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Transformation of Furan-2,3-diones with 1,8-Diaminonaphthalene to Naphtho-[1,8-*ef*][1,4]diazepin-2(1*H*)-ones

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Abstract: Naphtho[1,8-*ef*][1,4]diazepin-2(1*H*)-ones were obtained from furan-2,3-diones with 1,8-diaminonaphthalene.

Keywords: 1,8-Diaminonaphthalene, 2,3-furandiones, naphtho[1,4]diazepines, 1,2,4-triones

INTRODUCTION

Naturally occuring or synthetic heterocyclic amino acid derivatives constitute an important resource for new drugs. For instance, derivatives of pyrrole,[1] isoxazole,[2] tetrazole,[3] and pyrazole[4] containing an amino acid/amide moiety have been reported as bioactive materials. Among these types of heterocycles, 1,4-benzodiazepines (like diazepam) are therapeutically used as drugs acting on the central nervous system (CNS).[5] The clinical importance of 1,4-benzodiazepines has led to extensive synthetic studies on 1,4-benzodiazepines fused heterocycles.

Just like benzodiazepines and its related heterocyclic compounds, naphtho[1,4]diazepine derivatives might also exhibit psychotherapeutic effects with a functional 1,4-arodiazepine ring. Therefore, we have studied the synthesis of novel naphtho[1,4]diazepines containing an α-amino

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acid moiety. Our approach was to react 1,8-diaminonaphthalene with both furan-2,3-diones and 1,2,4-triketones to yield naphtho[1,8-*ef*][1,4] diazepin-2(1*H*)-ones.

RESULTS AND DISCUSSION

Naphtho[1,8-*ef*][1,4]diazepin-2(1*H*)-ones **3** were readily obtained by cyclocondensation of 2,3-furandiones (**1a–d**) with 1,8-diaminonaphthalene (**2**) (72–83%). When the reaction of **1** and **2** was carried out at room temperature in benzene, compounds **3a–d** precipitated as pure crude products, and additional purifications were redundant. However, when the reactions of **1a–d** and **2** were conducted at high temperatures in solvents, no isolable products were obtained.

Formation of **3a–d** is thought to proceed via a sequence as outlined in Scheme 1. The reaction is started by nucleophilic attack of the amino group of 1,8-diaminonaphthalene on the carbonyl group at position 3 of furan-2,3-dione, forming a Schiff base, which was not isolated. Through attack of a second amino group on the lactone carbonyl group, ring opening occurs, and naphthodiazepin rings are formed simultaneously.

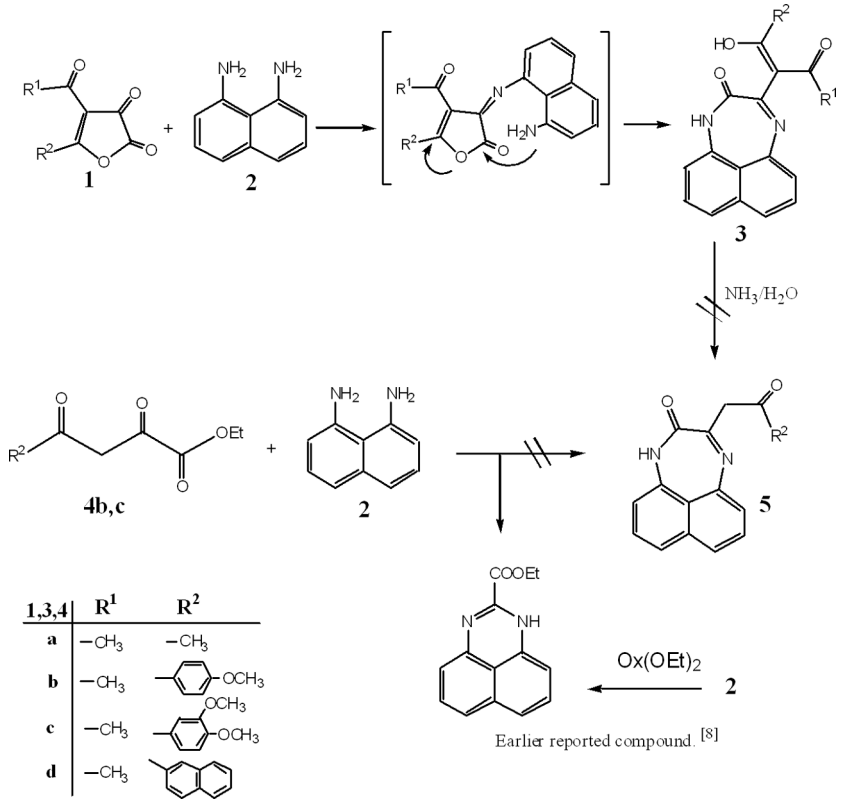
The NH and OH proton signals of compounds **3a–d** were detected between 8.49–9.20 and 5.60–6.55 ppm as broad bands, respectively. Although aryl′ C=O was not observed in the ^{13}C NMR spectra, the acetyl′ C=O of **3a–d** were found between 193.68 and 194.30 ppm. In the infrared (IR) spectra, the C=O absorptions of **3a** at 1710 (acetyl), 1644 cm^{-1} (ring), and C=N absorption at 1635 cm^{-1} were detected.

There was no indication of the tautomeric forms of **3a–d**, both by their IR spectra in the solid state and by their NMR spectra in $CDCl_3$ solution, and they exist exclusively in the enolic form.

On the other hand, direct reactions of 1,2,4-triones (**4a**, **b**) with **2** produced ethyl 1*H*-perimidine-2-carboxylate instead of naphtho[1,8-*ef*][1,4]diazepin-2(1*H*)-ones (**5**). Synthesis of ethyl 1*H*-perimidine-2-carboxylate was previously reported from the reaction of **2** with diethyl oxalate.[6] In addition, hydrolysis of compound **3** with ammonia solution did not give an isolable product of compound **5** (Scheme 1).

EXPERIMENTAL

1a–d were prepared according to published method.[8,6] Melting points were determined on an Electrothermal 9200 apparatus and are uncorrected. Elemental analyses were carried out using a LECO-932 CHNSO analyzer. IR spectra were recorded on a Jasco Plus model 460



Scheme 1. Reactions of 1,8-diaminonaphthalene with 2,3-furandiones and 1,2,4-triones.

Fourier transform (FT–IR) spectrometer as KBr pellets. ^{1}H (400-MHz) and ^{13}C NMR (100-MHz) spectra were obtained on a Bruker Avance DPX-400 spectrometer in $CDCl_3$. The chemical shifts are reported in parts per million (ppm) from tetra methyl silane (TMS) and are given in δ units. All experiments were followed by thin-layer chromatography (TLC) using DC Alufolien Kieselgel 60 F 254 Merc and Camag TLC lamb (254/366 nm).

General Procedure for 3

A solution of furan-2,3-diones (**1a–d**) (1 mmol) in dry benzene (30 ml) and **2** (0.158 g, 1 mmol) were stired for 24 h. After solvents were removed by

filtration, the crude products (**3a–d**) were washed with benzene and diethyl ether.

3-(1-Acetyl-2-hydroxy-1-propen-1-yl)naphtho[1,8-*ef*][1,4]diazepin-2(1*H*)-one (**3a**)

Compound **3a** was prepared from 0.154 g **1a** and 0.158 g **2**. Orange crystals. Yield 0.245 g (83%); mp 143°C. IR (KBr): $\nu = 3332\,cm^{-1}$ (N-H), 3297 (O-H, br.), 1710 (MeC=O), 1664 (C=O, ring), 1635 (C=N). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.63$ (s, 3H, C=C−CH_3), 2.68 (s, 3H, $COCH_3$), 5.60 (s, 1H, broad OH), 6.78–8.03 (m, 6H, Ar-H), 8.64 ppm (s, 1H, broad NH). ^{13}C NMR ($CDCl_3$) $\delta = 23.37$ ($\underline{C}H_3$−C=C−OH), 30.57 ($\underline{C}H_3C$=O), 109.84, 114.68, 115.24, 118.58, 121.20, 125.20, 126.23, 127.59, 127.94, 128.32, 134.09, 137.65 (arom. and aliph. C=C and C=N), 161.76 (NHC=O), 194.30 (MeC=O). $C_{17}H_{14}N_2O_3$ (294): calcd. C, 69.38; N, 9.52; H, 4.79; found C, 69.19; N, 9.64; H, 4.73.

3-[1-Acetyl-2-hydroxy-2-(4-methoxyphenyl)vinyl]naphtho[1,8-*ef*][1,4]diazepin-2(1*H*)-one (**3b**)

Compound **3b** was prepared from 0.246 g **1b** and 0.158 g **2**. Orange crystals. Yield 0.306 g (79%); mp 210°C. IR (KBr): $\nu = 3433$ (O-H, br) cm^{-1}, 3332 (N-H), 1710 (MeC=O), 1664 (C=O, ring), 1635 (C=N). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.50$ (s, 3H, $COCH_3$), 3.66 (s, 3H, OCH_3), 6.48 (s, 1H, broad OH), 6.65–7.97 (m, 10H, Ar-H), 9.20 ppm (s, 1H, broad NH). ^{13}C NMR ($CDCl_3$) $\delta = 30.05$ ($\underline{C}H_3C$=O), 55.07 (OCH_3), 110.14, 113.85, 115.41, 115.73, 118.99, 122.01, 125.28, 126.19, 127.49, 128.86, 128.32, 129.49, 134.04, 137.89, 159.28 (arom. and aliph. C=C and C=N), 162.57 (NHC=O), 193.69 (MeC=O). $C_{23}H_{18}N_2O_4$ (386): calcd. C, 71.49; N, 7.25; H, 4.70; found C, 71.56; N, 7.14; H, 4.78.

3-[1-Acetyl-2-(3,4-dimethoxyphenyl)-2-hydroxyvinyl]naphtho[1,8-*ef*][1,4]diazepin-2(1*H*)-one (**3c**)

Compound **3c** was prepared from 0.276 g **1c** and 0.158 g **2**. Orange crystals. Yield 0.308 g (74%); mp 198°C. IR (KBr): $\nu = 3434$ (O-H, br.) cm^{-1}, 3350 (N-H), 1708 (MeC=O), 1656 (C=O, ring), 1624 (C=N). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.63$ (s, 3H, C=C-CH_3), 2.68 (s, 3H, $COCH_3$), 5.60 (s, 1H, broad OH), 6.78–8.03 (m, 6H, Ar-H), 8.49 ppm (s, 1H, broad NH). ^{13}C NMR ($CDCl_3$) $\delta = 29.90$ ($\underline{C}H_3C$=O), 55.67, 55.89 (OCH_3), 110.01, 110.13, 110.89, 115.39, 119.21, 119.42, 121.75,

125.32, 126.26, 127.47, 128.40, 130.09, 134.09, 137.89, 148.68, 148.86 (arom. and aliph. C=C and C=N), 162.58 (NHC=O), 193.68 (MeC=O). $C_{24}H_{20}N_2O_5$ (416): calcd. C, 69.22; N, 6.73; H, 4.84; found C, 69.07; N, 6.68; H, 4.84.

3-[1-Acetyl-2-hydroxy-2-(2-naphthyl)vinyl]naphtho[1,8-*ef*][1,4]-diazepin-2(1*H*)-one (**3d**)

Compound **3d** was prepared from 0.266 g **1d** and 0.158 g **2**. Orange crystals. Yield (0.292 g, 72%); mp 231°C. IR (KBr): $\nu = 3385$ (O-H, br.) cm^{-1}, 3347 (N-H), 1710 (MeC=O), 1659 (C=O, ring), 1638 (C=N). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.48$ (s, 3H, $COCH_3$), 6.55 (s, 1H, broad OH), 7.20–8.05 (m, 6H, Ar-H), 9.18 ppm (s, 1H, broad NH). ^{13}C NMR ($CDCl_3$) $\delta = 30.00$ ($\underline{C}H_3C=O$), 110.06, 115.44, 119.18, 121.78, 123.49, 125.38, 126.19, 126.21, 126.55, 126.89, 127.32, 127.56, 128.24, 128.55, 132.75, 134.03, 135.11, 137.97 (arom. and aliph. C=C and C=N), 162.50 (NHC=O), 193.62 (MeC=O). $C_{26}H_{18}N_2O_3$ (406): calcd. C, 76.83; N, 6.89; H, 4.46; found C, 76.71; N, 6.80; H, 4.49.

Ethyl 1H-Perimidine-2-carboxylate

A mixture of powdered **2** (0.158 g, 1 mmol) and **4b** (0.250 g, 1 mmol) or **4c** (0.280 g, 1 mmol) were heated at 90°C for 1 h in a tube. Residue was recrystallized from dry xylene to give ethyl 1*H*-perimidine-2-carboxylate as scarlet powders. Yield (56% from **4b**, 65% from **4c**); mp 199–201°C (lit.[8] mp 200.5–202.5°C).

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