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RESEARCH ARTICLE

# Synthesis of Narrative Fluorine Containing Acylhydrazones

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## ABSTRACT

Synthesis of a series of N'-(substitutedbenzylidene/methelene)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide. ***(4a-o)*** was achieved from different aryl aldehyde and 2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide using few drops of acetic acid added and refluxed with good yield. The structures of the products were supported by FTIR, PMR and mass spectral data.

## KEYWORDS

2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide, aryl aldehyde, acetic acid, only refluxed

## INTRODUCTION

Hydrazones have two attached nitrogen atoms of different nature and a C-N double bond that is conjugated with a lone electron pair of the terminal nitrogen atom. These structural fragments are mostly responsible for the physical and chemical properties of hydrazones. Both nitrogen atoms of the hydrazone group are nucleophilic, although the amino type nitrogen is more reactive. Hydrazone group has both electrophilic and nucleophilic character.[1]

The substituted 1,3,4-oxadiazole derivatives have been obtained from hydrazide-hydrazones by the oxidative cyclization.[2-4] The hydrazone functional group is usually not stable in vivo[5,6] and in vitro.[7,8] However the hydrolytic stability of hydrazones are depend on the structure of the substituent.[1] 2,3-Dihydro- 1,3,4-oxadiazol derivatives are stable structures[9] and obtained from intramoleculer cyclization of hydrazide hydrazones by acid anhydrides or acylchlorides.[10-16]

In 1953, Yale and co-workers[11] reported the publication of related compounds. In 2002, Rollas and co-workers[15] demonstrated that some hydrazones of 4-fluorobenzoic acid hydrazide and their 1,3,4-oxadiazoline derivatives showed antibacterial and antifungal activities. The aroyl hydrazone chelator 2-hydroxy-1-naphthyladehyde isonicotinoyl hydrazone greater antimalarial activity than desferrioxamine against chloroquine - resistant and –sensitive parasites.[17]

Novel Hydrazide-Hydrazone derivatives were synthesized and their Utilization in the Synthesis of Coumarin, Pyridine, Thiazole and Thiophene Derivatives with Antitumor activity.[18]

To evade these problems, we have developed a new etiquette for the synthesis of N'-(substitutedbenzylidene/methelene)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide ***(4a-o)*** with the advantage of good yield and environmentally friendliness (**Scheme-a**).

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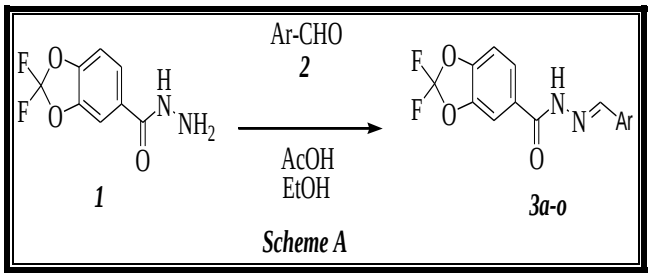


Scheme A

## EXPERIMENTAL

**Typical Experimental Procedure for the Synthesis of Acylhydrazones.**

To the mixture of 2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide (1 mmol) and aryl aldehyde (1 mmol) in 20 mL ethanol was added three drops of acetic acid with stirring for 6 h at ambient temperature. Insoluble solid was gradually generated, then filter and wash with ethanol. After drying pure target compound was afforded as crystalline solid.

**N'-(3,4-dimethoxybenzylidene)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide 3a.** Yield: 91%; mp 190-191$^{o}$C; HR-MS (ESI): calcd for $C_{17}H_{14}F_2N_2O_5$ ($M^+$+H): 364.09; C, 56.05; H, 3.87; F, 10.43; N, 7.69; O, 21.96; Found: C, 56.23; H, 3.92; F, 10.08; N, 7.86; O, 21.91;$^1$H NMR (400 MHz, DMSO): $\delta$= 11.77 (s, 1H), 8.36 (s, 1H), 7.91 (s, 1H), 7.82 (d, J= 8.4Hz, 1H), 7.58 (d, J= 8.4Hz, 1H), 7.34 (s, 1H), 7.22 (d, J=8 Hz, 1H), 7.03 (d, J= 8.4 Hz, 1H), 3.81 (s, 6H); IR (cm$^{-1}$): 3215 (N-H), 3070 (C-H aromatic ring), 2980 (C-H), 2843 (C-H), 1651 (C=O), 1512 (C=N), 1421 (C=C), 1332 (C-H), 1309 (C-H), 1274 (C-N), 1168 (C-O), 1028 (C-F).

**2,2-difluoro -N'-((thiophen-2-yl)methylene)benzo[d][1,3]dioxole-5-carbohydrazide 3b.** Yield: 87%; mp 210-211$^{o}$C; HR-MS (ESI): calcd for $C_{13}H_8F_2N_2O_3S$ ($M^+$+H): 310.02; C, 50.32; H, 2.60; F, 12.25; N, 9.03; O, 15.47; S, 10.33; Found: C, 50.28; H, 2.21; F, 12.27; N, 9.18; O, 15.11; S, 10.95; $^1$H NMR (400 MHz, DMSO): $\delta$= 11.85 (s, 1H), 8.64 (s, 1H), 7.91 (s, 1H), 7.82 (d, J= 8Hz, 1H), 7.68 (d, J= 4.8Hz, 1H), 7.58 (d, J= 8.4Hz, 1H), 7.49 (d, J= 2.8Hz, 1H), 7.15 (t, J= 4Hz, 1H); IR (cm$^{-1}$): 3304 (N-H), 3068 (C-H aromatic ring), 1654 (C=O), 1560 (C=N), 1490 (C=C), 1429 (C=C), 1234 (C-N), 1155 (C-O), 1033 (C-F).

**2,2-difluoro -N'-((furan-2-yl)methylene)benzo[d][1,3]dioxole-5-carbohydrazide 3c.** Yield: 85%; mp 225$^{o}$C; HR-MS (ESI): calcd for $C_{16}H_{12}F_2N_2O_4$ ($M^+$+H): 294.05; C, 53.07; H, 2.74; F, 12.91; N, 9.52; O, 21.75; Found: C, 53.41; H, 2.52; F, 12.49; N, 9.63; O, 21.95; $^1$H NMR (400 MHz, DMSO): $\delta$= 11.87 (s, 1H), 8.61 (s, 1H), 7.90 (s, 1H), 7.84 (d, J= 8Hz, 1H), 7.76 (d, J= 4.8Hz, 1H), 7.57 (d, J= 8.4Hz, 1H), 7.52 (d, J= 2.8Hz, 1H), 7.22 (t, J= 4.4Hz, 1H); IR (cm$^{-1}$): 3298 (N-H), 3072 (C-H aromatic ring), 2987 (C-H), 2853 (C-H), 1651 (C=O), 1547 (C=N), 1482 (C=C), 1368 (C-H), 1243 (C-N), 1158 (C-O).

**N'-(3-chloro-2-fluorobenzylidene)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide 3d.** Yield: 87%; mp 173-175$^{o}$C; HR-MS (ESI): calcd for $C_{15}H_8ClF_3N_2O_3$ ($M^+$+H): 356.02; C, 50.51; H, 2.26; Cl, 9.94; F, 15.98; N, 7.85; O, 13.46; Found: C, 50.32; H, 2.68; Cl, 9.73; F, 15.83; N, 7.74; O, 13.70; $^1$H NMR (400 MHz, DMSO): $\delta$= 11.68 (s, 1H), 8.64 (s, 1H), 7.92 (s, 1H), 7.86 (d, J= 8.4Hz, 1H), 7.82 (d, J= 8Hz, 1H), 7.78 (d, J= 8Hz, 1H), 7.58 (d, J= 7.6Hz, 1H), 7.66 (d, J= 8Hz, 1H); IR (cm$^{-1}$): 3270 (N-H), 3068 (C-H aromatic ring), 2932 (C-H), 2838 (C-H), 1656 (C=O), 1541 (C=N), 1437 (C=C), 1311 (C-H), 1251 (C-N), 1157 (C-O), 1013 (C-F).

**N'-(4-nitrobenzylidene)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide 3e.** Yield: 83%; mp 235-238$^{o}$C; HR-MS (ESI): calcd for $C_{15}H_9F_2N_3O_5$ ($M^+$+H): 349.05; C, 51.59; H, 2.60; F, 10.88; N, 12.03; O, 22.91; Found: C, 51.32; H, 2.91; F, 10.76; N, 12.63; O, 22.38; $^1$H NMR (400 MHz, DMSO): $\delta$= 11.81 (s, 1H), 8.50 (s, 1H), 8.31 (dd, J= 7.6, 1.2 Hz, 2H), 7.91 (s, 1H), 7.81 (d, J= 8Hz, 1H), 7.57 (d, J= 8.4Hz, 1H), 7.44 (dd, J= 8.4, 8 Hz, 2H); IR (cm$^{-1}$): 3336 (N-H), 3052 (C-H aromatic ring), 2924 (C-H), 2810 (C-H), 1654 (C=O), 1536 (C=N), 1451 (C=C), 1369 (C-H), 1243 (C-N), 1148 (C-O), 983 (C-F).

**N'-(4-methoxybenzylidene)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide 3f.** Yield: 89%; mp 189-191°C; HR-MS (ESI): calcd for $C_{16}H_{12}F_2N_2O_4$ ($M^+$+H): 334.08; C, 57.49; H, 3.62; F, 11.37; N, 8.38; O, 19.15; Found: C, 57.10; H, 3.73; F, 11.59; N, 8.09; O, 19.49; $^1$H NMR (400 MHz, DMSO): $\delta$= 11.78 (s, 1H), 8.38 (s, 1H), 7.92 (d, J= 1.2Hz, 1H), 7.83 (dd, J= 8.4, 8 Hz, 1H), 7.69 (d, J= 8.8, 1.2 Hz, 2H), 7.58 (d, J= 8.4 Hz, 1H), 7.03 (d, J= 8.8Hz, 2H), 3.80 (s, 3H); IR ($cm^{-1}$): 3240 (N-H), 3078 (C-H aromatic ring), 2843 (C-H), 1653 (C=O), 1548 (C=N), 1444 (C=C), 1367 (C-H), 1244 (C-N), 1168 (C-O).

**N'-(4-methylbenzylidene)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide 3g.** Yield: 92%; mp 213°C; HR-MS (ESI): calcd for $C_{16}H_{12}F_2N_2O_3$ ($M^+$+H): 318.08; C, 60.38; H, 3.80; F, 11.94; N, 8.80; O, 15.08; Found: C, 60.57; H, 3.48; F, 11.83; N, 8.77; O, 15.31; $^1$H NMR (400 MHz, DMSO): $\delta$= 11.73 (s, 1H), 8.38 (s, 1H), 7.91 (s, 1H), 7.82 (d, J= 8Hz, 1H), 7.58 (d, J= 8.4Hz, 1H), 7.43 (dd, J= 8.4, 2 Hz, 2H), 7.16 (dd, J= 8, 1.2 Hz, 2H), 2.42 (s, 3H); IR ($cm^{-1}$): 3286 (N-H), 3082 (C-H aromatic ring), 2937 (C-H), 2848 (C-H), 1655 (C=O), 1543 (C=N), 1461 (C=C), 1358 (C-H), 1305 (C-H), 1256 (C-N), 1162 (C-O), 994 (C-F).

**N'-(4-chlorobenzylidene)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide 3h.** Yield: 86%; mp 241°C; HR-MS (ESI): calcd for $C_{15}H_9ClF_2N_2O_3$ ($M^+$+H): 338.03; C, 53.19; H, 2.68; Cl, 10.47; F, 11.22; N, 8.27; O, 14.17; Found: C, 53.04; H, 2.83; Cl, 10.16; F, 11.53; N, 8.12; O, 14.32; $^1$H NMR (400 MHz, DMSO): $\delta$= 11.70 (s, 1H), 8.31 (s, 1H), 7.91 (s, 1H), 7.84 (d, J= 8Hz, 1H), 7.70 (dd, J= 8, 1.6 Hz, 2H), 7.58 (d, J= 8.4Hz, 1H), 7.41 (dd, J= 7.6Hz, 2H), 2.42 (s, 3H); IR ($cm^{-1}$): 3286 (N-H), 3089 (C-H aromatic ring), 2918 (C-H), 2852 (C-H), 1655 (C=O), 1543 (C=N), 1437 (C=C), 1366 (C-H), 1312 (C-H), 1264 (C-N), 1173 (C-O).

**N'-(2-chlorobenzylidene)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide 3i.** Yield: 83%; mp 198-200°C; HR-MS (ESI): calcd for $C_{15}H_9ClF_2N_2O_3$ ($M^+$+H): 338.03; C, 53.19; H, 2.68; Cl, 10.47; F, 11.22; N, 8.27; O, 14.17; Found: C, 53.25; H, 2.91; Cl, 10.12; F, 11.36; N, 8.09; O, 14.27; $^1$H NMR (400 MHz, DMSO): $\delta$= 11.72 (s, 1H), 8.34 (s, 1H), 7.92 (s, 1H), 7.82 (d, J= 8Hz, 1H), 7.58 (d, J= 8.4Hz, 1H), 7.32-7.24 (m, 4H); IR ($cm^{-1}$): 3277 (N-H), 3079 (C-H aromatic ring), 2924 (C-H), 2846 (C-H), 1658 (C=O), 1537 (C=N), 1473 (C=C), 1363 (C-H), 1301 (C-H), 1263 (C-N), 1171 (C-O), 1003 (C-F).

**N'-(4-fluorobenzylidene)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide 3j.** Yield: 88%; mp 182-183°C; HR-MS (ESI): calcd for $C_{15}H_9F_3N_2O_3$ ($M^+$+H): 322.06; C, 55.91; H, 2.82; F, 17.69; N, 8.69; O, 14.90; Found: C, 55.74; H, 2.90; F, 17.73; N, 8.93; O, 14.70; $^1$H NMR (400 MHz, DMSO): $\delta$= 11.68 (s, 1H), 8.37 (s, 1H), 7.91 (s, 1H), 7.82 (d, J= 8Hz, 1H), 7.68 (dd, J= 8.4, 1.6 Hz, 2H), 7.58 (d, J= 8.4Hz, 1H), 7.21 (dd, J= 8.4Hz, 2H); IR ($cm^{-1}$): 3245 (N-H), 3055 (C-H aromatic ring), 2918 (C-H), 2841 (C-H), 1653 (C=O), 1543 (C=N), 1471 (C=C), 1364 (C-H), 1305 (C-H), 1236 (C-N), 1164 (C-O), 1021 (C-F).

**N'-(3-bromobenzylidene)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide 3k.** Yield: 89%; mp 219-222°C; HR-MS (ESI): calcd for $C_{16}H_9BrF_2N_2O_3$ ($M^+$+H): 381.98; C, 47.02; H, 2.37; Br, 20.85; F, 9.92; N, 7.31; O, 12.53; Found: C, 47.38; H, 2.45; Br, 20.72; F, 9.64; N, 7.61; O, 12.20; $^1$H NMR (400 MHz, DMSO): $\delta$= 11.80 (s, 1H), 8.42 (s, 1H), 8.21 (s, 1H), 8.07 (d, J= 8Hz, 1H), 7.92 (s, 1H), 7.86 (d, J= 8Hz, 1H), 7.82 (d, J= 8Hz, 1H), 7.63 (t, J= 7.6Hz, 1H), 7.58 (d, J= 8.4Hz, 1H); IR ($cm^{-1}$): 3281 (N-H), 3083 (C-H aromatic ring), 2916 (C-H), 2850 (C-H), 1654 (C=O), 1541 (C=N), 1432 (C=C), 1359 (C-H), 1308 (C-H), 1268 (C-N), 1169 (C-O), 780 (C-Br).

**N'-(3-nitrobenzylidene)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide 3l.** Yield: 81%; mp 254-256°C; HR-MS (ESI): calcd for $C_{15}H_9F_2N_3O_5$ ($M^+$+H): 349.05; C, 51.59; H, 2.60; F, 10.88; N, 12.03;

O, 22.91; Found: C, 51.23; H, 2.83; F, 10.51; N, 12.67; O, 22.76; $^1$H NMR (400 MHz, DMSO): $\delta$= 11.79 (s, 1H), 8.40 (s, 1H), 8.38 (s, 1H), 8.13 (d, J= 8Hz, 1H), 7.98 (d, J= 8.4Hz, 1H), 7.91 (s, 1H), 7.83 (d, J= 8Hz, 1H), 7.71 (t, J= 7.6Hz, 1H), 7.58 (d, J= 8.4Hz, 1H); IR (cm$^{-1}$): 3245 (N-H), 3075 (C-H aromatic ring), 2920 (C-H), 2847 (C-H), 1658 (C=O), 1543 (C=N), 1450 (C=C), 1372 (C-H), 1309 (C-H), 1247 (C-N), 1154 (C-O), 1017 (C-F).

**N'-(4-hydroxybenzylidene)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide 3m.** Yield: 78%; mp 171-174$^o$C; HR-MS (ESI): calcd for $C_{15}H_{10}F_2N_2O_4$ ($M^+$+H): 320.06; C, 56.26; H, 3.15; F, 11.86; N, 8.75; O, 19.98; Found: C, 56.08; H, 3.32; F, 11.71; N, 8.83; O, 20.06; $^1$H NMR (400 MHz, DMSO): $\delta$= 11.73 (s, 1H), 8.37 (s, 1H), 7.90 (s, 1H), 7.86 (d, J= 8Hz, 1H), 7.58 (d, J= 8.4Hz, 1H), 7.45-7.31 (m, 4H), 5.12 (s, 1H); IR (cm$^{-1}$): 3463 (O-H), 3241 (N-H), 3078 (C-H aromatic ring), 2919 (C-H), 2832 (C-H), 1651 (C=O), 1539 (C=N), 1462 (C=C), 1370 (C-H), 1314 (C-H), 1253 (C-N), 1168 (C-O).

**N'-(2-methylbenzylidene)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide 3n.** Yield: 89%; mp 188$^o$C; HR-MS (ESI): calcd for $C_{16}H_{12}F_2N_2O_3$ ($M^+$+H): 318.08; C, 60.38; H, 3.80; F, 11.94; N, 8.80; O, 15.08; Found: C, 60.72; H, 3.74; F, 11.82; N, 8.63; O, 15.09; $^1$H NMR (400 MHz, DMSO): $\delta$= 11.67 (s, 1H), 8.34 (s, 1H), 7.91 (s, 1H), 7.82 (d, J= 8Hz, 1H), 7.58 (d, J= 8.4Hz, 1H), 7.21-7.09 (m, 4H), 2.47 (s, 3H); IR (cm$^{-1}$): 3251 (N-H), 3081 (C-H aromatic ring), 2925 (C-H), 2839 (C-H), 1657 (C=O), 1543 (C=N), 1429 (C=C), 1367 (C-H), 1307 (C-H), 1251 (C-N), 1134 (C-O), 1012 (C-F).

**N'-(4-bromo-2-fluorobenzylidene)-2,2-difluorobenzo[d][1,3]dioxole-5-carbohydrazide 3o.** Yield: 83%; mp 236-239$^o$C; HR-MS (ESI): calcd for $C_{15}H_8BrF_3N_2O_3$ ($M^+$+H): 399.97; C, 44.91; H, 2.01; Br, 19.92; F, 14.21; N, 6.98; O, 11.97; Found: C, 44.74; H, 2.32; Br, 19.82; F, 14.42; N, 6.80; O, 11.90; $^1$H NMR (400 MHz, DMSO): $\delta$= 11.77 (s, 1H), 8.46 (s, 1H), 8.04 (t, J= 8Hz, 1H), 7.91 (s, 1H), 7.85 (d, J= 8Hz, 1H), 7.78 (d, J= 8Hz, 1H), 7.58 (d, J= 8.4Hz, 1H), 7.66 (d, J= 8.4Hz, 1H); IR (cm$^{-1}$): 3318 (N-H), 3069 (C-H aromatic ring), 2934 (C-H), 2872 (C-H), 1655 (C=O), 1547 (C=N), 1428 (C=C), 1361 (C-H), 1304 (C-H), 1257 (C-N), 1164 (C-O), 1015 (C-F), 783 (C-Br).

## CONCLUSION

In conclusion, we have synthesized a library of fluorine containing acylhydrazones using simple and convenient method. This method produces these products in good yields, with a short reaction time and easy workup. Product is isolated by simple vaccum filteration. The isolated products are very pure and do not need any column purification. This study opens up a new area of cost-effective synthesis of potentially biologically active fluorine-based acylhydrazone compounds.

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