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Communications

Synthetic Studies on Fused Nitrogen-heterocycles from *N*-Amino-*N,N'*-dihydrodiazinediones (III). Synthesis of Fused Mesoionic 1,2,4-Triazolium-3-thiolates

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A number of monocyclic 1,2,4-triazolium-3-thiolates are known[1], but derivatives constaining fused rings are less common[2-5]. In connection with our work on the synthesis of fused nitrogen-heterocycles from *N*-amino-*N,N'*-dihydrodiazinediones[6,7], we report here a synthesis of fused 1,2,4-triazolium-3-thiolates.

A number of methods are available for the synthesis of monocyclic 1,2,4-triazolium-3-thiolates. One such method involves heating of *N*-acylthiosemicarbazides[2,8,9]. Compound such as 2-amino-2,3-dihydro-1,4-phthalazinedione (**1**), 1-amino-1,2-dihydro-3,6-pyridazinedione (**2**), and 1-amino-1,4-dihydro-2,3-quinoxalinedione (**3**) would react with aryl and alkyl isothiocyanates to give *N,N'*-disubstituted thioureas, which possess the *N*-acylthiosemicarbazide moiety and are hoped to afford fused 1,2,4-triazolium-3-thiolates by cyclization.

The compound **1** and **2** react with alkyl (or aryl) isothiocyanates at room temperature in DMF, giving *N,N'*-disubstituted thioureas (**4, 5**) which are converted into the mesoionic compounds (**7, 8**) on refluxing in acetic acid in the presence of $ZnCl_2$ and acetic anhydride.

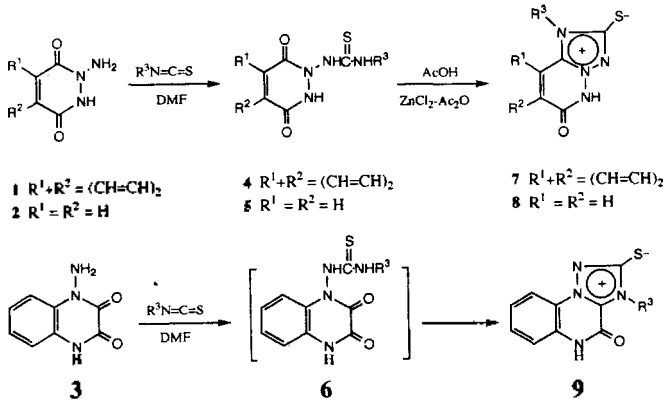
The representative experimental procedure for the preparation of **7** is as follows: To a stirred suspension of **1** (1.0 g, 5.6 mmol) in 20 m*l* of DMF was added ethyl isothiocyanate (0.4 g, 5.6 mmol). After stirring for 1 hr at room temperature clear solution was produced. The solvent was removed under reduced pressure to give solid. Water was added and allowed to stand overnight at room temperature. The solid was filtered and recrystallized from ethanol to give 2,3-dihydro-2-(3-ethylthioureido)-1,4-phthalazinedione (**4a**, 2 g, 81%). Compound **4a** (0.50 g, 1.9 mmol) was added to 10 m*l* of acetic acid and the mixture was heated to reflux temperature. Acetic anhydride (1 m*l*) and $ZnCl_2$ (0.26 g, 1.9 mmol) were added to produce a clear solution. The resultant solution was refluxed for 1 hr and allowed to stand overnight at room temperature. The solvent was removed under reduced pressure and the residue was recrystallized from ethanol to give 1-ethyl-5,6-dihydro-6-oxo-[1,2,4]triazolo[3,2-a]phthalazinium-2-thiolate (**7a**, 0.10 g, 21%).

When **3** reacts with two equivalents of alkyl (or aryl) isothiocyanates at reflux temperature in DMF, giving directly the mesoionic compounds, [1,2,4]triazolo[2,3-a]quinoxalinium-2-thiolates (**9**) in moderate yields. It is believed that **3** reacts with isothiocyanates giving intermediates, *N,N'*-disubstituted thioureas (**6**), which are cyclized easily to mesoionic

Table 1. Compounds **4, 5, 7, 8** and **9** Prepared

Product No.	R^3	Reaction conditions time/temperature	Yield[a] (%)	m.p.[b] (℃)
4a	Et	1 hr/r.t	81	207°
4b	Pr	1 hr/r.t	86	180-181°
4c	C_6H_{11}	30 min/r.t.	90	204-206°
4d	Ph	30 min/r.t.	92	182°
5a	C_6H_{11}	30 min/r.t.	77	222°(dec)
5b	Ph	30 min/r.t.	68	184°(dec)
7a	Et	1 hr/reflux	21	315-316°
7b	Pr	1 hr/reflux	17	312°
7c	C_6H_{11}	3 hr/reflux	18	338-339°
7d	Ph	30 min/reflux	17	357°
8a	C_6H_{11}	3 hr/reflux	16	362°(dec)
8b	Ph	10 min/reflux	23	300°
9a	Et	7 hr/reflux	70	309-310°
9b	Pr	7 hr/reflux	69	290-291°
9c	C_6H_{11}	12 hr/reflux	58	288-290°
9d	Ph	7 hr/reflux	61	323-324°

[a]Yield of isolated pure products; [b]Uncorrected.



Scheme 1.

compounds (**9**) without activation by Lewis acid, because the carbonyl group in **6** is activated by the adjacent carbonyl group.

A typical procedure for the preparation of **9** from **3** is exemplified as follows: To a stirred suspension of **3** (0.35 g, 2.0 mmol) in 10 m*l* of DMF was added ethyl isothiocyanate (0.35 g, 4.0 mmol). The mixture was heated under reflux for 7 hr to produce a clear solution. The resultant solution was allowed to stand overnight at room temperature to give a solid. It was recrystallized from methanol to give pure 3-ethyl-4,5-dihydro-4-oxo-[1,2,4]triazolo[2,3-a]quinoxalinium-2-thiolate (**9a**, 0.36 g, 70%).

Compounds **7-9** show absorption at 1310-1370 cm^{-1} attributable to C=S stretching which may be compared in position with thione stretching shown in the related compounds[2,4,5,8,10]. In the ^{1}H-NMR and IR of compounds **7-9**, proton resonance in the range of 8.68-12.94 ppm and broad band in the range of 2200-3600 cm^{-1}, respectively, indicate that they exist as a mixture with their own enolic tautomer. The possible formation of isomeric 1,3,4-thiadiazolo-2-aminides of **7-9** was ruled out on the basis of their known thermal unstability and absence of thioacyl cation fragments in mass spectra, which are commonly observed in the related systems[11].

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12. The spectral data for all products are summerized. **4a**: ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ 1.13 (t, 3H, J=7 Hz, CH_3), 3.23-3.90 (m, 2H, CH_2), 7.60-8.50 (m, 6H, C_6H_4+2NH), 10.16 (s, 1H, NH); IR (KBr) 3320, 3200-2400 (br), 1650, 1560, 1490, 1220, 1190, 745, 680 cm^{-1}. **4b**: ^{1}H-NMR ($CDCl_3$ +DMSO-d_6) δ 0.87 (t, 3H, J=7 Hz, CH_3), 1.56 (sext, 2H, J=7 Hz, CH_2), 3.45 (q, 2H, J=7 Hz, CH_2), 7.68-8.40 (m, 6H, C_6H_4+2NH), 11.15 (s, 1H, NH); IR (KBr) 3340, 3300-2400 (br), 1670, 1640, 1600, 1550, 1300, 1090 cm^{-1}. **4c**: ^{1}H-NMR (DMSO-d_6) δ 0.90-2.00 (m, 10H, $5CH_2$), 4.02 (m, 1H, CH), 7.60-8.30 (m, 4H, C_6H_4), 9.90 (s, 1H, NH), 11.60 (s, 1H, enolic OH); IR (KBr) 3000 (br), 1680, 1530, 1210 cm^{-1}. **4d**: ^{1}H-NMR (DMSO-d_6) δ 7.90-8.45 (m, 9H, C_6H_4 +C_6H_5), 9.81 (s, 1H, NH), 10.35 (s, 1H, NH), 11.40 (s, 1H, enolic OH); IR (KBr) 3000 (br), 1660, 1550, 1210 cm^{-1}. **5a**: ^{1}H-NMR (DMSO-d_6) δ 0.90-2.00 (m, 10H, $5CH_2$), 4.07 (m, 1H, CH), 6.94 (d, 1H, J=8.9 Hz, CH=), 7.11 (d, 1H, J=8.9 Hz, CH=), 7.86 (s, 1H, NH), 10.06 (s, 1H, NH), 11.25 (s, 1H, enolic OH); IR (KBr) 3000 (br), 1600, 1200 cm^{-1}. **5b**: ^{1}H-NMR (DMSO-d_6) δ 6.75 (d, 1H, J=10 Hz, CH=), 7.99 (d, 1H, J=10 Hz, CH=), 7.11-7.50 (m, 5H, C_6H_5), 9.80 (s, 1H, NH), 10.97 (s, 1H, enolic OH); IR (KBr) 3000 (br), 1680, 1550, 1230 cm^{-1}. **7a**: ^{1}H-NMR (DMSO-d_6) δ 1.26 (t, 3H, J=7.2 Hz, CH_3), 3.42 (q, 2H, J=7.2 Hz, CH_2), 7.74-8.28 (m, 4H, C_6H_4), 8.79 (s, 1H, enolic OH or NH); IR (KBr) 3600-2200 (br), 1600, 1510, 1340, 1270, 1200, 760 cm^{-1}; MS m/e 246 (M^+, 52.2), 178 (12.3), 130 (13.8), 120 (100). **7b**: ^{1}H-NMR (DMSO-d_6) δ 1.01 (t, 3H, J=7.2 Hz, CH_3), 1.50-1.95 (m, 2H, CH_2), 3.37 (t, 2H, J=6.2 Hz, CH_2), 7.74-8.43 (m, 4H, C_6H_4), 8.68 (s, 1H, enolic OH or NH); IR (KBr) 3600-2400 (br), 1570, 1540, 1340, 1200 cm^{-1}; MS m/e 260 (M^+, 89.90), 178 (28.8), 130 (24.2), 120 (100), 43 (29.5). **7c**: ^{1}H-NMR (DMSO-d_6) δ 1.00-2.55 (m, 10H, $5CH_2$), 3.65 (m, 1H, CH), 7.80-8.37 (m, 4H, C_6H_4), 8.80 and 8.90 (s, 1H, enolic OH or NH); IR (KBr) 3000 (br), 1310 cm^{-1}; MS m/e 301 (M+1, 14.4), 300 (M^+, 67.5), 120 (100), 83 (12.8), 76 (9.8), 55 (47.1). **7d**: ^{1}H-NMR (DMSO-d_6) δ 7.14-8.24 (m, 9H, C_6H_5+C_6H_4), 9.25 (s, 1H, NH); IR (KBr) 3000 (br), 1640, 1310 cm^{-1}; MS m/e 295 (M+1, 58), 294 (M^+, 81), 178 (35.9), 120 (77.0), 104 (100), 77 (31.2). **8a**: ^{1}H-NMR (DMSO-d_6) δ 0.90-2.60 (m, 10H, $5CH_2$), 3.60 (m, 1H, CH), 6.82 (d, 1H, J=10 Hz, CH=), 7.92 (d, 1H, J=10Hz, CH=), 8.66 and 8.76 (s, 1H, enolic OH or NH); IR (KBr) 3000 (br), 1600, 1310 cm^{-1}; MS m/e 250 (M^+, 57.7), 168 (71.3), 140 (39.2), 98 (64.4), 70 (100), 83 (1.4), 55 (55.5), 53 (13.3). **8b**: ^{1}H-NMR (DMSO-d_6) δ 6.75 (d, 1H, J=10 Hz, CH=), 7.99 (d, 1H, J=10 Hz, CH=), 7.08-7.68 (m, 5H, C_6H_5), 9.45 (s, 1H, enolic OH); IR (KBr) 3000 (br), 1340 cm^{-1}; MS m/e 244 (M^+, 100), 128 (8.9), 118 (29.7), 98 (27.7); 91 (13.7), 77 (5.9), 70 (34.2), 55 (5.8), 53 (1.3). **9a**: ^{1}H-NMR (DMSO-d_6) δ 1.36 (t, 3H, J=7 Hz, CH_3), 4.58 (q, 2H, J=7 Hz, CH_2), 7.43-8.26 (m, 4H, C_6H_4), 12.84 (s, 1H, enolic OH); IR (KBr) 3300-2400 (br), 1700, 1555, 1370, 1340, 1130 cm^{-1}; MS m/e 246 (M^+, 100), 218 (98.7), 172 (24.3), 160 (13.4), 118 (21.1), 90 (37.7). **9b**: ^{1}H-NMR (DMSO-d_6) δ 1.01 (t, 3H, J=7.3 Hz, CH_3), 1.68-2.15 (m, 2H, CH_2),

4.58 (t, 2H, J=7.5 Hz, CH_2), 7.36-8.21 (m, 4H, C_6H_4), 12.94 (s, 1H, enolic OH); IR (KBr) 3340-2200 (br), 1700, 1555, 1345, 1210, 760 cm^{-1}; MS m/e 260 (M^+, 51.8), 218 (100), 172 (20), 160 (9.5), 145 (11.4), 90 (15.6). **9c**: ^{1}H-NMR (DMSO-d_6) δ 1.35-1.81 (m, 10H, $5CH_2$), 5.40 (m, 1H, CH), 7.43-8.24 (m, 4H, C_6H_4), 12.85 (s, 1H, enolic OH); IR (KBr) 3600-2400 (br), 1720, 1540, 1350, 1330, 1190, 1140, 760 cm^{-1}; MS m/e 300 (M^+, 8.9), 218 (100), 172 (14.4), 160 (9.0), 145 (11.7), 90 (16.6), 82 (19.6), 41 (46.2). **9d**: ^{1}H-NMR (DMSO-d_6) δ 7.33-8.28 (m, 9H, $C_6H_4+C_6H_5$), 12.80 (s, 1H, enolic OH); IR (KBr) 3600-2400 (br), 1690, 1640, 1540, 1345, 1320, 1180, 770 cm^{-1}; MS m/e 295 ($M+1$, 18), 294 (M^+, 94), 236 (15), 208 (6), 135 (3), 106 (12), 77 (23), 76 (6), 65 (5), 58 (2).

A Novel Synthesis of 1H, 1H-Perfluoroalkyl Aromatics *via* Reduction of Perfluoroalkylated Dithioketals[1]

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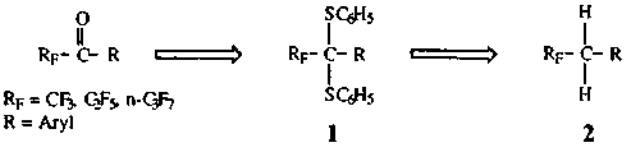
The introduction of a perfluoroalkyl functionality into organic compounds is an important subject in organofluorine chemistry because the resultant molecules exhibit unique properties in the areas of agrochemicals and pharmaceuticals and material.[2] Numerous methods for the perfluoroalkylation of organic compounds have been intensively developed during the last two decades and a couple of reviews has been reported in recent years.[3] In particular, trifluoromethyl functionality in aromatic compounds has attracted much attention mainly due to the profound enhancement in biological activities as compared to those of nonfluorinated aromatics.[4] However, it has been well known that perfluoroalkyl-functionalized aromatic compounds are very slowly metabolized in biological systems because of high stability of a perfluoroalkyl group connected directly to an aromatic ring.[5] Therefore, it has been suggested that introduction of 1H, 1H-perfluoroalkyl functionality into aromatic compounds, in which a methylene unit links a perfluoroalkyl group to the aromatic ring, may overcome the drawback of perfluoroalkyl-functionalized aromatic compounds. Although the methods for the preparation of perfluoroalkylated aromatic compounds has been well established,[3b] there are only limited reports on the synthesis of 1H, 1H-perfluoroalkylated aromatic compounds. Most of these methods[6] have disadvantages such as low yields, vigorous reaction conditions, the use of toxic reagents, multistep procedure and lack of generality. As part of our continuing studies on the chemistry and application of 1,1-bis(phenylthio)perfluoroalkyl aromatic compounds **1**,[7] we now describe a general approach for the preparation of 1H, 1H-perfluoroalkylated aromatic compounds **2**.



Recently, we developed a general and efficient method for the synthesis of **1** from the reaction of aryl perfluoroalkyl ketones with thiophenol at −78℃ in the presence of aluminum chloride.[8] Therefore, desulfurization of **1** would be a promising pathway for the synthesis of **2** because Clemmensen reduction of aryl perfluoroalkyl ketones failed to provide **2**.[9] Although only one successful example for the synthesis of **2** from aryl perfluoroalkyl ketones has been reported by DePuy and Schultz,[6f] this example shows multistep procedure and relatively low yield.

Compound **1a** was easily reduced by treatment with 2.2 equiv. of Bu_3SnH and 10 mol% AIBN without solvent at 80-90℃ for 1 hour and gave excellent yield of **2a**. The use of 1.1 equiv. of Bu_3SnH in this reaction resulted in the formation of 1-phenylthio-2,2,2-trifluoroethylbenzene **4a** in 82% yield. Product **2a** was easily isolated by flash distillation after reaction was finished, followed by simple distillation. Several substituents on the benzene ring did not interfere desulfurization of **1a** and provided excellent yields of **2**. Also, 1,1-bis(phenylthio)-trifluoroethylthiophene **1j** was easily reduced to give the corresponding product **2j**. Similar reduction of pentafluoroethyl and heptafluoropropyl substituted compounds **1k** and **1l** under the same reaction condition afforded the corresponding products **2k** and **2l** in 96% and 90% yields, respectively. All results are summarized in Table 1.

In a typical experimental procedure, a 50 m*l* two-necked round bottomed flask equipped with a septum, magnetic stir bar and a nitrogen inlet was charged with 1,1-bis(phenylthio)-trifluoroethylbenzene (4.70 g, 12.5 mmol),[8] tributyltin hydride (7.62 m*l*, 27.5 mmol) and AIBN (0.20 g). The mixture was heated at 80-90℃ (oil bath temperature) for 1 hour and then cooled to room temperature. Flash distillation of the mixture, followed by simple redistillation provided 1.60 g (80% yield) of 2,2,2-trifluoroethylbenzene **2a**. bp. 123-125℃; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 3.31 (q, J=10.6 Hz, 2H); ^{19}F NMR (80 MHz, $CDCl_3$) δ −50.32 (t, J=10.9 Hz); MS, m/e (relative intensity) 160 (M^+, 87.6), 91 (100); IR (neat) 3005, 2900, 1490, 1425, 1350, 1250, 1200, 1130, 1090, 1065, 905, 750, 690, 660 cm^{-1}.

Initially, we began our studies by examing the desulfurization of **1** under a couple of conditions which has been employed in the desulfurization of nonfluorinated dithioacetals or dithioketals. When **1a** reacted with a large excess of Raney Ni (20 equiv.) in acetone at reflux temperature for 2 hours, unexpected 2,2-difluoro-1-phenylthiostyrene **3a** which would be very useful synthetic intermediate was obtained in 63% yield and 1-phenylthio-2,2,2-trifluoroethylbenzene **4a** was obtained in 10% yield. No 1H,1H-trifluoroethylbenzene **2a** was detected. This result indicates that β-defluorination after insertion of Ni into carbon-sulfur bond may occur much faster than reduction. Similarly, treatment of **1a** with a mixture of 2 equiv. of $TiCl_4$ and 4 equiv. of $LiAlH_4$