RING TRANSFORMATION OF HETEROCYCLES: PART 3.[1] A CONVERSION OF 4-AMINO-Δ^2-1,2,4-OXADIAZOLINES INTO 2-ARYLAMINO-1,3,4-THIADIAZOLES AND OXA-ANALOGUES

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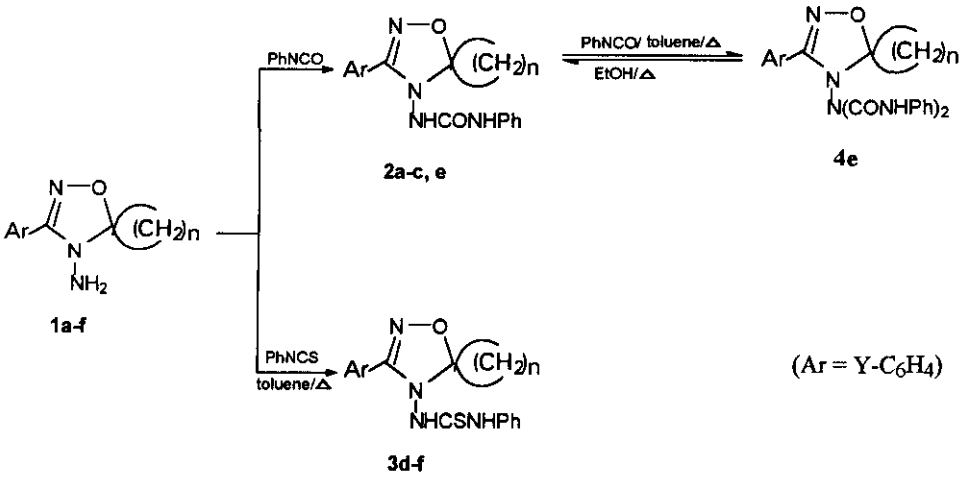
Abstract - 4-Amino-Δ^2-1,2,4-oxadiazolines (**1**) are transformed into the corresponding 2-arylamino-1,3,4-oxadiazoles (**5**) or thiadiazoles (**6**) *via* reaction with phenyl isocyanate (or phenyl isothiocyanate), followed by brief treatment of the resulting adducts (**2** and **3**) with trifluoroacetic anhydride at ambient temperature. Treatment of compounds (**1**) with trifluoroacetic anhydride gave 2-trifluoromethyl-1,3,4-oxadiazoles (**8**).

Recently, we reported[1] on the transformation of 4-amino-Δ^2-1,2,4- oxadiazolines (**1**) into 1,3,4-oxadiazoles upon treatment of the former compounds, or their *N*-acyl derivatives, with chloroacetic anhydride in boiling toluene.

In extension of this work, we now describe the preparation of some *N*-carboxamido- (**2**) and *N*-thiocarboxamido derivatives (**3**) of compounds (**1**) and their facile transformation into 2-arylamino-1,3,4-oxadiazoles (**5**) and 2-arylamino-1,3,4-thiadiazoles (**6**). Compounds (**2**) and (**3**) were accessible through condensation of 4-amino-Δ^2-1,2,4-oxadiazolines (**1**) with phenyl isocyanate and phenyl isothiocyanate, respectively.

The reaction of compounds (**1**) with phenyl isothiocyanate to give compounds (**3**) proceeded rather sluggishly and required prolonged heating. Under similar conditions, the reaction of compound (**1e**) with phenyl isocyanate afforded the bis-carboxamide derivative (**4e**). However, the latter compound reverts readily into compound (**2e**) upon brief refluxing in ethanol.

Scheme 1



Entry	a	b	c	d	e	f
Y	*p*-NO2	*m*-NO2	*p*-NO2	*p*-Cl	*m*-NO2	*p*-NO2
n	4	6	6	6	7	7

The structures of compounds (**2**)-(**4**) were supported by elemental analysis (Table 1) and spectral data. The infrared spectra revealed two N-H absorption bands at about 3340 and 3260 cm^{-1} for compounds (**2**) and at around 3340 and 3220 cm^{-1} for compounds (**3**). The absorptions at about 1685 and 1600 cm^{-1} were assigned to the C=O and C=N stretching modes, respectively. In the ^{1}H-nmr spectra of compounds (**2**) and (**3**) the N-H protons appeared as two exchangeable singlets in the range 7.4-10.3 ppm. In the ^{13}C-nmr spectra, the C=O carbon in compounds (**2**) appeared at 154-155 ppm and the C=S carbon in compounds (**3**) appeared at 180-181 ppm. Compounds (**2**) and (**3**) displayed a charecteristic ^{13}C-signal in the range 103-105 ppm, ascribed to the sp^3 carbon (C-5) of the heteroring (Table 2).

Table 1. Physical and Analytical Data for Compounds (**2-8**).

Compd[a]	mp(°C)	Yield (%)	Mol. Formula	Calcd / Found (%) C	H	N
2a	205-206	83	$C_{19}H_{19}N_5O_4$	59.84	5.02	18.36
				59.69	5.18	18.18
2b	196-197	80	$C_{21}H_{23}N_5O_4$	61.60	5.66	17.10
				61.76	5.54	16.89
2c	208-209	65	$C_{21}H_{23}N_5O_4$	61.60	5.66	17.10
				61.44	5.46	16.96
2e	198-199	77	$C_{22}H_{25}N_5O_4$	62.40	5.95	16.54
				62.10	5.68	16.37
3d	170-171	70	$C_{21}H_{23}N_4OClS$	60.70	5.58	13.48
				60.60	5.33	13.38
3e	171-172	65	$C_{22}H_{25}N_5O_3S$	60.12	5.73	15.93
				60.35	5.91	15.79
3f	173-174	87	$C_{22}H_{25}N_5O_3S$	60.12	5.73	15.93
				60.10	5.82	15.93
4e	162-163	75	$C_{29}H_{30}N_6O_5$	64.19	5.57	15.48
				64.04	5.36	15.23
5a	270-271[b]	60	$C_{14}H_{10}N_4O_3$	59.57	3.57	19.85
				59.49	3.38	19.65
5b	222-223	55	$C_{14}H_{10}N_4O_3$	59.57	3.57	19.85
				59.60	3.41	19.77
6d	221-222[b]	70	$C_{14}H_{10}N_3ClS$	58.43	3.50	14.60
				58.29	3.67	14.61
6e	277-278[b]	74	$C_{14}H_{10}N_4O_2S$	56.37	3.38	18.78
				56.12	3.50	18.66
6f	286-287[b]	88	$C_{14}H_{10}N_4O_2S$	56.37	3.38	18.78
				56.21	3.50	18.66
8a	120-121	70	$C_9H_4F_3N_3O_3$	41.71	1.56	16.21
				41.98	1.52	16.37
8b	85-86	75	$C_9H_4F_3N_3O_3$	41.71	1.56	16.21
				41.93	1.52	16.61

[a]Data for compounds (**1a-f**) are given in refs. 2 and 3.

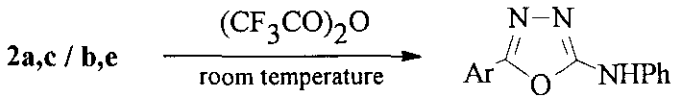
[b]Lit. mp of **5a**[4] 270-271, **6d**[5] 221-222, **6e**[6] 250, **6f**[5] 272-273 °C.

Table 2. ^{1}H-Nmr and ^{13}C-Nmr Data for Compounds (**2-8**).

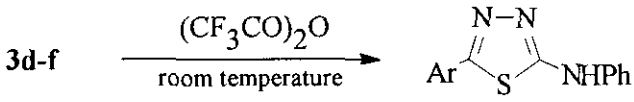
	^{1}H-Nmr (ppm)			^{13}C-Nmr (ppm)			
Compd	N-H	-(CH_2)-	Aromatic	C=O/ C=S	C-5	Others	Solvent
2a	7.4 8.8	1.63(4H, m) 2 08(4H, m)	7.90(d, *J*=9 Hz) 8.30(d, *J*=9 Hz) 6 88-7.30(m)	154.8	105.0	-	DMSO-d_6
2b	7.6 8.8	1 52(8H, br s) 1 85-2 23(4H, m)	6 90-8.46(m)	155.1	104.6	-	DMSO-d_6
2c	7 5 9.0	1 54(8H, br s) 1.86-2 20(4H, m)	7.92(d, *J*=9 Hz) 8 32(d, *J*=9 Hz)	155.2	103 8	-	DMSO-d_6
2e	7.4 8.7	1 53(6H, br s) 1.63(4H, br s) 1.96(4H, m)	6 98-8.48(m)	155.4	103 4	-	DMSO-d_6
3d	8.7 8.9	1.64(8H, br s) 2.03(4H, m)	7.25-7 70 (m)	180.2	105.0	-	$CDCl_3$
3e	10.2 10.4	1.58(10H, m) 2.02-2.36(4H, m)	7.20-8.38(m)	180.8	105.6	-	DMSO-d_6
3f	10 1 10 3	1.55(10H, m) 2.00-2.34(4H, m)	7.93(d, *J*=9 Hz) 8.40(d, *J*=9 Hz) 7 25-7.53(m)	180.4	105 1	-	DMSO-d_6
4e	9.9	1.62(8H, br s) 1 91-2.34(6H, m)	7 16-8.56(m)	153 9	104.4	-	$CDCl_3$
5b	10.8	-	7 02-8 55(m)	-	153.4	C-2: 161 4	DMSO-d_6
8a	-	-	8 32(d, *J*=9 Hz) 8 41(d, *J*=9 Hz)	-	150.4	CF3: 116 1 (q, $J_{C\text{-}F}$ 270 Hz) C-2: 155.6 (q, $J_{C\text{-}F}$ 45 Hz)	$CDCl_3$
8b	-	-	7 83-8.94(m)	-	148 7	CF3· 116.1 (q, $J_{C\text{-}F}$ 270 Hz) C-2: 155 4 (q, $J_{C\text{-}F}$ 45 Hz)	$CDCl_3$

Treatment of compounds (**2**) with trifluoroacetic anhydride in dry benzene at room temperature transformed them into the corresponding 2,5-disubstituted-1,3,4-oxadiazoles (**5**)[7] (Scheme 2).

Scheme 2



5a / b



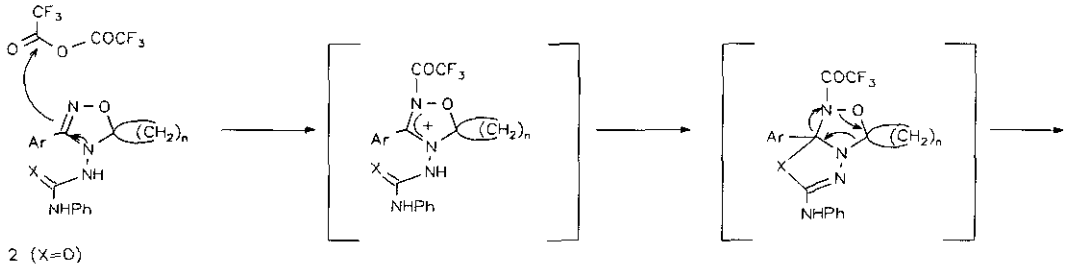
6d-f

Compounds (**3**), under similar conditions, were likewise transformed into the respective 1,3,4-thiadiazoles (**6**).[8] The structures of compounds (**5**) and (**6**) were supported by elemental analysis (Table 1) and spectral data.

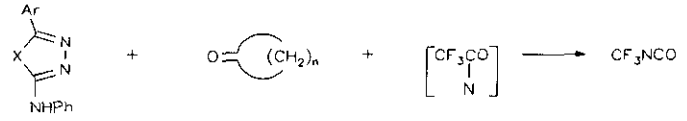
A plausible reaction mechanism for this heteroring transformation of compounds (**2**) and (**3**) into compounds (**5**) and (**6**) is depicted in Scheme 3.

It is anticipated that the nucleophilic attack at C-3 of the heteroring by the oxygen or sulfur atom of the *N*-acyl or the *N*-thioacyl moiety is significantly facilitated through acylation at N-2 by the trifluoroacetic anhydride, which functions as a catalyst. The resulting presumed transient bicyclic adduct eventually decomposes into the corresponding 1,3,4-oxadiazole (**5**) or thiadiazole (**6**), the ketone component, and trifluoroacetyl nitrene, which rearranges into the volatile trifluoromethyl isocyanate. In a selected case, the ketone was converted to its 2,4-dinitrophenylhydrazone and identified through comparison with an authentic sample.

Scheme 3



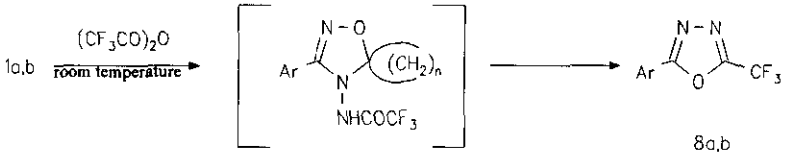
2 (X=O)
3 (X=S)



5 (X=O)
6 (X=S)

In a control experiment, the parent 4-amino-Δ^2-1,2,4-oxadiazolines (**1a,b**) were treated with trifluoroacetic anhydride in dry benzene at ambient temperature. The initially orange coloration of the solution started to fade and finally disappeared within a few minutes. Workup of the reaction mixture gave the corresponding 2-trifluoromethyl-1,3,4-oxadiazoles (**8a,b**). Isolation of the intervening *N*-trifluoroacetyl intermediate (**7**) was not possible (Scheme 4).

Scheme 4

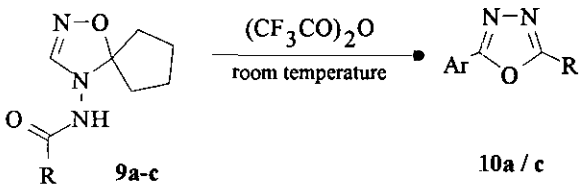


7 8a,b

Compounds (**8a,b**) exhibited two charachteristic ^{13}C-nmr signals for the CF_3 and the adjacent C-2 carbons which appeared as quartets at 116.1 ($J_{C\text{-}F}$ = 270 Hz) and 155.6 ppm ($J_{C\text{-}F}$ = 45 Hz), respectively.

In a previous work, we reported[2] similar transformation of the *N*-acyl derivatives (**9**) into 1,3,4-oxadiazoles (**10**) using chloroacetic anhydride in benzene under reflux for few hours. In the present study, trifluoroacetic anhydride was also found to bring about smooth transformation of compounds (**9**) into the corresponding 2-acyl-1,3,4-oxadiazoles (**10**) at room temperature within a few minutes (Scheme 5).

Scheme 5



9a-c **10a / c**

9 / 10	Ar	R
a	C_6H_4	C_6H_5
b	*m*-$NO_2C_6H_4$	CH_3
c	*m*-$NO_2C_6H_4$	H

This reagent is, therefore, superior to chloroacetic anhydride previously employed[2] for such type of heteroring transformation. The latter reagent gave only poor yields of compounds (**6**) upon reaction with compounds (**3**) and failed to convert compounds (**2**) into (**5**).

EXPERIMENTAL

Melting points, uncorrected, were determined with an electrothermal Mel-Temp apparatus Infrared spectra (KBr pellets) were recorded on a Perkin Elmer 577 spectrophotometer. Nmr spectra were measured with a Varian XL 200 or Bruker AMX 300 spectrometer for solutions in $CDCl_3$ or DMSO-d_6. Mass spectra were obtained with a Finnigan MAT 731 at 70 eV. Microanalyses were performed at M.H.W. Laboratories at Phoenix, Arizona, USA.

4-Amino-3-aryl-Δ^2-1,2,4-oxadiazolines (1a-f)

These compounds were prepared through the reaction of the appropriate hydroxamoyl chlorides and hydrazones in chloroform and in the presence of triethylamine following a previously described procedure.[2,3]

3-Aryl-4-(*N'*-Phenylcarbamoylamino)-Δ^2-1,2,4-oxadiazolines (2)

Compound (**1**) (10 mmol) was stirred with phenyl isocyanate (6.0 g, 50 mmol) in dry benzene (30 ml) for 24 h at room temperature. The solvent was then evaporated in vacuo and the residue was recrystallized from chloroform / petroleum ether (bp 40-60 °C).

3-Aryl-4-(*N'*-Phenylthiocarbamoylamino)-Δ^2-1,2,4-oxadiazolines (3)

Compound (**1**) (10 mmol) was refluxed with phenyl isothiocyanate (6.8 g, 50 mmol) in dry benzene (50 ml) containing pyridine (2 ml) for 24 h. The solvent was evaporated in vacuo, and the residual solid was triturated with little ethanol and recrystallized from chloroform / petroleum ether (bp 40-60 °C).

3-(*m*-Nitrophenyl)-4-[*N'*-bis(phenylcarbamoyl)amino]-5-hexamethylene-Δ^2-1,2,4-oxadiazoline (4e)

Compound (**1e**) or (**2e**) (10 mmol) was refluxed with excess phenyl isocyanate (6.0 g, 50 mmol) in dry toluene (50 ml) for 6 h. The solvent was then evaporated in vacuo, and the residual solid was crystallized from chloroform / petroleum ether (bp 40-60 °C). Upon refluxing in ethanol for 15 min, compound (**4e**) reverted quantitatively to compound (**2e**).

5-Aryl-2-phenylamino-1,3,4-oxadiazoles and 5-Aryl-2-phenylamino-1,3,4-thiadiazoles (5, 6)

A solution of compound (**2**) or (**3**) (2 mmol) in dry benzene (20 ml) containing trifluoroacetic anhydride (2 ml, 14 mmol) was stirred at room temperature for 6 h. The solvent was then evaporated and the residual solid was triturated with little ethanol and recrystallized from chloroform / petroleum ether (bp 40-60 °C). In case of compound (**2a**) the alcoholic washings were treated with 2,4-dinitrophenylhydrazine and the cyclopentanone 2,4-dinitrophenylhydrazone, which formed immediately, was collected and identified.

5-Aryl-2-trifluoromethyl-1,3,4-oxadiazoles (8a,b)

To a solution of **1a** or **1b** (10 mmol) in dry benzene (50 ml) was added trifluoroacetic anhydride (2 ml, 14 mmol). The solution was stirred at room temperature for 5 min, the solvent was evaporated and the residue recrystallized from chloroform / petroleum ether (bp 40-60 °C).

3-Aryl-1,3,4-oxadiazoles (10a-c)

These compounds were obtained in quantitative yields from **9a-c**[2] by treatment of the latter compounds (10 mmol) with trifluoroacetic anhydride (2 ml, 14 mmol) in dry

benzene (50 ml) in a similar manner to compounds (**8**) above. The products were identical with authentic samples described previously.[2]

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