A NEW SYNTHESIS OF SUBSTITUTED BENZALDEHYDE *N*-[(*E*)-PHENYLMETHYLIDENE]HYDRAZONES

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Abstract

Reaction of substituted *tert*-butyl 2-(phenylmethylidene)-1-hydrazinecarboxylates with gaseous HCl in various anhydrous solvents affords benzaldehyde *N*-(phenylmethylidene)-hydrazones in very good yields. A series of substituted benzaldehydes was used for the preparation of this type of compounds. The structure of the resulting compounds was investigated by ^{1}H-NMR, IR and MS spectra.

Introduction

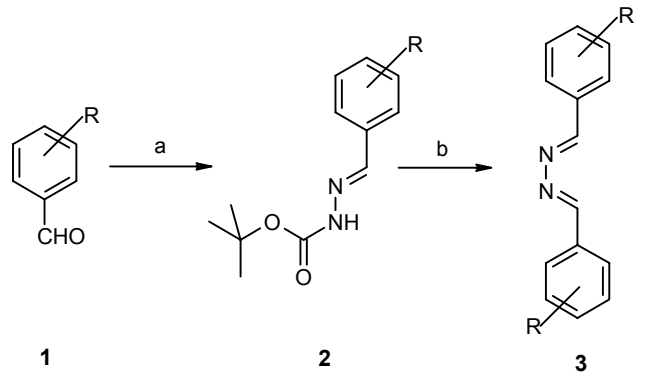
In the course of our research on the design of serine protease inhibitors para substituted benzaldehyde hydrazones would be interesting synthons that can be easily functionalized on both nitrogen atoms.[1,2] To prevent the formation of bis substituted hydrazones the series of substituted *tert*-butyl 2-(phenylmethylidene)-1-hydrazinecarboxylates **2** were prepared from corresponding benzaldehydes **1** and *tert*-butyl 1-hydrazinecarboxylate.[3]

Results and discussion

In this paper we report the unexpected reaction that took place during the deprotection of Boc-group in compounds **2a-i**. After two minutes of influx of gaseous hydrogen chloride in solution of **2a-i** in anhydrous tetrahydrofurane, dichloromethane or acetic acid at room temperature or with slight cooling benzaldehyde *N*-(phenylmethylidene)hydrazones **3a-i** were formed as yellow or orange precipitates.

Concerning the mechanism of the reaction we at first stipulated that the first step was the removal of Boc-protecting group, followed by the hydrolysis of imino bond. Substituted benzaldehydes and protonated hydrazine would be the corresponding intermediates that take part in condensation reaction. Reaction between benzaldehydes

and hydrazine hydrate has been known for a long time and is the standard procedure in the synthesis of benzaldehyde *N*-(phenylmethylidene) hydrazones.[4,5]



1 **2** **3**

a: NHNHBoc, EtOH, 5h; b: HCl/AcOH, r.t., 2 min

1,2,3	a	b	c	d	e	f	g	h	i
R	H	4-Me	4-NO_2	3-NO_2	4-COOH	4-$CONH_2$	4-$CH_2NHCOCH_3$	4-NMe_2	4-CN

Scheme 1

To prove the above-mentioned mechanism various reaction conditions were used. Substituted benzaldehydes were dissolved in different solvents saturated with gaseous hydrogen chloride. Hydrazine in the form of hydrazine hydrate, hydrazine chloride or boc-karbazate was added and the reaction mixture was stirred at room temperature. In neither case the product was formed as proved by NMR-spectra and mass spectrometry.

Probably during the removal of Boc-group benzaldehyde hydrazones are formed. One resulting molecule reacts with another to yield the final product.

Experimental

Synthesis of compounds 2a-2i (General procedure): The mixture of substituted benzaldehyde (10 mmol) and *tert*-butyl 1-hydrazinecarboxylate (10 mmol) in absolute ethanol (25 ml) was refluxed for 5 hours. The solution was diluted with water and the resulting precipitate filtered to yield compounds **2a-i** as white or pale yellow solids.

***tert*-Butyl 2-[(*E*)-phenylmethylidene]-1-hydrazinecarboxylate (2a).**

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (s, 9H, C($\underline{CH_3}$)$_3$), 7.36 (d, 2H, J=2.38 Hz, Ar-$\underline{H}$), 7.38 (m, 1H, Ar-$\underline{H}$), 7.68 (m, 2H, Ar-$\underline{H}$), 7.86 (s, 1H, Ar- $\underline{CH}$), 8.06 (s, 1H, N$\underline{H}$) ppm; **MS** (FAB+): m/z (%): 221 (MH^+, 16), 165 (100); **IR** (KBr): ν 3250, 2982, 1690, 1529, 1372, 1272, 1165, 1058, 861, 759, 693 cm^{-1}; **Anal. Calcd for $C_{12}H_{15}N_2O_2$×1/3 H_2O**: 63.70% C, 6.98% H, 12.38% N; Found: 63.78% C, 7.27% H, 12.47% N. **mp** = 151 °C. **Yield** = 94%.

***tert*-Butyl 2-[(*E*)-(4-nitrophenyl)methylidene]-1-hydrazinecarboxylate (2c).**

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (s, 9H, C($\underline{CH_3}$)$_3$), 7.83 (d, 2H, J=8.84 Hz, Ar-$\underline{H}$), 7.98 (s, 1H, Ar-$\underline{CH}$), 8.22 (d, 2H, J=8.84 Hz, Ar-$\underline{H}$), 8.40 (s, 1H, $\underline{NH}$) ppm; **MS** (FAB+): m/z (%): 266 (MH^+,24), 210 (100); **IR** (KBr): ν 3281, 2987, 1705, 1528, 1347, 1252, 1144, 1060, 850, 614 cm^{-1}; **Anal. Calcd for $C_{12}H_{15}N_3O_4$**: 54.33% C, 5.70% H, 15.84% N; Found: 54.17% C, 5.84% H, 15.51% N. **mp** = 169-171 °C. **Yield** = 90%.

***tert*-Butyl 2-[(*E*)-(3-nitrophenyl)methylidene]-1-hydrazinecarboxylate (2d).**

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (s, 9H, C($\underline{CH_3}$)$_3$), 7.56 (t, 1H, J=7.98 Hz, Ar-$\underline{H}$), 8.00 (s, 1H, Ar-$\underline{CH}$), 8.08 (d, 1H, J=7.81 Hz, Ar-$\underline{H}$), 8.20 (m, 1H, Ar-$\underline{H}$), 8.27 (s, 1H, $\underline{NH}$), 8.43 (m, 1H, Ar-$\underline{H}$) ppm; **MS** (FAB+): m/z (%): 266 (MH^+, 7), 210 (100); **IR** (KBr): ν 3221, 2980, 1713, 1530, 1354, 1270, 1165, 1054, 870, 680 cm^{-1}; **Anal. Calcd for $C_{12}H_{15}N_3O_4$**: 54.33% C, 5.70% H, 15.84% N; Found: 54.33% C, 5.70% H, 15.74% N. **mp**= 158-159 °C. **Yield** = 90%.

4-{[(*E*)-2-(*tert*-Butoxycarbonyl)hydrazono]methyl}benzoic acid (2e).

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.48 (s, 9H, C($\underline{CH_3}$)$_3$), 7.66 (d, 2H, J=7.78 Hz, Ar-$\underline{H}$), 7.91 (d, 2H, J=7.78 Hz, Ar-$\underline{H}$), 8.02 (s, 1H, Ar-$\underline{CH}$), 10.85 (s, 1H, $\underline{NH}$), 13.00 (s, 1H, $\underline{COOH}$) ppm; **MS** (FAB+): m/z (%): 265 (MH^+, 17), 209 (100); **IR** (KBr): ν 3491, 3286, 2986, 1708, 1678, 1356, 1266, 1161, 1059, 858, 775, 608 cm^{-1}; **Anal. Calcd for $C_{13}H_{16}N_2O_4$**: 59.08% C, 6.10% H, 10.60% N; Found: 59.12% C, 6.07% H, 10.36% N. **mp** = 322-325 °C. **Yield** = 94%.

***tert*-Butyl 2-{(*E*)-[4-(aminocarbonyl)phenyl]methylidene}-1-hydrazinecarboxylate (2f).**

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.48 (s, 9H, C($\underline{CH_3}$)$_3$), 7.37 and 7.99 (2s, 2H, $\underline{CONH_2}$), 7.66 (d, 2H, J=8.28 Hz, Ar-$\underline{H}$), 7.90 (d, 2H, J=8.28 Hz, Ar-$\underline{H}$), 8.04 (s,1H, Ar-$\underline{CH}$), 10.99 (s,1H, $\underline{NH}$) ppm; **MS** (FAB+): m/z (%): 264 (MH^+, 34), 154 (100); **IR** (KBr): ν 3378, 3282, 3175, 2985, 1707, 1654, 1622, 1533, 1419, 1360, 1269, 1159, 1059, 946, 854, 760, 609, 536 cm^{-1}; **Anal. Calcd for $C_{13}H_{17}N_3O_3$**: 59.30% C, 6.51% H, 15.96% N; Found: 59.17% C, 6.62% H, 16.21% N. **mp** = 204-206 °C. **Yield** = 92%.

***tert*-Butyl 2-((*E*)-{4-[(acetylamino)methyl]phenyl}methylidene)-1-hydrazine-carboxylate (2g).**

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (s, 9H, C($\underline{CH_3}$)$_3$), 2.04 (s, 3H, CO$\underline{CH_3}$), 4.42 (d, 2H, J=5.84 Hz, Ar-$\underline{CH_2}$), 6.19 (s, 1H, $\underline{NH}$CO), 7.23 (d, 2H, J=8.17 Hz, Ar-$\underline{H}$), 7.59 (d, 2H, J=8.17 Hz, Ar-$\underline{H}$), 7.83 (s, 1H, Ar-$\underline{CH}$), 8.27 (s, 1H, $\underline{NH}$COO) ppm; **MS** (FAB+): m/z (%): 292 (MH^+, 16), 236 (100); **IR** (KBr): ν 3315, 3194, 2976, 1718, 1657, 1555, 1364, 1278, 1180, 1058, 882, 805, 714, 664 cm^{-1}; **Anal. Calcd for $C_{15}H_{21}N_3O_3$×1/6 H_2O**: 61.20% C, 7.41% H, 14.27% N; Found: 61.08% C, 7.24% H, 13.92% N. **mp** = 183-187 °C. **Yield** = 87%.

***tert*-Butyl 2-{(*E*)-[4-(dimethylamino)phenyl]methylidene}-1-hydrazinecarboxylate (2h).**

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (s, 9H, C($\underline{CH_3}$)$_3$), 3.01 (s, 6H, N($\underline{CH_3}$)$_2$), 6.68 (d, 2H, J=8.51 Hz, Ar-$\underline{H}$), 7.56 (d, 2H, J=8.51 Hz, Ar-$\underline{H}$), 7.42 (s, 1H, Ar-$\underline{CH}$), 7.74 (s, 1H, $\underline{NH}$) ppm; **MS** (FAB+): m/z (%): 263 (M^+, 100); **IR** (KBr): ν 3253, 2982, 1688, 1615, 1518, 1369, 1272, 1166, 1056, 866, 817 cm^{-1}; **Anal. Calcd for $C_{14}H_{21}N_3O_2$**: 63.85% C, 8.04% H, 15.96% N; Found: 63.93% C, 7.89% H, 16.23% N. **mp** = 156-157 °C. **Yield** = 92%.

Synthesis of compounds 3a-3i (General procedure): 9.5 mmol of compounds **3a-3i** was dissolved in 15 ml of anhydrous acetic acid (or appropriate amount of other above mentioned anhydrous solvents) and gaseous hydrogen chloride was bubbled in for 2

minutes. The resulting yellow or orange precipitates were filtered, washed with ether and crystalized from ethanol to yield benzaldehyde *N*-[(*E*)-phenylmethylidene]-hydrazones **3a-i**.

Benzaldehyde *N*-[(*E*)-phenylmethylidene]hydrazone (3a).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.51 (2d, 6H, J=7.16 Hz, Ar-H), 7.89 (2d, 4H, J=7.16 Hz, Ar-H), 8.72 (s, 2H, Ar-CH) ppm; **MS** (70 eV, EI): m/z (%): 208 (M^+, 23), 77 (100); **IR** (KBr): ν 2914, 2063, 1941, 1815, 1709, 1482, 1239, 1088, 882 cm^{-1}; **Anal. Calcd for $C_{14}H_{12}N_2$**: 80.74% C, 5.81% H, 13.45% N; Found: 80.59% C, 6.03% H, 13.34% N. **mp** = 92-94 °C (lit.[5]: 93 °C). **Yield** = 92%.

4-Methylbenzaldehyde *N*-[(*E*)-(4-methylphenyl)methylidene]hydrazone (3b).

^{1}H NMR (300 MHz, DMSO-d_6): δ 2.33 (s, 6H, CH_3), 7.76 (d, 4H, J=8.24 Hz, Ar-H), 8.01 (d, 4H, J=8.24 Hz, Ar-H), 8.67 (s, 2H, Ar-CH) ppm; **MS** (70 eV, EI): m/z (%): 236 (M^+, 44), 77 (100); **IR** (KBr): ν 2951, 2069, 1945, 1816, 1483, 1094, 876 cm^{-1}; **Anal. Calcd for $C_{16}H_{16}N_2$**: 81.32% C, 6.82% H, 11.85% N; Found: 81.02% C, 7.10% H, 11.59% N. mp= 151-153 °C (lit.[4]: 153 °C). **Yield** = 79%.

4-Nitrobenzaldehyde *N*-[(*E*)-(4-nitrophenyl)methylidene]hydrazone (3c).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.17 (d, 4H, J=8.85 Hz, Ar-H), 8.38 (d, 4H, J=8.85 Hz, Ar-H), 8.87 (s, 2H, Ar-CH) ppm; **MS** (70 eV, EI): m/z (%): 298 (M^+, 63), 271 (13), 251 (34), 205 (17), 176 (100), 149 (15), 130 (39), 103 (37), 89 (17), 76 (51), 63 (23); **IR** (KBr): ν 2967, 2564, 2070, 1946, 1597, 1519, 1483, 1346, 1093, 952, 839, 952, 839, 746, 684 cm^{-1}; **Anal. Calcd for $C_{14}H_{10}N_4O_4$**: 56.38% C, 3.38% H, 18.78% N; Found: 56.29% C, 3.51% H, 18.62% N. **mp** = 296-298 °C (lit.[5]: 297-298 °C). **Yield** = 93%.

3-Nitrobenzaldehyde *N*-[(*E*)-(3-nitrophenyl)methylidene]hydrazone (3d).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.83 (t, 2H, J=7.98 Hz, Ar-H), 8.33 (d, 2H, J=7.81 Hz, Ar-H), 8.37 (m, 2H, Ar-H), 8.72 (m, 2H, Ar-H), 8.93 (s, 2H, Ar-CH) ppm; **MS** (70 eV, EI): m/z (%): 298 (M^+, 67), 176 (100); **IR** (KBr): ν 2961, 2729, 2558, 1947, 1625, 1525, 1482, 1354, 1092, 809, 736 cm^{-1}; **Anal. Calcd for $C_{14}H_{10}N_4O_4$**: 56.38% C, 3.38%

H, 18.78% N; Found: 56.17% C, 3.65% H, 18.57% N. mp= 175-179 °C (lit.[5]: 196-197 °C). **Yield** = 95%.

4-({(*E*)-2-[(*E*)-(4-Carboxyphenyl)methylidene]hydrazono}methyl)benzoic acid (3e).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.87 (d, 4H, J=8.27 Hz, Ar-H), 8.06 (d, 4H, J=8.27 Hz, Ar-H), 8.80 (s, 2H, Ar-CH), 12.03 (s,2H, COOH) ppm; **MS** (70 eV, EI): m/z (%): 296 (M^+, 39), 124 (100); **IR** (KBr): ν 3408, 2982, 1685, 1626, 1428, 1292, 1217, 1097, 952, 769 cm^{-1}; **Anal. Calcd for $C_{16}H_{12}N_2O_4$**: 64.86% C, 4.08% H, 9.46% N; Found: 65.00% C, 4.23% H, 9.18% N. **mp** = 287-289 °C. **Yield** = 98%.

4-[((*E*)-2-{(*E*)-[4-(Aminocarbonyl)phenyl]methylidene}hydrazono)methyl]-benzamide (3f).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.73 (d, 4H, J=8.16 Hz, Ar-H), 8.02 (d, 4H, J=8.16 Hz, Ar-H), 8.74 (s, 2H, Ar-CH), 9.33 and 6.84 (2s,4H, CONH_2) ppm; **MS** (70 eV, EI): m/z (%):294 (M^+,46), 122 (100); **IR** (KBr): ν 3384, 2967, 2034, 1662, 1534, 1430, 1276, 1199, 1087, 966, 784 cm^{-1}; **Anal. Calcd for $C_{16}H_{14}N_4O_2$**: 65.30% C, 4.79% H, 19.04% N; Found: 65,18% C, 4,81% H, 19,20% N. **mp** = 236-238 °C. **Yield** = 83%.

***N*-(4-{[(*E*)-2-((*E*)-{4-[(acetylamino)methyl]phenyl}methylidene)hydrazono]methyl}-benzyl)acetamide (3g).**

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.91 (s, 6H, CH_3), 4.31 (d,4H, J=5.78 Hz, CH_2), 4.88 (s, 2H, NH), 7.37 (d, 4H, J=8.09 Hz, Ar-H), 7.83 (d, 4H, J=8.09 Hz, Ar-H), 8.45 (s, 2H, Ar-CH) ppm; **MS** (FAB+): m/z (%): 351 (MH^+,52) 154 (100); **IR** (KBr): ν 3422, 2904, 2731, 2580, 1945, 1655, 1560, 1425, 1187, 1096, 1030, 821, 663, 602cm^{-1}; **Anal. Calcd for $C_{20}H_{22}N_4O_2$**: 68.55% C, 6.33% H, 15.99% N; Found: 68.27% C, 6.51% H, 11.59% N. **mp** = 230-232 °C. **Yield** = 91%.

4-(Dimethylamino)benzaldehyde *N*-{(*E*)-[4-(dimethylamino)phenyl]methylidene}-hydrazone (3h).

^{1}H NMR (300 MHz, DMSO-d_6): δ 3.02 (s, 12H, N(CH_3)$_2$), 7.12 (d, 4H, J=8.43 Hz, Ar-H), 7.89 (d, 4H, J=8.43 Hz, Ar-H), 8.13 (s, 2H, Ar-CH) ppm; **MS** (FAB+): m/z (%): 295 (MH^+, 100); **IR** (KBr): ν 3401, 2908, 2571, 1607, 1551, 1432, 1197, 1094 cm^{-1}; **Anal.**

Calcd for $C_{18}H_{22}N_4$: 73.44% C, 7.53% H, 19.03% N; Found: 73.20% C, 7.71% H, 18.82% N. **mp** = 226-228 °C (lit.[6]: 228-229 °C). **Yield** = 97%.

4-({(*E*)-2-[(*E*)-(4-Cyanophenyl)methylidene]hydrazono}methyl)benzonitrile (3i). **^{1}H NMR** (300 MHz, DMSO-d_6): δ 7.86 (d, 4H, J=8.60 Hz, Ar-H), 8.07 (d, 4H, J=8.60 Hz, Ar-H), 8.79 (s, 2H, Ar-CH) ppm; **MS** (70 eV, EI): m/z (%): 258 (M^+, 52), 156 (100); **IR** (KBr): ν 2922, 2565, 2226, 1944, 1670, 1610, 1482, 1411, 1286, 1214, 1094, 1020, 833, 549 cm^{-1}; **Anal. Calcd for $C_{16}H_{10}N_4$**: 74.40% C, 3.90% H, 21.69% N; Found: 74.62 % C, 4.11% H, 21.25% N. **mp** = 316-319 °C (lit.[7]: 318-320 °C). **Yield** = 100%.

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References and Notes

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Povzetek

Pri reakciji substituiranih *terc*-butil 2-(fenilmetiliden)-1-hidrazinkarboksilatov s plinastim HCl v različnih brezvodnih topilih dobimo benzaldehid N-(fenilmetiliden)hidrazone z zelo visokimi izkoristki. Za sintezo spojin tega tipa smo uporabili vrsto različnih, substituiranih benzaldehidov. Strukturo nastalih produktov smo dokazali z uporabo ^{1}H-NMR in IR spektroskopije ter masne spektrometrije.