Synthesis of 1*H*-1,5-Benzodiazepin-2(3*H*)-ones from 5(4*H*)-Isoxazolone, a Heterocyclic Bifunctional C-3 Synthon

M. Hanumantha Rao, A. Pandu Ranga Reddy, V. Veeranagaiah*
Department of Chemistry, Osmania University, Hyderabad 500007, India

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Unsubstituted and 7- or 8-substituted 4-aryl-1*H*-1,5-benzodiazepin-2(3*H*)-ones **3a–t** have been synthesized by the condensation of 3-aryl-5(4*H*)-isoxazolones **1a–e** and parent 4-substituted 1,2-benzenediamines **2a–d** under acidic conditions.

1,5-Benzodiazepin-2-ones[1–8] are an important class of compounds due to their biological activity. It is known that, for instance, 2-[2,3-dihydro-4-(3-iodo-4-chlorophenyl)-2-oxo-1*H*-1,5-benzodiazepin-1-yl]acetic acid is useful for treatment of diabetic complications. There are a few, limited, methods for the preparation of 1,5-benzodiazepin-2-ones; by treatment of 1,2-benzenediamine with β-oxo esters,[1] 1-aryl-3,3-dimercapto-2-propen-1-ones,[2–5] 1-aryl-3,3-bis(methylthio)-2-propen-1-ones,[6] dioxinones,[7] and isoxazoles.[8]

In continuation of our synthesis of heterocyclic compounds[9–11] with potential biological activity, we report here an alternative and efficient approach to the synthesis of 1*H*-1,5-benzodiazepin-2(3*H*)-ones from 3-aryl-5(4*H*)-isoxazolones and 1,2-benzenediamines.

The reaction of 3-aryl-5(4*H*)-isoxazolones[12–15] **1a–e** and 1,2-benzenediamine **(2a)** was carried out in acetic acid in a water bath at 90°C. Neutralisation of the reaction mixture followed by extraction with chloroform and chromatographic separation afforded two crystalline compounds **3a–e** (major) and **4a** (minor). Based on spectral and analytical data **3a–e** was assigned the 4-aryl-1*H*-1,5-benzodiazepin-2(3*H*)-one structure, and **4a** the 2-methylbenzimidazole structure.

The formation of **3** and **4** in the above reaction may be explained through the intermediacy of ω-substituted acetophenone oxime **5**. The intramolecular nucleophilic attack of the second amino group of **5** on the oxime carbon and subsequent elimination of a hydroxylamine molecule results in **3**. While, the intramolecular nucleophilic attack of second amino group of **5** on the carbonyl carbon and subsequent dehydration of benzimidazoline derivative results in a 2-benzimidazolylacetophenone oxime **6**, which on 1,4-hydrogen shift and subsequent elimination of a molecule of benzonitrile oxide, leads to the formation of **4**.

To study the influence the substitution pattern in 1,2-benzenediamine on the course of the reaction, which may lead to the formation of isomeric 1,5-benzodiazepin-2-ones, the condensation of 1,2-benzenediamine with electron-donating groups such as 4-methyl, **4b**, and 4-chloro, **4c**, and electron-withdrawing group like 4-nitro, **4d**, as substituents with 3-aryl-5(4*H*)-isoxazolones in acetic acid has been carried out.

3-Aryl-5(4*H*)-isoxazolones **1a–e** when reacted with 4-methyl-1,2-benzenediamine **(2b)** in acetic acid in water bath at 90°C furnished two products which have been characterised as 4-aryl-7-methyl-1*H*-1,5-benzodiazepin-2(3*H*)-ones **3f–j** (major) along with a minor product 2,5(or 6)-dimethylbenzimidazole **4b**. Similarly, **1a–e** on reaction with 4-chloro-1,2-benzenediamine **(2c)** followed the same course to yield 4-aryl-7-chloro-1*H*-1,5-benzodiazepin-2(3*H*)-ones **3k–o** and 5(or 6)-chloro-2-methylbenzimidazole **4c** as major and minor products, respectively. The electron-donating groups in 1,2-benzenediamine exclusively yielded 7-substituted 1,5-benzodiazepin-2-one derivatives. On the other hand, 4-nitro-1,2-benzenediamine **(4d)**, with an electron-withdrawing group, reacted differently, with **1a–e** and afforded corresponding 4-aryl-8-nitro-1*H*-1,5-benzodiazepin-2(3*H*)-ones **3p–t** (major) and 2-methyl-5(or 6)-nitrobenzimidazole **(4d)** (minor).

The regioselective formation of 7- or 8-substituted 1,5-benzodiazepin-2-ones may be explained by considering the basicity of two amino groups of 4-substituted 1,2-benzenediamines. The more basic 1-amino group of 4-methyl- or 4-chloro-1,2-benzenediamine (K_b values of anilines[16] are tabulated) and 2-amino group of 4-nitro-1,2-benzenediamine participates in the initial step of the reaction leading to the formation of 7-substituted and 8-substituted 4-aryl-1*H*-1,5-benzodiazepin-2(3*H*)-ones,

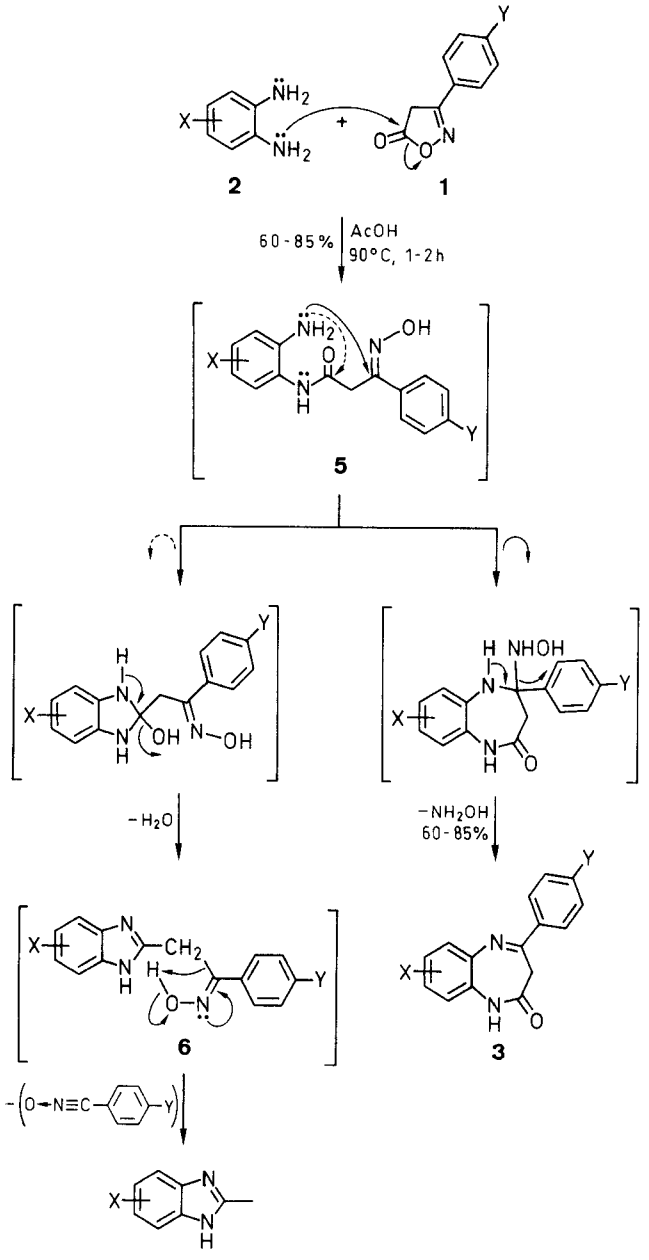
respectively. However, it is observed that the change in substitution at 3-position of isoxazolone has no effect on the course of the reaction except in the yields.

All reagents were of commercial quality from freshly opened containers. Ethyl 3-oxo-3-phenylpropanoate, ethyl 3-oxobutanoate, 4-methylbenzoyl chloride, 4-chlorobenzoyl chloride, 4-nitrobenzoyl chloride, ammonium chloride, $NH_2OH \cdot HCl$, were purchased from Aldrich and Fluka Chemical Co. Reagent quality solvents were used without further purification. Analytical TLC plates of silica gel (230–400 mesh) were prepared in the laboratory and silica gel (230–400 mesh) were purchased from Cipla Co. Melting points were taken using H_2SO_4 bath and are uncorrected. Microanalyses were obtained using a Perkin-Elmer 240 element analyser. Mass spectra were obtained using a VG micromass 7070H and Finnigan Mat 1020 B mass spectrometers. IR spectra were obtained using Shimadzu IR-435 spectrophotometer. ^1H NMR spectra were obtained using a Varian FT-80A and JEOL FX-90Q NMR spectrometers.

Table. Unsubstituted and 7- or 8-Substituted 4-Aryl-1*H*-1,5-benzodiazepin-2(3*H*)-ones **3a–t**

Product	Yield (%)[a]	Eluent PE/benzene)[b]	mp (°C)[c] (solvent)	Molecular Formula[d] or Lit. mp (°C)	MS (70 eV)[e] *m/z* (%)	IR (KBr)[f] ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS)[g] δ
3a	70	4:1	206 (benzene/EtOAc)	205[7]	236 (32), 94 (100)	1670, 3200	3.60 (s, 2H, CH_2), 7.10–8.15 (m, 9H_{arom}), 8.75 (br, 1H, NH)[h]
3b	62	4:1	233 (benzene/EtOAc)	232–233[7]	250 (40), 208 (100)	1665, 3190	2.40 (s, 3H, CH_3), 3.56 (s, 2H, CH_2), 6.90–8.10 (m, 8H_{arom}), 8.65 (br, 1H, NH)[h]
3c	65	7:3	203 (EtOAc)	202[7]	266 (38), 224 (100)	1670, 3200	3.71 (s, 3H, CH_3), 3.58 (s, 2H, CH_2), 6.90–8.00 (m, 8H_{arom}), 8.70 (br, 1H, NH)[h]
3d	65	7:3	208 (EtOAc)	208[7]	270 (46), 228 (100)	1670, 3200	3.54 (s, 2H, CH_2), 6.95–8.20 (m, 8H_{arom}), 8.72 (br, 1H, NH)[h]
3e	77	1:1	242 (MeOH)	$C_{15}H_{11}N_3O_3$ (281.3)	281 (36), 239 (100)	1680, 3220	3.62 (s, 2H, CH_2), 7.00–8.22 (m, 8H_{arom}), 8.76 (br, 1H, NH)[h]
3f	80	4:1	226 (benzene/EtOAc)	225[17]	250 (60), 208 (100)	1660, 3180	2.60 (s, 3H, CH_3), 3.57 (s, 2H, CH_2), 6.92–8.00 (m, 8H_{arom}), 8.66 (br, 1H, NH)[h]
3g	70	7:3	239 (benzene/EtOAc)	$C_{17}H_{16}N_2O$ (264.3)	264 (62), 222 (100)	1660, 3180	2.39 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.50 (s, 1H, CH_2), 7.00–8.13 (m, 7H_{arom}), 8.60 (br, 1H, NH)[h]
3h	72	3:2	222 (EtOAc)	222[19]	280 (65), 238 (100)	1665, 3185	2.58 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 3.60 (s, 2H, CH_2), 7.00–8.20 (m, 7H_{arom}), 8.75 (br, 1H, NH)[h]
3i	74	3:2	228 (EtOAc)	$C_{16}H_{13}ClN_2O$ (284.7)	284 (48), 242 (100)	1665, 3190	–
3j	85	1:1	248 (MeOH)	$C_{16}H_{13}N_3O_3$ (295.3)	295 (56), 253 (100)	1670, 3200	2.58 (s, 3H, CH_3), 3.62 (s, 2H, CH_2), 7.00–8.30 (m, 7H_{arom}), 8.80 (br, 1H, NH)[h]
3k	68	7:3	232 (EtOAc)	230[17]	270 (46), 228 (100)	1680, 3210	3.56 (s, 2H, CH_2), 6.9–8.2 (m, 8H_{arom}), 8.74 (br, 1H, NH)[h]
3l	60	7:3	243 (EtOAc)	$C_{16}H_{13}ClN_2O$ (284.7)	284 (43), 242 (100)	1670, 3200	2.4 (s, 3H, CH_3), 3.54 (s, 2H, CH_2), 6.91–8 (m, 7H_{arom}), 8.69 (br, 1H, NH)[h]
3m	64	3:2	218 (EtOAc)	$C_{16}H_{13}ClN_2O_2$ (300.7)	300 (42), 258 (100)	1675, 3210	3.66 (s, 3H, CH_3), 3.58 (s, 2H, CH_2), 6.98–8.2 (m, 7H_{arom}), 8.72 (br, 1H, NH)[h]
3n	65	3:2	238 (EtOAc)	$C_{15}H_{10}Cl_2N_2O$ (305.2)	304 (52), 262 (100)	1675, 3210	3.6 (s, 2H, CH_2), 7–8.25 (m, 7H_{arom}), 8.75 (br, 1H, NH)[h]
3o	68		252 (MeOH)	$C_{15}H_{10}ClN_3O_3$ (315.7)	315 (38), 273 (100)	1680, 3220	–
3p	65	1:1	246 (MeOH)	239[18]	281 (36), 239 (100)	1680, 3200	3.6 (s, 2H, CH_2), 7–8.53 (m, 8H_{arom}), 8.76 (br, 1H, NH)[h]
3q	60	1:1	258 (MeOH)	$C_{16}H_{13}N_3O_3$ (295.3)	295 (45), 253 (100)	1670, 3200	2.4 (s, 3H, CH_3), 3.6 (s, 2H, CH_2), 6.9–8.4 (m, 7H_{arom}), 8.74 (br, 1H, NH)[h]
3r	63	1:1	232 (MeOH)	$C_{16}H_{13}N_3O_4$ (311.3)	311 (48), 269 (100)	1685, 3210	–
3s	61	2:3	244 (MeOH)	250[18]	315 (38), 273 (100)	1685, 3210	3.62 (s, 2H, CH_2), 7.1–8.49 (m, 7H_{arom}), 8.72 (br, 1H, NH)[h]
3t	70	9:1	268 (MeOH)	$C_{15}H_{10}N_4O_5$ (326.3)	326 (42), 284 (100)	1690, 3220	–

[a] Yield of isolated product **3** based on **1**.
[b] Exceptions: for **3o**: benzene; **3t** benzene/EtOAc (9:1).
[c] Uncorrected, measured with H_2SO_4 bath.
[d] Satisfactory microanalyses obtained: C ±0.19, H ±0.13, N ±0.27.
[e] Recorded on VG micromass 7070H and Finnigan Mat 1020B mass spectrometers.
[f] Recorded on a Shimadzu IR-435 Spectrophotometer.
[g] Recorded on Varian FT-80A and JEOL FX-90Q NMR spectrometers.
[h] Exchangeable with D_2O.



Scheme

Product	X	Y	Product	X	Y	Product	X	Y
3a	H	H	**3h**	7-Me	OMe	**3o**	7-Cl	NO_2
3b	H	Me	**3i**	7-Me	Cl	**3p**	8-NO_2	H
3c	H	OMe	**3j**	7-Me	NO_2	**3q**	8-NO_2	Me
3d	H	Cl	**3k**	7-Cl	H	**3r**	8-NO_2	OMe
3e	H	NO_2	**3l**	7-Cl	Me	**3s**	8-NO_2	Cl
3f	7-Me	H	**3m**	7-Cl	OMe	**3t**	8-NO_2	NO_2
3g	7-Me	Me	**3n**	7-Cl	Cl			

Compound	K_b value	Product	X
aniline	4.2×10^{-10}	**4a**	H
3-methylaniline	5.0×10^{-10}	**4b**	Me
4-methylaniline	12.0×10^{-10}	**4c**	Cl
3-chloroaniline	0.3×10^{-10}	**4d**	NO_2
4-chloroaniline	1.0×10^{-10}		
3-nitroaniline	0.019×10^{-10}		
4-nitroaniline	0.001×10^{-10}		

Preparation of 3-Aryl-5(4*H*)-isoxazolones 1a–e: General Procdure:
A mixture of ethyl 3-oxocarboxylate (10 mmol) and $NH_2OH \cdot HCl$ (10 mmol) in EtOH was reacted according to the procedure of Claisen and Zedel[17] to give the 3-aryl-5(4*H*)-isoxazolones: **1a** mp 152°C (Lit.[12] 152°C); **1b** mp 124°C (Lit.[13] 123°C); **1c** mp 143°C (Lit.[13] 141–144°C); **1d** mp 182°C (Lit.[14] 183°C); **1e** mp 196°C (Lit.[15] 194–195°C).

Unsubstituted and 7- or 8-Substituted 4-Aryl-1*H*-1,5-benzodiazepin-2(3*H*)-ones 3a–t; General Procedure:
Equimolar amounts of 3-aryl-5(4*H*)-isoxazolone **1a–e** (10 mmol) and 4-substituted 1,2-benzenediamine **2a–d** (10 mmol) in AcOH acid (10 mL) were heated in a water bath at 90°C for 1–2 h. The mixture was allowed to cool to r.t. and poured onto crushed ice. The solution was neutralised with ammonia and the organic layer was extracted with $CHCl_3$ (3 × 50 mL). The combined $CHCl_3$ extracts on concentration yielded a gummy solid. The latter was chromatographed on a silica gel column (18 cm × 3 cm, 230–400 mesh) using the eluants given in Table 2, to afford pure crystalline unsubstituted and 7- or 8-substituted 4-aryl-1*H*-1,5-benzodiazepin-2(3*H*)-ones as major products **3a–t** and 5(or 6)-substituted 2-methylbenzimidazoles **4a–d** as minor products.

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