JOC The Journal of Organic Chemistry

J. Org. Chem., 1997, 62(5), 1240-1256, DOI:10.1021/jo9622845

The Solid-Phase Synthesis of 1,4-Benzodiazepine-2,5-diones. Library Preparation and Demonstration of Synthesis Generality

Constantine G. Boojamra, Kristina M. Burow, Lorin A. Thompson, and Jonathan A. Ellman*
Contribution from the Department of Chemistry, University of California, Berkeley, CA 94720

Supplementary Material

^{1}H NMR data for a subset of the benzodiazepines from the library that were directly evaluated by ^{1}H NMR are listed below.

entry	R^1	R^2	R^3
1	7-Br	*c*-$(C_3H_5)CH_2$	$CH_2C_6H_5$
2	9-Br, 7-Me	H	CH_3
3	8-Cl	4-phenylBn	$CH_2CH(CH_3)_2$
4	7-Cl	piperonyl	$CH_2C_6H_4OH$
5	8-Cl	2-MeOBn	$(CH_2)_2CO_2H$
6	9-Br, 7-Me	methyl	$CH_2C_6H_5$
7	8-OMe	NH_2COCH_2	CH_3
8	no subst.	NH_2COCH_2	$CH_2CH(CH_3)_2$
9	9-Me	4-phenylBn	$CH_2C_6H_4OH$
10	8-Cl	4-phenylBn	H
11	6-F	4-phenylBn	$(CH_2)_4NH_2$
12	8-Cl	benzyl	$CH_2CH(CH_3)_2$
13	7-Cl	CH_2-2-$(C_{10}H_7)$	CH_3
14	9-Me	2-MeOBn	H
15	8-OMe	*c*-$(C_3H_5)CH_2$	$CH_2C_6H_4OH$
16	no subst.	H	2-thienylmethyl
17	9-Me	H	H
18	8-Cl	Me	$(CH_2)_4NH_2$
19	8-Cl	ethyl	CH_3
20	7-Br	ethyl	$CH_2C_6H_5$
21	9-Me	benzyl	CH_2-2-$(C_{10}H_7)$
22	9-Me	4-phenylBn	$CH_2C_6H_4OH$

Benzodiazepine (entry 1). ^{1}H NMR (400 MHz, d_3-CH_3CN): δ 0.07-0.09 (m, 1), 0.10-0.13 (m, 1), 0.30-0.36 (m, 2), 0.75-0.89 (m, 1), 2.95 (dd, 1, J = 8.4, 12.8), 3.22-3.25 (m, 1), 3.49 (dd, 1, J = 6.7, 14.4), 4.03-4.06 (m, 1), 4.11 (dd, 1, J = 7.3, 14.4), 6.96 (b s, 1), 7.15-7.25 (m, 5), 7.34 (d, 1, J = 8.7), 7.79 (dd, 1, J = 2.5, 8.7), 7.81 (d, 1, J = 2.5).

Benzodiazepine (entry 2). ^{1}H NMR (400 MHz, d_3-CH_3CN, 5 drops d_4-methanol): δ 1.30 (d, 3, J = 6.8), 2.33 (s, 3), 3.86 (q, 1, J = 6.8), 7.59 (s, 1), 7.69 (s, 1).

Benzodiazepine (entry 3). ^{1}H NMR (400 MHz, d_3-CH_3CN): δ 0.83 (d, 3, J = 5.7), 0.92 (d, 3, J = 6.0), 1.60-1.90 (m, 3), 3.86-3.91 (m, 1), 4.94 (d, 1, J = 16.0), 5.40 (d, 1, J = 16.0), 6.90 (b s, 1), 7.21 (d, 2, J = 8.1), 7.28 (d, 1, J = 8.4), 7.34 (t, 1, J = 7.5), 7.41-7.44 (m, 3), 7.50-7.56 (m, 2), 7.59 (d, 2, J = 7.8), 7.69 (d, 1, J = 8.4).

Benzodiazepine (entry 4). ^{1}H NMR (400 MHz, d_3-CH_3CN): δ 2.88 (dd, 1, J = 8.4, 14.6), 3.17-3.22 (m, 1), 3.70-3.77 (m, 1), 4.74 (d, 1 J = 15.6), 5.27 (d, 1, J = 15.5), 5.89-5.90 (m,

2), 6.56-6.58 (m, 2), 6.68-6.73 (m, 3), 6.92-6.95 (m, 2), 7.08 (d, 2, J = 8.4), 7.34 (d, 1, J = 8.8). 7.48 (dd, 1, J = 2.6, 8.8), 7.61 (d, 1, J =2.6).

Benzodiazepine (entry 5). ^{1}H NMR (500 MHz, d_3-CH_3CN): δ. 1.94-1.99 (m, 2), 2.12-2.17 (m, 2), 3.66 (s, 3), 3.84-3.88 (m 1), 4.74 (d, 1, J = 15.5), 5.43 (d, 1, J = 15.5), 6.79-6.82 (m, 2), 7.08-7.10 (m, 1), 7.16-7.23 (m, 3), 7.40 (b s, 1), 7.60-7.61 (m, 1).

Benzodiazepine (entry 6). ^{1}H NMR (400 MHz, d_3-CH_3CN):.δ. 2.35 (s, 3), 2.94 (dd, 1, J = 8.7, 14.4), 3.18-3.22 (m, 4), 4.03-4.08 (m, 1), 6.79 (b s, 1), 7.20-7.27 (m, 5), 7.47 (s, 1), 7.70 (s, 1).

Benzodiazepine (entry 7). ^{1}H NMR (500 MHz, d_3-CH_3CN, 5 drops d_4-methanol): δ. 1.31 (d, 3, J = 6.8), 3.81 (s, 3), 3.81-3.93 (m, 1), 4.17 (d, 1, J = 16.8), 4.57 (d, 1, J = 16.8), 6.83 (d, 1, J = 2.3), 6.90 (dd, 1, J = 2.4, 8.7), 7.69 (d, 1, J = 8.7).

Benzodiazepine (entry 8). ^{1}H NMR (400 MHz, d_3-CH_3CN): δ. 0.80 (d, 3, J = 5.9), 0.89 (d, 3, J = 5.9), 1.62-1.72 (m, 3), 3.70-3.82 (m, 1), 4.22 (d, 1, J = 16.7), 4.49 (d, 1, 16.7), 5.87 (b s, 1), 6.37 (b s, 1), 6.76 (b s, 1), 7.30-7.34 (m, 2), 7.57 (t, 1, J = 7.2), 7.75 (d, 1, 7.5).

Benzodiazepine (entry 9). ^{1}H NMR (500 MHz, d_3-CH_3CN): δ 2.62 (s, 3), 2.81 (dd, 1, J = 8.9, 14.7), 3.11 (dd, 1, J = 5.7, 14.6), 3.93-3.95 (m, 1), 4.29 (d, 1, J = 15.0), 5.53 (d, 1, J = 14.8), 7.69 (d, 2, J = 8.5), 7.04 (d, 2, J = 8.4), 7.13 (d, 2, J = 8.2), 7.20-7.38 (m, 3), 7.40-7.48 (m, 5), 7.57 (d, 2, J = 7.2), 7.67 (d, 1, J = 7.2), 7.76 (d, 1, J = 8.0).

Benzodiazepine (entry 10). ^{1}H NMR (500 MHz, d_4-methanol): δ 3.75 (b d, 1, J = 14.9), 3.89 (b d, 1, 14.9), 4.93 (d, 1, J = 15.6), 5.50 (d, 1, J = 15.6), 7.22 (d, 2, J = 8.2), 7.29-7.34 (m, 2), 7.37-7.40 (m, 2), 7.46-7.55 (m, 4), 7.59 (d, 1, J = 1.9), 7.72 (d, 1, J = 8.4).

Benzodiazepine (entry 11). ^{1}H NMR (500 MHz, d_3-CH_3CN): δ 1.80-1.93 (m, 6), 2.95 (b m, 2), 3.89-3.91 (m, 1), 4.92 (d, 1, J = 15.9), 5.42 (d, 1, J = 15.9), 7.04 (t, 1, J = 8.7), 7.21-7.25 (m, 2), 7.33-7.35 (m, 1), 7.41-7.43 (m, 3), 7.47-7.55 (b m, 5), 7.59 (d, 2, J = 7.4), 7.68 (d, 1, J = 7.7), 7.77 (d, 1, 7.9).

Benzodiazepine (entry 12). ^{1}H NMR (500 MHz, d_3-CH_3CN): δ 0.82 (d, 3, J = 6.1), 0.91 (d, 3, J = 6.2), 1.63-1.73 (m, 3), 3.84-3.88 (m, 1), 4.87 (d, 1, J = 15.9), 5.38 (d, 1, J = 15.9), 6.89 (b s, 1), 7.12 (d, 2, J = 7.2), 7.19-7.28 (m, 4), 7.41 (d, 1, J = 1.9), 7.66 (d, 1 J = 8.4).

Benzodiazepine (entry 13). ^{1}H NMR (500 MHz, d_3-CH_3CN): δ 1.38 (d, 3, J = 6.7), 4.03-4.08 (m, 1), 5.02 (d, 1, J = 15.9), 5.53 (d, 1, J = 15.9), 6.93 (b s, 1), 7.25 (dd, 1, J = 1.6, 8.4), 7.40 (d, 1, J = 8.8), 7.44-7.49 (m, 3), 7.61-7.65 (m, 2), 7.74-7.83 (m, 3).

Benzodiazepine (entry 14). ^{1}H NMR (400 MHz, d_3-CH_3CN): δ 2.45 (s, 3) 3.44 (dd, 1, J = 6.8, 14.6), 3.54 (s, 3), 3.68 (dd, 1, J = 5.4, 14.6), 4.29 (d, 1, J = 14.3), 5.46 (d, 1, J = 14.3), 6.69-6.74 (m, 2), 7.08 (dd, 1, J = 1.6, 7.5), 7.12-7.15 (m, 2), 7.20 (t, 1, J = 7.6), 7.39-7.41 (m, 2).

Benzodiazepine (entry 15). ^{1}H NMR (400 MHz, d_3-CH_3CN): δ 0.09-0.12 (m, 1), 0.13-0.16 (m, 1), 0.33-0.35 (m, 2), 0.86-0.89 (m, 1), 2.79-2.86 (m, 1), 3.14 (dd, 1, J = 6.0, 14.4), 3.53-3.58 (m, 1), 3.84 (s, 3), 3.91-3.94 (m, 1), 4.03-4.10 (m, 1), 6.69 (d, 2, J = 8.5), 6.68-6.70 (b s, 1) 6.87 (dd, 1, J = 2.4, 8.6), 6.90 (d, 1, J = 2.3), 7.06 (d, 2, J = 8.4), 7.62 (d, 1, J = 8.6).

Benzodiazepine (entry 16). ^{1}H NMR (500 MHz, d_3-CH_3CN): δ 3.19 (dd, 1, J = 8.9, 15.3), 3.41 (dd, 1, J = 5.6, 15.3), 3.97-4.02 (m, 1), 6.58-6.70 (b m, 2), 6.93-6.95 (m, 1), 7.07-7.10 (m, 1), 7.23-7.27 (m, 2), 7.52 (dd, 1, J = 7.4, 8.0), 7.98 (d, 1, J = 7.9), 8.50 (b s, 1).

Benzodiazepine (entry 17). ^{1}H NMR (500 MHz, d_3-CH_3CN): δ 2.32 (s, 3), 3.63 (d, 1, J = 5.9), 4.00 (d, 1, J = 5.9), 6.97 (b s, 1), 7.13-7.19 (m, 1), 7.40 (d, 1, J = 7.5), 7.64 (d, 1, J = 7.6), 7.79 (b s, 1).

Benzodiazepine (entry 18). ^{1}H NMR (500 MHz, d_3-CH_3CN): δ 1.50-1.95 (m, 6), 2.94 (b s, 2), 3.68-3.72 (b m, 1), 7.27 (b s, 4), 7.30 (d, 1, J = 8.3), 7.38 (s, 1), 7.72 (d, 1, J = 8.4).

Benzodiazepine (entry 19). ^{1}H NMR (500 MHz, d_3-CH_3CN): δ 1.09 (t, 3, J = 7.1), 1.30 (d, 3, J = 6.6), 3.67-3.74 (m, 1), 3.84-3.87 (m, 1), 4.08-4.14 (m, 1), 6.83 (b s, 1), 7.37 (d, 1, J = 8.8), 7.56 (dd, 1, J = 2.6, 8.8), 7.72 (d, 1, J = 2.5).

Benzodiazepine (entry 20). ^{1}H NMR (400 MHz, d_3-CH_3CN): δ 1.08 (t, 3, J = 7.1), 2.94 (dd, 1, J= 8.6, 14.4), 3.21-3.27 (m, 1), 3.69-3.74 (m, 1), 4.01-4.08 (m, 1), 4.10-4.14 (m, 1), 6.85 (b s, 1), 7.24-7.25 (m, 5), 7.30 (d, 1, J = 8.7), 7.69 (dd, 1, J = 2.5, 8.8), 7.79 (d, 1, J = 2.4).

Benzodiazepine (entry 21). ^{1}H NMR (500 MHz, d_4-methanol): δ 2.35 (s, 3), 3.10 (dd, 1, J = 8.6, 14.4), 3.39 (dd, 1, J = 6.1, 14.4), 4.07-4.10 (m, 1), 4.25 (d, 1, J = 14.4), 5.51 (d, 1, J = 14.5), 7.02-7.04 (m, 2), 7.13-7.14 (m, 2), 7.28-7.31 (m, 2), 7.38-7.45 (m, 4), 7.48-7.50 (m, 2), 7.67-7.76 (m, 3).

Benzodiazepine (entry 22). ^{1}H NMR (500 MHz, d_4-methanol): δ 2.45 (s, 3), 2.88-2.90 (m, 1), 3.13 (dd, 1, J = 6.1, 14.6), 3.89-3.91 (m, 1), 4.29 (d, 1, J = 14.5), 5.52 (d, 1, J = 14.5), 6.62 (d, 2, 8.5), 7.00 (d, 2, J = 8.5), 7.10 (d, 2, J = 8.3), 7.20 (d, 1, J = 7.3), 7.33-7.35 (m, 1), 7.36 (t, 2, J = 7.5), 7.40-7.43 (m, 2), 7.48-7.54 (m, 2), 7.63 (d, 1, J = 7.2), 7.75 (d, 1, J = 8.3).