.79; N, 13.51.

10-Imino-7-chloro-3,4,9,10-tetrahydro-1H-furo[3,4-b][1,5]benzodiazepin-1-one hydrobromide (5f). Yield: 50 %. mp 293-295 °C. ^1H NMR (DMSO-d_6) δ (ppm): 4.92 (s, 2H, OCH_2), 6.81-7.31 (m, 3H, Ar-H), 8.9 (s, 1H, N-H), 8.85 (s, 1H, N-H), 10.20 (s, 1H, N^+-H), 11.00 (s, 1H, N^+-H). ^{13}C NMR (DMSO-d_6) δ (ppm): 67.2, 118.5, 122.2, 126.0, 127.5, 129.0, 130.1, 134.9, 138.0, 157.6, 171.8. MS (70 eV, electron impact) m/z: 250 (MH^+, 14 %), 193 (22 %), 180 (31 %), 44 (100 %). Anal. calcd for $C_{13}H_8ClN_3O_2$.HBr: C, 39.97; H, 2.74; N, 12.71. Found: C, 39.89; H, 2.69; N, 12.68.

Procedure for the preparation of compound 6. To a solution of 5a (0.324 g, 1.0 mmol) in water (20 mL) was added $NaHCO_3$ 5% (100 mL) and the mixture was stirred at room temperature for 2 h. The precipitate was then collected, washed with water and recrystallized from ethanol to give compound 6.

11-Amino-3-methyl-4,5-dihydropyrano[4,3-b][1,5]benzodiazepin-1(3H)-one (6). Yield: 45 %. mp 234-236 °C. ^1H NMR (DMSO-d_6) δ (ppm): 1.44 (d, J =6 Hz, 3H, CH_3CHCH_2), 2.26 (dd, J =16 and 11 Hz, 1H, $CHCH_2$), 2.48 (dd, J =16 and 4 Hz, 1H, $CHCH_2$), 4.33 (m, 1H, CH_3CH), 6.63-6.89 (m, 4H, Ar-H), 9.10 (brs, 3H, N-H and N-H_2). ^{13}C NMR (DMSO-d_6) δ (ppm): 20.0, 55.5, 70.7, 124.3, 125.1, 126.4, 128.5, 130.9, 133.1, 135.2, 138.8, 165.2, 168.2. MS (70 eV, electron impact) m/z: 243 (M^+, 55 %), 228 (32 %), 200 (28 %), 44 (100 %). Anal. calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.03; H, 5.33; N, 17.31.

Procedure for the preparation of compound 7. To a solution of 5a (0.324 g, 1 mmol) in acetone (20 mL) containing potassium carbonate (0.276 g, 2.0 mmol), was added 2-chloroethanal (0.078 g, 1.0 mmol), and the mixture was stirred at room temperature for 2h. After filtration and evaporation to dryness, water was added, and extracted with chloroforme (4 times). The organic layer was then removed under reduced pressure. After addition of ethanol and filtration, the precipitate was collected, washed with water, and recrystallized from ethanol to give compound 7.

(11-Imino-3-methyl-1-oxo-3,4,5,11-tetrahydropyrano[4,3-b][1,5]benzodiazepin-10(H)-yl) acetaldehyde (7). Yield: 60 %. mp 152-154 °C. ^1H NMR (DMSO-d_6) δ (ppm): 1.40 (d, J = 6 Hz, 3H, CH_3CHCH_2), 2.24 (dd, J = 16 and 11 Hz, 1H, CHCH), 2.45 (dd, J 16 and 4 Hz, 1H, $CHCH_2$), 3.05 (d, J = 12 Hz, 2H, H-$COCH_2N$), 4.28 (m, 1H, CH_3CH), 6.73-6.98 (m, 4H, Ar-H), 9.10 (s, 1H, N-H), 11.20 (s, 1H, CO-H). ^{13}C NMR (DMSO-d_6) δ (ppm): 21.0, , 43.2, 55.8, 70.9, 125.2, 125.3, 126.7, 129.6, 130.0, 134.2, 136.0, 138.1, 165.6, 166.5, 168.5. MS (70 eV, electron impact) m/z: 285 (M^+, 100 %), 270 (17 %), 258 (33 %), 242 (15 %). Anal. calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found:C, 63.35; H, 5.13; N, 14.44.

Procedure for the preparation of compound 8.

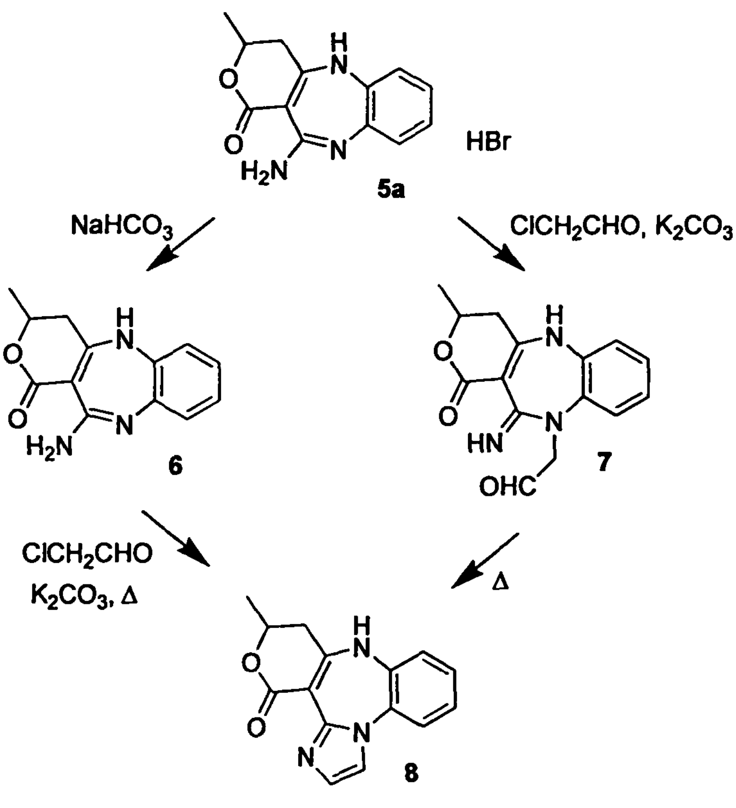
Preparation of compound 8 from 6: to a solution of 6 (0.243 g, 1.0 mmol) in n-butanol (20 mL) containing potassium carbonate (0.138 g, 1.0 mmol) was added 2-chloroethanal (0.078 g, 1 mmol), and the mixture was stirred at room temperature for 2 h and then refluxed for 5h. After filtration and evaporation to dryness, water was added, and extracted with chloroforme (3 x). The organic layer was then removed under reduced pressure. After addition of ethyl ether, the formed precipitate was collected, washed with water, and recrystallized from ethanol to give compound 8. Yield: 43 %

Preparation of compound 8 from 7: a solution of 7 in n-butanol (30 mL) was refluxed for 4 h, the solid that formed was collected and recrystallized from ethanol to give compound 8. Yield: 60 %.

3-Methyl-1-oxo-4,5,10,11-tetrahydropyrano[4,3-b]-6H-imidazo[1,2-a][1,5]benzodiazepin-1(3H)one (8). mp 129-231 °C. ^1H NMR (DMSO-d_6) δ (ppm): 1.45 (d, J = 6 Hz, 3H, CH_3CHCH_2), 2.23 (dd, J = 16 and 11 Hz, 1H, $CHCH_2$), 2.41 (dd, J = 16 and 4 Hz, 1H, $CHCH_2$), 4.24 (m, 1H, CH_3CH), 7.13-8.10 (m, 4H, Ar-H), 8.20 (d, J = 4 Hz, 1H, NCH=), 8.25 (d, J = 4 Hz, 1H, NCH=), 8.90 (s, 1H, N-H). ^{13}C NMR (DMSO-d_6) δ (ppm): 20.3, 55.8, 70.8, 125.1, 125.5, 127.1, 129.2, 130.0, 132.0, 133.5, 134.3, 135.6, 138.1, 166.0, 168.7. MS (70 eV, electron impact) m/z: 267 (M^+, 100 %), 252 (16 %), 239 (12 %), 223 (44 %). Anal. calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.33; H, 4.95; N, 15.57.

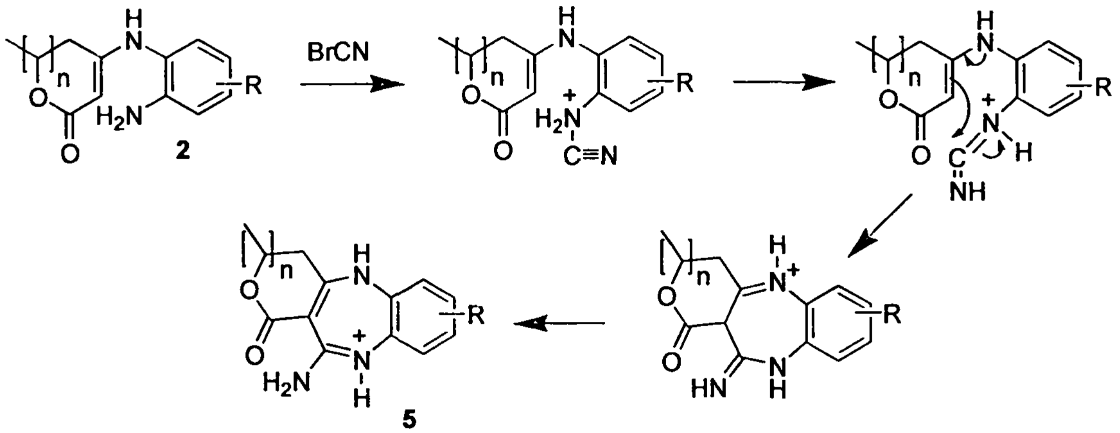
Results and Discussion

The starting point for the construction of aminobenzodiazepine derivatives (5, 6) are the enaminone compounds 2, which were prepared by reaction of commercially available 5,6-dihydropyrone 1a or tetronic acid 1b with o-phenylenediamine, as previously reported (11,12). In the presence of different electrophiles, we showed in previous studies that these enaminones allowed versatile access to different heterocyclic structures, i.e. benzotriazoles (13), benzimidazoles, benzimidazolones or benzodiazepines (10,11). Thus depending on the nature of electrophile used, cyclization occurred either through nitrogen to five-membered ring structures, or through double bound yielding to a seven-membered diazepine ring. In conjunction with these efforts, herein we report the use of these enaminone systems for the preparation of pyrano[4,3-b][1,5]benzodiazepine 6 and its fused derivatives 8 via N-alkylated intermediates 7 (Scheme 2).



Scheme 2. Synthetic route to pyrano[4,3-b]imidazo[1,2-a]benzodiazepine 8.

As expected, enaminone compounds 2 reacted with cyanobromide in refluxing ethanol, under conditions similar to already described procedures (14,15), to give the desired pyrano[4,3-b][1,5]benzodiazepines as hydrobromide salts 5 in moderate yields (Scheme 1). This cyclization reaction is expected to follow a similar mechanism pathway as that observed in the benzodiazepin-2-thiones synthesis, as shown in Scheme 3. It is proposed that enaminones reacted with cyanobromide to form a reactive iminium ion, and that ring-closure exclusively proceeded by intramolecular nucleophilic attack of the double bond of the pyrone moiety on the iminium intermediate to produce the expected pyranobenzodiazepine hydrobromides 5 (Scheme 3).



Scheme 3. Postulated mechanism for the formation of pyranobenzodiazepines.

Treatment of hydrobromide salt 5a (the same behaviour was observed for all other compounds 5) in basic conditions gave then the desired pyrano[4,3-b][1,5]benzodiazepine 6. With the latter compound in hand, we first investigated the alkylation reaction in the presence of 2-chloroethanal and found that the N-alkylation was regioselective to yield compound 7 (Scheme 2). In refluxing n-butanol, the N-alkylated compound 7 underwent a cyclization to yield the expected pyrano[4,3-b]imidazo[1,2-a]benzodiazepine 8. It is noteworthy that the latter compound could also be prepared directly from compound 6 in the presence of 2-chloroethanal and potassium carbonate (Scheme 2).

Conclusions

As a consequence of the intrinsic features of enaminone compounds 2, a wide variety of heterocyclic structures can be prepared from simple reagents which are commercially available. In this study we used cyanobromide to prepare a series of tricyclic amino-pyranobenzodiazepines 5, which allowed the access to novel fused tetracyclic compounds.

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