HETEROCYCLES, Vol. 92, No. 4, 2016, pp. 701 - 707. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 2nd December, 2015, Accepted, 9th February, 2016, Published online, 12th February, 2016
DOI: 10.3987/COM-15-13385

A SIMPLE SYNTHESIS OF BENZODIAZONINES FROM C-2 ARYLATED 1, 3-INDANEDIONES

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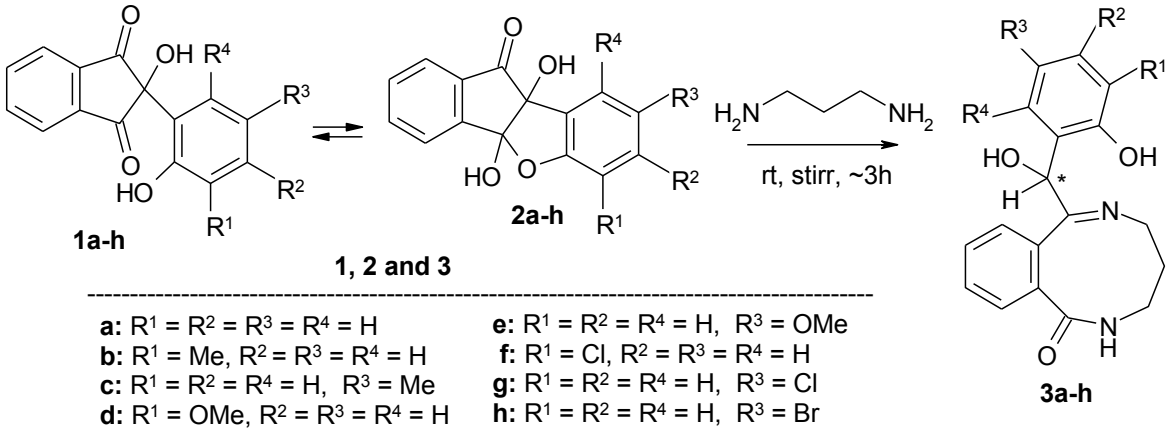
Abstract – A simple, facile, one-pot procedure for the synthesis of substituted benzodiazonines from phenolic adducts of ninhydrin is described. The process involves a base-catalyzed rearrangement followed by condensation of 1,3-propanediamine to furnish nine-membered heterocyclic ring system.

Benzodiazonines are an important class of naturally occuring heterocycles with interesting biological activities. The diazonine ring occurs in the alkaloids such as teleocidine and lingbiatoxin[1] which can stimulate the nervous system, possess antifungal and antihypertensive properties. Besides alkaloids, there are synthetically prepared compounds containing diazonine skeleton as well. For example, 2,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-benzo[*h*][1,4]diazonine acts as a CCK_2-receptor antagonist,[2] and 5-phenyl-7*H*-dibenzo[*b*,*g*][1,5]diazonine can be used as antidepressant.[3] Therefore, benzodiazonine derivatives have become the synthetic targets of many organic and medicinal chemists. In fact, heterocyclic system containing a diazonine fragment is very difficult to prepare due to entropic factors and transannular interaction.[4] In the literature, methods for synthesizing this type of medium ring heterocycles are extremely limited. Among the strategies, a copper-complex catalyzed closing of a nine-membered ring in the reaction of *o*-halophosphoramidates with carbamates leads to the formation of benzodiazonine skeleton.[5] Another method involves the transformation of *o*-(azetidinon-1-yl)aminoethylarenes.[6] Other notable synthetic methods include ring expansion resulting from oxidation,[7] benzodiazepines,[8] or Sommlet-Hauser rearrangement.[9] However, most of the above reported procedures employ multi-step, harsh reaction condition, metal-catalysis to achieve the target molecule. Herein we report a simple, mild

and straightforward procedure for the synthesis of substituted benzodiazonines from easily accessible 2-hydroxy-2-(2′-hydroxyaryl)-1,3-indanediones under metal free condition.

Recently we have reported 2-hydroxy-2-(2′-hydroxyaryl)-1,3-indanediones as starting material for the synthesis of fused heterocyclic compounds, namely, benzimidazo[2,1-*a*]isoindoles.[10] Previously it was shown that phenolic adducts of ninhydrin is a good precursor to afford benzodiazocine skeleton.[11] In the present work, we extend the scope of the reaction using same substrate to achieve the benzodiazonine framework. To the best of our knowledge, nine-membered heterocyclic ring system has not been obtained yet exploiting ninhydrin adducts.

We have prepared 2-hydroxy-2-aryl-1,3-indanediones **1** by refluxing phenols and ninhydrin in acid medium.[12] The adducts so formed preferentially remain in the cyclic hemiketal form **2**.[12a-c] On the basis of our previous experience in the synthesis of heterocyclic skeletons from ninhydrin, we thought that phenolic adducts **1** could also be a flexible precursor for the preparation of nine-membered ring. To achieve this, 1,3-propanediamine was chosen as nucleophile for the reaction. Initially, the reaction of 2-hydroxy-2-(2′-hydroxyphenyl)-1,3-indanedione **1a** with 1,3-propanediamine was examined at room temperature. During stirring, formation of orange colour solution indicates completion of the reaction (TLC) and the product 7-[α-hydroxy-α-(2-hydroxyphenyl)methyl-3,4,5-trihydro-2,6-benzodiazonin-1(2*H*)-one **3a** is formed within 3 h. In order to establish the scope of the procedure, various substituted phenolic adducts of ninhydrin, viz. 2-hydroxy-2-(2′-hydroxyaryl)-1,3-indanediones **1b-h** are employed. To our satisfaction, **1b-h** affords substituted benzodiazonines **3b-h** in moderate yields (Scheme 1, Table 1). The reaction holds good for ninhydrin adducts of phenols containing halogen substituent (entry 6-8).



a: $R^1 = R^2 = R^3 = R^4 = H$
b: $R^1 = Me$, $R^2 = R^3 = R^4 = H$
c: $R^1 = R^2 = R^4 = H$, $R^3 = Me$
d: $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
e: $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
f: $R^1 = Cl$, $R^2 = R^3 = R^4 = H$
g: $R^1 = R^2 = R^4 = H$, $R^3 = Cl$
h: $R^1 = R^2 = R^4 = H$, $R^3 = Br$

Scheme 1

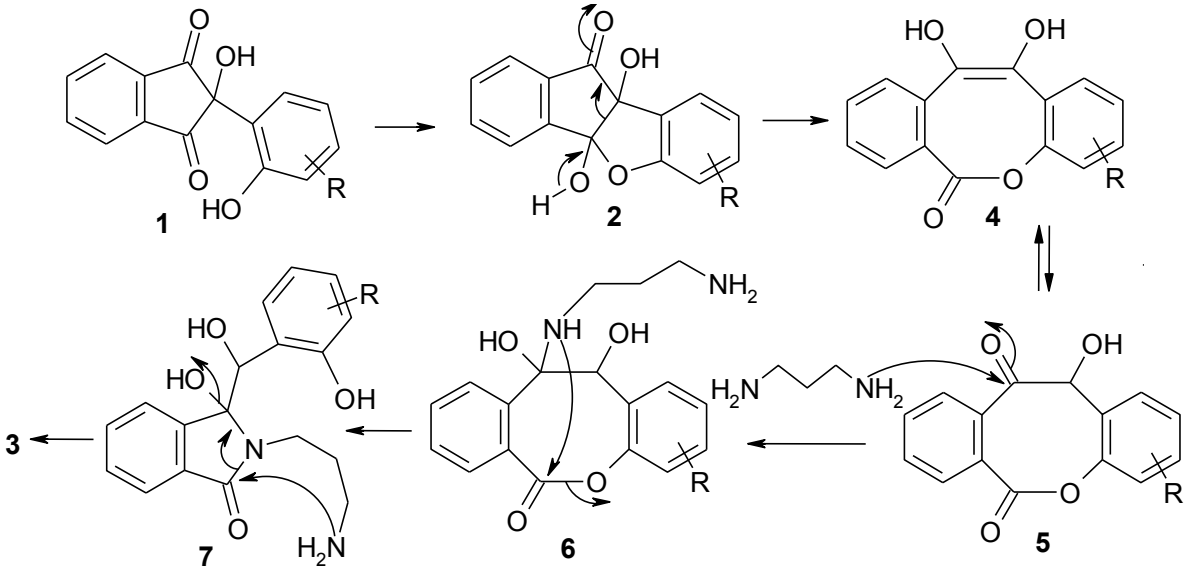
Table 1. Synthesis of 2, 6- benzodiazonin-1(2*H*)-one derivatives **3**

Entry	Substrates	Product	Time (h)	Yield/%[a]	Mp/°C[b]
1	**1a**	**3a**	3.0	58	154-155
2	**1b**	**3b**	2.5	50	165-166
3	**1c**	**3c**	2.5	50	110-111
4	**1d**	**3d**	2.5	48	102-103
5	**1e**	**3e**	2.5	52	115-116
6	**1f**	**3f**	3.0	45	163-164
7	**1g**	**3g**	3.0	48	180-181
8	**1h**	**3h**	3.0	42	158-159

[a]Yields are for isolated products. [b]Mps are uncorrected.

The present protocol provides a simple work-up procedure, requiring acidification with 6N HCl followed by filtration of the precipitated products. The structures of products were established on the basis of spectral data. As an example, the spectral data of compound **3e** are as follows: the most important absorption band in the IR spectrum due to the carbonyl group stretching frequencies of amide of nine-membered ring appeared as 1685 cm^{-1}. The ^{1}H NMR spectrum of **3e** exhibited a singlet at δ 12.07 due to N-H proton. A sharp singlet at δ 3.80 was identified as methoxy protons of the aromatic ring. The ^{13}C NMR spectrum of **3e** showed nineteen distinct signals, in agreement of the proposed structure. The signals at δ 36.8, 35.6 and 27.9 were due to three CH_2 groups of the benzodiazonine ring system and the carbon of the –CHOH group was observed at δ 82.4.

The formation of **3** can be explained from the proposed mechanism depicted in Scheme 2 and in accordance with our previous results.[10] Under the basic conditions nucleophilic attack of phenolic OH on either carbonyl group of **1** produces a bicyclo[3.3.0]octane system **2** which initiates the cleavage of the central C-C bond to afford an eight-membered lactone intermediate **4**. The intermediate **4** tautomerizes to keto form **5**. Subsequently amino group of 1,3-propanediamine attacks the ketone carbonyl to produce intermediate **6**. Then intramolecular nucleophilic attack of nitrogen on the lactone carbonyl affords isoindolone skeleton **7**. Finally, attack of amino group and breaking of C-N bond result in the formation of benzodiazonine skeleton **3**. It is noteworthy that none of the intermediates **4-7** was possible to isolate under the reaction conditions.



Scheme 2

In conclusion, we have developed a simple and efficient procedure for the synthesis of novel benzodiazonine scaffold from 2-hydroxy-2-(2′-hydroxyaryl)-1,3-indanediones through a base-catalyzed rearrangement followed by condensation with 1, 3-propanediamine. The present method provides a mild and one-pot reaction from easily prepared starting materials towards the synthesis of medium ring heterocycles which is otherwise difficult to achieve. Further studies for exploring the scope of the reaction are now in progress.

EXPERIMENTAL

Melting points were determined in open capillary and were uncorrected. IR spectra were examined in KBr disc on a Perkin Elmer-782 spectrophotometer. Proton magnetic resonance (^{1}H NMR) and carbon magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker Avance 300 spectrometer in the solvents indicated. TLC analyses were run on a Merck Kieselgel 60 PF_{254}. Elemental analyses were performed on a Perkin-Elmer 240C analyser.

General procedure for the preparation of 3a-h: The appropriate substrate **1a-h** (1.4 mmol) was added to 1,3-propanediamine (5 mL) and the mixture was stirred at room temperature for about 3 h. The reaction mixture was then acidified with 6N HCl. The solid products separated was filtered and washed thoroughly with cold water. Crystallization from acetone gives pure products **3a-h**.

7-[α-Hydroxy-α-(2-hydroxyphenyl)]methyl-3,4,5-trihydro-2,6-benzodiazonin-1(2*H*)-one (3a): white solid, mp 154-155 °C. IR (KBr): 3306, 1690, 1597 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$/2-drops DMSO-d_6) δ: 8.34 (s, 1H), 7.83-7.57 (m, 2H), 7.54-7.41 (m, 3H), 7.32-7.27 (m, 1H), 6.87-6.79 (m, 2H), 5.74 (s, 1H), 3.73-3.45 (m, 4H), 3.32-3.22 (m, 1H), 1.97-1.81 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$/2-drops DMSO-d_6) δ: 169.7, 168.3, 161.2, 144.4, 133.5, 131.9, 131.3, 129.3, 126.2, 123.2, 122.7, 118.5, 117.8, 114.5, 82.2,

36.6, 35.4, 27.8. Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.55; H, 5.89; N, 9.12.

7-[α-Hydroxy-α-(2-hydroxy-3-methylphenyl)]methyl-3,4,5-trihydro-2,6-benzodiazonin-1(2*H*)-one (3b): white solid, mp 165-166 °C. IR (KBr): 3342, 3312, 1690, 1591 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$/2-drops DMSO-d_6) δ: 8.25 (s, 1H), 7.71(d, J = 7.3 Hz, 1H), 7.56-7.41 (m, 4H), 7.17 (d, J = 7.0 Hz, 1H), 6.72 (t, J = 7.8 Hz, 1H), 5.74 (s, 1H), 3.72-3.45 (m, 4H), 3.30-3.19 (m, 1H), 2.17 (s, 3H), 1.93-1.80 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$/2-drops DMSO-d_6) δ: 170.3, 168.4, 159.8, 144.4, 134.3, 132.0, 131.4, 129.4, 126.8, 123.5, 123.2, 122.8, 117.8, 113.6, 82.2, 36.6, 35.5, 27.9, 15.5. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.26; H, 6.15; N, 8.78.

7-[α-Hydroxy-α-(2-hydroxy-5-methylphenyl)]methyl-3,4,5-trihydro-2,6-benzodiazonin-1(2*H*)-one (3c): white solid, mp 110-111 °C. IR (KBr): 3339, 1687, 1591 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 12.25 (s, 1H), 8.75 (s, 1H), 7.58-7.50 (m, 4H), 7.47-7.41(m, 1H), 7.12 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.57(d, J = 8.1 Hz, 1H), 5.78 (d, J = 7.5 Hz, 1H), 3.59-3.49 (m, 1H), 3.35-3.27 (m, 3H), 2.15 (s, 3H), 1.86-1.74 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.2, 167.1, 157.8, 145.2, 134.8, 132.6, 131.8, 129.8, 128.0, 127.9, 124.0, 122.8, 117.6, 115.4, 81.3, 38.4, 37.2, 28.2, 20.5. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.25; H, 6.17; N, 8.76.

7-[α-Hydroxy-α-(2-hydroxy-3-methoxyphenyl)]methyl-3,4,5-trihydro-2,6-benzodiazonin-1(2*H*)-one (3d): white solid, mp 102-103 °C. IR (KBr): 3298, 1688, 1597 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 12.75 (s, 1H), 8.80 (s, 1H), 7.62-7.49 (m, 4H), 7.36 (d, J = 7.8 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.60 (d, J = 8.7 Hz, 1H), 5.82 (d, J = 8.7 Hz, 1H), 3.74 (s, 3H), 3.60-3.56 (m, 1H), 3.40-3.20 (m, 4H), 1.86-1.84 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.5, 166.3, 150.9, 148.6, 145.0, 131.9, 131.7, 129.3, 123.6, 122.3, 118.6, 117.8, 115.5, 115.0, 80.9, 55.9, 37.0, 36.9, 27.9. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.12; H, 5.98; N, 8.14.

7-[α-Hydroxy-α-(2-hydroxy-5-methoxyphenyl)]methyl-3,4,5-trihydro-2,6-benzodiazonin-1(2*H*)-one (3e): white solid, mp 115-116 °C. IR (KBr): 3314, 1685, 1597 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$/2-drops DMSO-d_6) δ: 12.07 (s, 1H), 8.39 (s, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.79-7.52 (m, 2H), 7.48-7.44 (m, 1H), 7.30 (d, J = 2.7 Hz, 1H), 6.94 (dd, J = 9.0, 3.0 Hz, 1H), 6.83 (d, J = 9.0 Hz, 1H), 6.10 (br s, 1H), 5.78 (br s, 1H), 3.80 (s, 3H), 3.72-3.64 (m, 2H), 3.58-3.50 (m, 1H), 3.38-3.27(m, 1H), 1.98-1.90 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.6, 168.3, 155.3, 151.7, 144.4, 132.0, 131.4, 129.4, 123.2, 122.9, 121.1, 118.6, 114.3, 109.9, 82.4, 55.8, 36.8, 35.6, 27.9. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.16; H, 5.99; N, 8.12.

7-[α-Hydroxy-α-(3-chloro-2-hydroxyphenyl)]methyl-3,4,5-trihydro-2,6-benzodiazonin-1(2*H*)-one (3f): white solid, mp 163-164 °C. IR (KBr): 3344, 1672, 1587 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 13.71 (s, 1H), 9.08 (s, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.62-7.46 (m, 5H), 6.87 (t, J = 7.8 Hz, 1H), 6.61 (d, J

= 9.0 Hz, 1H), 5.82 (d, *J* = 9.0 Hz, 1H), 3.63-3.53 (m, 1H), 3.41-3.31 (m, 3H), 1.93-1.84 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.2, 166.3, 156.8, 145.0, 133.8, 131.9, 131.7, 129.3, 125.8, 123.6, 122.3, 121.2, 118.8, 115.8, 80.9, 37.2, 36.9, 27.7. Anal. Calcd for $C_{18}H_{17}N_2O_3Cl$: C, 62.70; H, 4.97; N, 8.12. Found: C, 62.61; H, 4,91; N, 8.03.

7-[α-Hydroxy-α-(5-chloro-2-hydroxyphenyl)]methyl-3,4,5-trihydro-2,6-benzodiazonin-1(2*H*)-one (3g): white solid, mp 180-181 °C. IR (KBr): 3319, 1684, 1590 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.51 (s, 1H), 8.88 (s, 1H), 7.87 (d, *J* = 2.1 Hz, 1H), 7.61-7.48 (m, 4H), 7.39 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 1H), 6.58 (d, *J* = 9.0 Hz, 1H), 5.82 (d, *J* = 9.0 Hz, 1H), 3.70-3.50 (m, 2H), 3.37-3.32 (m, 3H), 1.90-1.80 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 167.4, 166.3, 158.5, 145.0, 133.2, 132.0, 131.7, 129.4, 127.4, 123.6, 122.4, 122.3, 119.3, 117.0, 80.9, 37.1, 36.8, 27.8. Anal. Calcd for $C_{18}H_{17}N_2O_3Cl$: C, 62.70; H, 4.97; N, 8.12. Found: C, 62.59; H, 4.87; N, 8.04.

7-[α-Hydroxy-α-(5-bromo-2-hydroxyphenyl)]methyl-3,4,5-trihydro-2,6-benzodiazonin-1(2*H*)-one (3h): white solid, mp 158-159 °C. IR (KBr): 3347, 1677, 1587 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.51 (s, 1H), 8.61 (br s, 1H), 8.24-8.11 (m, 5H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.21(d, *J* = 9.0 Hz, 1H), 6.44 (d, *J* = 9.0 Hz, 1H), 4.22-4.18 (m, 1H), 4.00-3.92 (m, 3H), 2.50-2.44 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 167.3, 166.2, 158.9, 145.0, 136.0, 131.9, 131.7, 130.2, 129.3, 123.5, 122.3, 119.7, 117.5, 109.7, 80.9, 37.1, 36.8, 27.7. Anal. Calcd for $C_{18}H_{17}N_2O_3Br$: C, 55.54; H, 4.40; N, 7.20. Found: C, 55.65; H, 4.34; N, 7.12.

ACKNOWLEDGEMENTS

S.D. and A.D. acknowledge University Grants Commission, New Delhi for Minor Research Projects [F.PSW-123/10-11 (ERO) and F.PSW-114/12-13 (ERO) respectively].

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