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A GENERALIZED SYNTHESIS OF 3-AMINO-5-ARYL- , 3-AMINO-5-POLYFLUOROPHENYL-, AND 3-AMINO-5-ALKYL-1,2,4-OXADIAZOLES THROUGH RING-DEGENERATE REARRANGEMENTS

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Abstract - A generalized synthesis of 3-amino-5-aryl-, 3-amino-5-poly-fluorophenyl- and 3-amino-5-alkyl-1,2,4-oxadiazoles has been developed starting from the 3-amino-5-methyl-1,2,4-oxadiazole as a common synthon. Aroylation or alkanoylation of this aminooxadiazole, followed by thermally-induced ring-degenerate equilibration of resulting 3-acylamino compounds, and final acid hydrolysis of the 3-acetylamino-5-aryl- (or 5-polyfluorophenyl-), or 3-acetylamino-5-alkyl-1,2,4-oxadiazoles counterpart which is formed, gave the expected 3-amino-5-substituted 1,2,4-oxadiazoles. In the case of some 3-aroylamino compounds, yields of final 3-amino-5-aryloxadiazoles are higher than that expected on the basis of the thermally-induced equilibrium composition, since acid hydrolysis plays a significant role in the shift of the equilibrium itself. Satisfactory direct procedures have also been described. As expected, restrictions to the above methodology were found in the synthesis of 5-perfluoroalkyl derivatives.

INTRODUCTION

The synthesis of heterocyclic compounds represents an increasingly valuable goal in view of their large range of applications as pharmaceuticals, agrochemicals and a variety of other products.[1] To this aim, efficient synthetic methodologies exploit ring-rearrangement reactions,[2] and among these, several examples regard rearrangements of O-N bond-containing azoles,[2,3] which have been studied both from mechanistic[4] point of view and synthetic applications.[3,5]

In the course of our work on the synthesis and reactivity of fluorinated heterocyclic compounds,[6,7] we were interested in an efficient synthesis of 3-amino-5-polyfluoroaryl- and 3-amino-5-heteroaryl-1,2,4-oxadiazoles. In the last years, since discovery of their applications in pharmaceuticals,[8,9] oxadiazoles have been receiving a growing interest; *inter alia*, some 3-amino derivatives have been found to act as

efficacious muscarinic agonists.[9] In principle, different methods are available for the synthesis of these functionalized oxadiazoles.[10] A general approach considers the reaction of *N*-acylcyanamides with hydroxylamine;[11] other methods use *N*-aroyl-*S*-methylisothioureas as starting reagent,[12] oxidative cyclization of *N*-acylguanidines,[13] and the reaction of *N*-hydroxyguanidine with acylating reagents in an acylation/cyclodehydration pattern.[9a-c] A photochemical approach, also applicable to the synthesis of *N*-substituted derivatives has been also pointed out.[14,15] Moreover, this photochemical methodology has been also applied for the synthesis of 3-amino- and 3-*N*-substituted amino-5-perfluoroalkyl-[6] or 5-perfluoroaryloxadiazoles.[7]

To contribute to the search of efficient methodologies for synthesis of these functionalized oxadiazoles, we have now considered the 3-amino-5-methyl-1,2,4-oxadiazole (**3**)[16] as a starting *synthon* to build 3-amino compounds variously substituted at the C(5) of the ring. In fact, it appears noteworthy to consider this synthon an *O*-protected amidoxime in one hand, or an *O,N*-protected hydroxyguanidine, in the other, both structures being precursors of the 1,2,4-oxadiazole nucleus.[10]

The construction of the new oxadiazole molecule from this synthon should involve ring-rearrangement reactions of its *N*-acylamino derivatives according to the well known Boulton-Katritzky general pattern.[3,17] These peculiar rearrangements (which can be of ring-degenerate or fully-degenerate type[18]) have been studied both from experimental[19-21] and theoretical[22] point of view. To our purposes it is noteworthy to bear in mind that: *i*) the thermally-induced equilibration between 3-aroylamino-5-methyl-oxadiazoles (at least when the aroyl moiety is *meta*- or *para*-substituted phenyl ring) and the corresponding 3-acetylamino-5-aryl derivatives has been found to be significantly shifted toward the 5-aryl substituted component as a result of its higher stabilization due to the diaryloid contribution;[19,21] *ii*) acidic hydrolysis of the 3-acylamino group to produce 3-amino compounds will proceed in different rate depending on the nature of the acylamino group itself (that is, an alkanoylamino or an aroylamino group); *iii*) finally, experimental conditions employed in the hydrolysis reaction could play a role in the overall equilibrium composition.

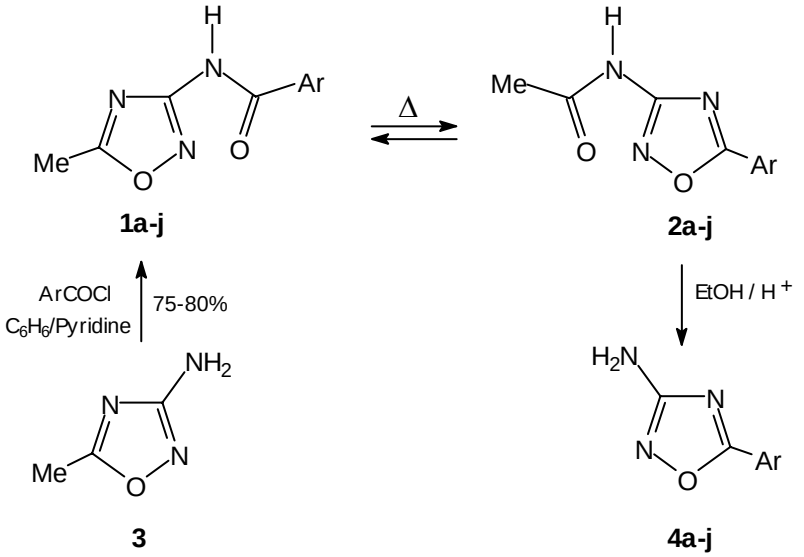
On the basis of the above considerations, we planned and succeeded in the synthesis of 3-amino-5-substituted oxadiazoles by realizing the following reaction steps: *i*) acylation of the 3-amino-5-methyl-oxadiazole; *ii*) thermal equilibration of resulting 3-acylamino derivatives; *iii*) acid hydrolysis of the 3-acetylamino components.

RESULTS AND DISCUSSION

Aroylation reactions of 3-amino-5-methyl-1,2,4-oxadiazole (**3**) and subsequent thermal equilibration between a series of *meta*- and *para*-substituted 3-aroylamino compounds (**1**) and the corresponding

3-acetylamino counterpart (**2**) have been previously reported.[19,21,23] When representative compounds (**1a-c**) were equilibrated in refluxing ethanol, subsequent acid hydrolysis of the resulting equilibrium mixture gave good yields of the corresponding 3-aminooxadiazoles (**4**) (see Table 1). In a synthetic approach, there is no need to separate the 3-acetylamino component (**2**) from the reaction mixture; in fact, apart from its much higher percentage, we observed that the acetylamino group is more easy to hydrolyze than the aroylamino group. Interestingly, as shown for representative example a direct procedure starting from compound (**3**) also gave good yields of the 3-aminooxadiazoles (**4**) (see Table 1).

Scheme 1



1, 2, 4

a: Ar = Ph
b: Ar = *p*-$CF_3C_6H_4$
c: Ar = *m*-$CF_3C_6H_4$
d: Ar = *o*-$NO_2C_6H_4$
e: Ar = *o*-$CF_3C_6H_4$
f : Ar = 2-Furyl
g: Ar = 2-Thienyl
h: Ar = C_6F_5
i : Ar = 2,3,4,5-Tetrafluorophenyl
j : Ar = 2,3,4-Trifluorophenyl

In the case of the *ortho*-substituted 3-aroylamino derivatives (**1d,e**) or 3-heteroaroylamino compounds (**1f,g**) the equilibrium composition shows a high concentration of the aroylamino- (or heteroaroylamino) component, even predominant in the cases of **1d** and **1f**. However, acid hydrolysis of the resulting equilibration mixture in ethanolic solution gave the 3-amino-5-aryl- (or 5-heteroaryl)-1,2,4-oxadiazoles in high yields, too. This means that: i) the ring-rearrangement is an acid-catalysed process (that is, a protonated starting ring could favor O-N bond fission); ii) hydrolysis of the 3-acetylamino component is coupled with an equilibrium shift; iii) finally, the ring rearrangement reaction could take place on an oxadiazoline species arising from an acid-catalysed nucleophilic addition of ethanol to the N(4)-C(5) double bond of the oxadiazole nucleus. Clearly, this addition should take place in the 5-methyl-

oxadiazole component (**1**) easier than in the 5-aryloxadiazole counterpart (**2**).[24] At this moment, however, we have no evidences to corroborate one of these reaction pathways.

Table 1. Equilibration between 3-Acylaminooxadiazoles (**1**) and (**2**) or (**5**) and (**6**). Preparation of 3-Aminooxadiazoles (**4**) and (**7**).

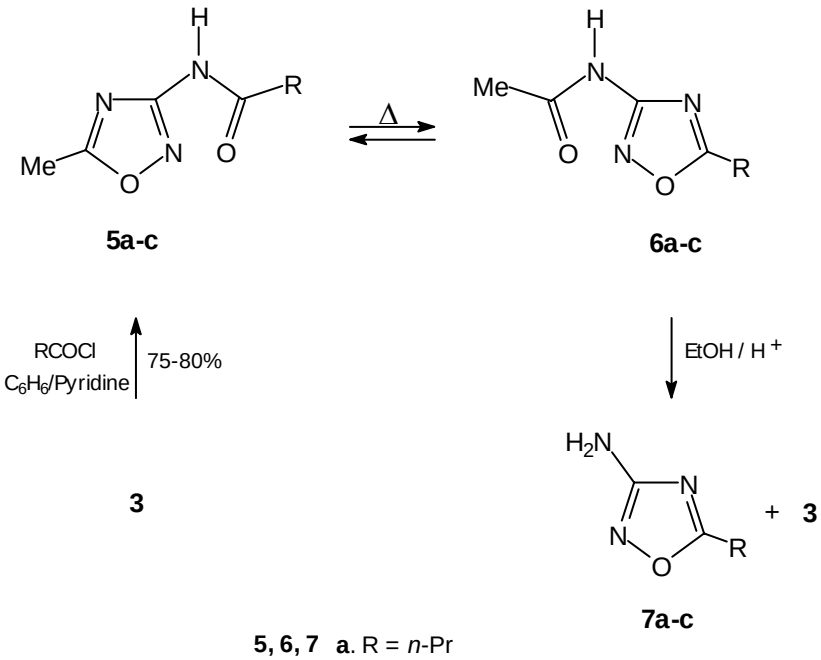
Starting Compound	Equilibrium composition[a] [**1**]/[**2**] or [**5**]/[**6**]	Compound (**4**) or (**7**) (%)[b]	
1a	9/91[c]	**4a**	90 (70)
1b	14/86[c]	**4b**	90
1c	17/83[c]	**4c**	75
1d	78/22[d]	**4d**	75
1e	58/42[d]	**4e**	90 (60)
1f	80/20[d]	**4f**	75 (60)
1g	42/58[d]	**4g**	75
1h	80/20[d]	**4h**	75 (60)
3		**4i**	(60)
3		**4j**	(60)
5a	40/60[e]	**7a**	(50)
5b	36/64[e]	**7b**	(50)
5c	40/60[e]	**7c**	(50)

[a] Composition (%) of the equilibrium mixture for the ring-degenerate rearrangements **1** ⇌ **2** or **5** ⇌ **6**.
[b] Yields of isolated product from acid hydrolysis of the equilibrium mixture. In parenthesis, yields in the direct (one-pot) procedure from **3** as starting material.
[c] Values from equilibration in methanol at 40 °C. Ref.[21]
[d] Values from equilibration in methanol at 40 °C. This work.
[e] Values from equilibration on melting compounds (**5**) at 120 °C.

On the basis of the above results and pursuing our studies on fluorinated heterocyclic compounds, we have then extended this methodology for the synthesis of 3-amino-5-polyfluorophenyoxadiazoles. In this respect, we note that the pentafluorophenyl derivative (**4h**) was recently[7] obtained (with modest yields, indeed) by a photochemical procedure (irradiation of 3-pentafluorobenzoylamino-4-methylfurazane in the presence of ammonia). When 3-pentafluorobenzoylamino-5-methyloxadiazole (**1h**) has been equilibrated in methanol, the composition of the mixture (20% of **2h** versus 80% of **1h**) reflected a balance between the electron withdrawing character of the pentafluorophenyl moiety, which will largely stabilize the carbamoyl function, and the rather meagre stabilization due to the diaryloid effect.[21] However, acid hydrolysis of this mixture, in spite of its actual composition, gave the expected 3-amino compound (**4h**) in 75% yields, thus corroborating the ring-degenerate equilibrium shift under hydrolytic conditions.

Acceptable results (60% of final yields) have been also obtained by adopting a direct (one-pot) procedure where the first step was the aroylation of the amino compound (**3**) with the pentafluorobenzoyl chloride. Furthermore, a similar procedure allowed us to obtain 3-amino-5-polyfluorophenyl-1,2,4-oxadiazoles (**4i,j**) in 60% yields. These results appear noteworthy in view of the fact that our attempts to obtain the pentafluorophenyloxadiazole (**4h**) by conventional routes were frustrating. In fact, the acylcyanamide method was unsuccessful, while the acylation/dehydration of hydroxyguanidine gave **4h** in a low yields.[7] Aiming to value restrictions of the above procedure, we then tested to synthesize 3-amino-5-alkyloxadiazoles. Thus, alkanoylation of **3** with some representative alkanoyl chlorides in benzene containing pyridine gave the 3-alkanoylaminooxadiazoles (**5a-c**). The ring-degenerate equilibration between **5a-c** and counterparts (**6a-c**) was analytically realized on melting compounds (**5**) at 120 °C. The equilibrium composition (by NMR spectral technique; see Table 1) showed a moderate predominance of the 5-alkyl component, thus indicating to some extent a stabilization effect of a 5-alkyl group in the respect of the 5-methyl substituent. Although we were unable to isolate the 3-acetylamino component (**6**) from the equilibration mixture, acid hydrolysis of these mixtures [also obtained in preparative scale by refluxing compounds (**5**) in ethanol] allowed us to isolate both the starting 3-amino compound (**3**) (40%) and the expected 3-amino-5-alkyloxadiazoles (**7a-c**) in 50% yields following a direct (one-pot) procedure.

Scheme 2



5, 6, 7 **a**. R = *n*-Pr
b: R = *t*-Bu
c: R = *n*-$C_{11}H_{23}$

Table 2. Physical and Analytical Data for 3-Acylaminooxadiazoles (**1**, **2**, **5, 6**).

Compound[a]	mp[b] (°C)	IR(nujol) ν (cm^{-1})	^{1}H NMR (DMSO-d_6/TMS), δ (ppm) *J* (Hz)	Molecular Formula (Solvent of Crystallization)	Anal. Calcd/(Found) C	H	N
1d	145	3230, 3180, 3100, 1680	2.62 (s, 3H), 7.79-8.29 (m, 4H), 11.86 (s, 1H)	$C_{10}H_8N_4O_4$ (benzene)	48.39 (48.20)	3.25 (3.20)	22.57 (22.60)
1e	138	3220, 3170, 3100, 1690	2.63 (s, 3H), 7.75-7.94 (m, 4H), 11.77 (s, 1H)	$C_{11}H_8N_3O_2F_3$ (benzene)	48.72 (48.60)	2.97 (2.90)	15.49 (15.40)
1f	129	3220, 3160, 3100, 1680	2.62 (s, 3H), 6.74.8.14 (m, 3H), 11.40 (s, 1H)	$C_8H_7N_3O_3$ (benzene)	49.75 (49.60)	3.65 (3.50)	21.75 (21.60)
1g	125	3220, 3160, 3080, 1660	2.63 (s, 3H), 7.18-8.21 (m, 3H), 11.57 (s 1H)	$C_8H_7N_3O_2S$ (benzene)	45.93 (45.80)	3.37 (3.50)	20.08 (20.20)
1h	164	3230, 3180, 3100, 1690	2.64 (s, 3H), 12.34 (s, 1H)	$C_{10}H_4N_3O_2F_5$ (benzene)	40.97 (40.80)	1.38 (1.50)	14.33 (14.10)
2d	163	3230, 3180, 3100, 1680	2.19 (s, 3H), 7.80- 8.29 (m, 4H), 11.38 (s, 1H)	$C_{10}H_8N_4O_4$ (Ethyl acetate)	48.39 (48.30)	3.25 (3.20)	22.57 (22.50)
2e	124	3200, 3180, 3100, 1690	2.18 (s, 3H), 7.60-8.13 (m, 3H), 11.39 (s, 1H)	$C_{11}H_8N_3O_2F_3$ (benzene)	48.72 (48.50)	2.97 (2.80)	15.49 (15.30)
2f	151[c]	3220, 3190, 3130, 1690	2.21 (s, 3H), 6.73-7.89 (m, 3H), 11.28 (s, 1H)				
2g	137	3220, 3190, 3100, 1690	2.17, (s, 3H), 7.18-8.20 (m, 3H), 11.28 (s, 1H)	$C_8H_7N_3O_2S$ (benzene)	45.93 (45.80)	3.37 (3.50)	20.08 (20.30)
2h	128	3220, 3160, 3100, 1680	2.20 (s, 3H), 11.55 (s, 1H)	$C_{10}H_4N_3O_2F_5$ (benzene)	40.97 (40.80	1.38 (1.20)	14.33 (14.20)
5a	72	3260, 3200, 3120, 1690	0,93 (t, 3H, *J* = 7), 1.63 (q, 2H, *J* = 7), 2.41 (t, 2H, *J* = 7), 2.59 (s, 3H), 11.01 (s, 1H)	$C_7H_{11}N_3O_2$ (benzene)	49.70 (49.80)	6.55 (6.60)	24.84 (24.70)
5b	81	3230, 3180, 3100, 1690	1.39 (s, 9H), 2.39 (s, 3H), 11.06 (s, 1H)	$C_8H_{13}N_3O_2$ (benzene)	52.45 (52.20)	7.15 (6.90)	22.94 (22.70)
5c	85	3240, 3180, 3100, 1690	0.91 (t, 3H, *J* = 7), 1.20-1.40 (m, 18H),2.41 (t, 2H, *J* = 7), 2.58 (s, 3H),10.95 (s, 1H)	$C_{15}H_{27}N_3O_2$ (benzene)	64.03 (64.10)	9.67 (9.60)	14.93 (14.80)
6a	82	3220, 3180, 3100, 1680	0.95 (t, 3H, *J* = 7), 1.75 (m, 2H), 2.12 (s, 3H), 2.88 (t, 2H, *J* = 7), 11.04 (s, 1H)	$C_7H_{11}N_3O_2$ (benzene)	49.70 (49.70)	6.55 (6.50)	24.84 (24.80)
6b	123	3240, 3180, 3100, 1690	1.41 (s, 9H), 2.11 (s, 3H), 11.11 (s, 1H)	$C_8H_{13}N_3O_2$ (benzene)	52.45 (52.30)	7.15 (7.20)	22.94 (22.90)
6c	90	3240, 3180, 3100, 1690	0.89 (t, 3H, *J* = 7), 1.20-1.40 (m, 18H), 2.12 (s, 3H), 2.86 (t, 2H, *J* = 7), 11.00 (s, 1H)	$C_{15}H_{27}N_3O_2$ (benzene)	64.03 (64.10)	9.67 (9.50)	14.93 (14.80)

[a] For compounds (**1a-c**) and (**2a-c**), see ref.[21]

[b] Melting points can be affected by the thermally induced rearrangement.

[c] Lit.,[25] mp 151°C.

Because of the expected structure-depending reactivity of 3-acylaminooxadiazoles towards the ring-degenerate interconversions,[2b,3c,21] it was not surprising that this approach was not applicable to the synthesis of 3-amino-5-perfluoroalkyl compounds. In fact, the representative 3-perfluorooctanoylamino

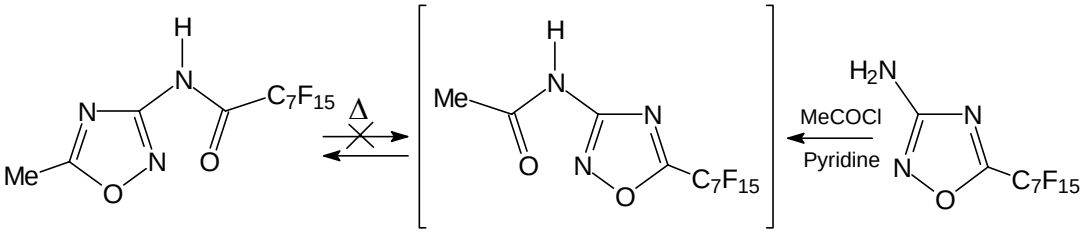
compound (**8**) remained unchanged both on melting at 120 °C and on refluxing in ethanol; obviously, this result reflects the low nucleophilicity of the carbamoyl oxygen in inducing the ring O-N bond fission.[27] On the other hand, acetylation of the 3-amino-5-perfluoroheptyloxadiazole (**10**) did not give the acetylamino compound (**9**) since the reaction directly gave the counterpart oxadiazole (**8**) as a result of the ring-rearrangement of the oxadiazole (**9**) soon after it is formed; in this case, both the nucleophilicity of the carbamoyl oxygen and the powerful electron withdrawing character of the perfluoroalkyl moiety would play a decisive role.

Table 3. Physical and Analytical Data for 3-Aminooxadiazoles (**4**) and (**7**).

Compound	mp (°C)	IR(nujol) ν (cm^{-1})	^{1}H NMR (DMSO-d_6/TMS), δ (ppm), *J* (Hz)	MS *m/z* (%)	Molecular Formula (Solvent of Crystallization)	Anal. Calcd/(Found) C	H	N
4a	170[a]							
4b	188	3320, 3190	6.60 (s, 2H), 8.00-8.25 (m, 4H)	229 (M^+) (72), 172 (100), 145 (37)	$C_9H_6N_3O F_3$ (Ethanol)	47.17 (47.20)	2.64 (2.60)	18.34 (18.10)
4c	149	3320, 3190	6.59 (s, 2H), 7.82-8.35 (m, 4H)	229 (M^+) (61), 172 (100), 145 (38)	$C_9H_6N_3OF_3$ (Ethanol)	47.17 (47.10)	2.64 (2.50)	18.34 (18.20)
4d	190	3380, 3320, 3240, 3180	6.65 (s, 2H), 7.94-8.20 (m, 4H)	206 (M^+) (2), 134 (100), 104 (88)	$C_8H_6N_4O_3$ (Ethanol)	46.61 (46.50)	2.93 (2.90)	27.18 (27.60)
4e	145	3360. 3170	6.59 (s, 2H), 7.91-8.07 (m, 4H)	229 (M^+) (42), 172 (40), 152 (100)	$C_9H_6N_3OF_3$ (Ethanol)	47.17 (47.10)	2.64 (2.60)	18.34 (18.30)
4f	163[b]	3320, 3180	6.51 (s, 2H), 6.84-8.12 (m, 3H)	151 (M^+) (100), 121 (6), 94 (79)				
4g	150[c]	3360, 3320, 3220, 3190	6.49 (s, 2H), 7.32-8.05 (m, 3H)	167 (M^+) (86), 137 (6),110 (100)	$C_6H_5N_3OS$ (Ethanol)	43.11 (43.20)	3.01 (2.90)	25.13 (25.00)
4h	175[d]							
4i	190	3360, 3330, 3240, 3200	6.67 (s, 2H), 8.05 (m, 2H),	233 (M^+) (99), 176 (83) 156 (24)99 (31), 58 (100)	$C_8H_3N_3OF_4$ (benzene)	41.22 (41.10)	1.30 (1.20)	18.02 (18.10)
4j	193	3340, 3240 3200	6.62 (s, 2H), 7.55-8.00 (m, 2H)	215 (M^+) (83), 158 (100), 138 (23), 81 (25), 58 (46)	$C_8H_4N_3O F_3$ (benzene)	44.66 (44.50)	1.87 (1.80)	19.53, (19.50)
7a	101[e]							
7b	74	3360, 3340, 3240, 3190	1.37 (s, 9H), 6.25 (s, 2H)	141 (M^+) (22), 126 (17), 111 (16)	$C_6H_{11}N_3O$ (benzene)	51.05 (51.00)	7.85 (7.80)	29.76 (29.80)
7c	65[f]	3340, 3300, 3220, 3180	0.91 (t, 3H, *J* = 7), 1.25-1.40 (m, 18H), 2.75 (t, 2H, *J* = 7)), 6.22 (s, 2H)	239 (M^+) (3), 223 (10),) 112 (100)	$C_{13}H_{25}N_3O$ (benzene)	65.23 (65.30)	10.53 (10.40)	17.55 (17.50)

[a] Lit.,[11a] mp 169-170 °C.
[b] Lit.,[25] mp 163 °C.
[c] Lit.,[26] mp 160-162 °C
[d] Lit.,[7] mp 174-175 °C.
[e] Lit.,[15] mp 101 °C.
[f] Lit.,[11b,e,13] does not report mp for **7c** prepared by the acylcyanamide method[11b,e] or by oxidative cyclization.[13]

Scheme 3



In conclusion, the use of the 3-amino-5-methyl-1,2,4-oxadiazole synthon as a *O,N*-protected *N*-hydroxyguanidine could represent a generalized and efficient methodology for the synthesis of 3-amino-5-substituted 1,2,4-oxadiazoles; moreover, this approach appears of some significance for those targeted 3-aminooxadiazoles (e.g., 5-polyfluoroaryl-substituted compounds) which would be hard to obtain by literature methods.

EXPERIMENTAL

General: Melting points were determined on a Reichart-Thermovar hot-stage apparatus and are uncorrected. IR spectra (Nujol) were determined with a Perkin Elmer 257 instrument; ^{1}H-NMR spectra were recorded on a Bruker AC 250 E spectrometer, and GC/MS determinations were carried out by using a VARIAN STAR 3400 CX/SATURN 2000 system. Flash chromatography was performed by using silica gel (Merck, 0.040-0.063 mesh) and mixtures of EtOAc and light petroleum (fraction boiling in the range 40-60°C) in varying ratios. Reagents and solvents were used as received from Aldrich.

Compound (**3**) has been prepared by a modification of the literature method.[16] Thus, a mixture of freshly purified cyanamide (9.5 g, 0.22 mol) and hydroxylamine hydrochloride (14.7 g, 0.22 mol) in dry ethanol (100 mL) was refluxed for 8 h. After removal of the solvent under reduced pressure, potassium acetate (30 g, 0.31 mol) and then acetic anhydride (50 mL, 0.53 mol) were added to the syrupy residue. The resulting mixture was gently refluxed (30 min) and then poured into ice-water (300 g). The solution was made strongly basic with solid sodium hydroxide (about 45 g) and then kept at 80 °C (boiling water-bath) for 45 min. After cooling, repeated extraction with ether (6 x 100 mL) and removal of the solvent gave 3-amino-5-methyl-1,2,4-oxadiazole (**3**) (8 g; 36%) which was crystallized from benzene (mp 119-121 °C; lit.,[16] mp 117-119 °C).

Analytical determinations of the equilibration mixtures were carried out by ^{1}H-NMR spectral technique, by integrating the methyl singlets in the δ ranges 2.39-2.65 [characteristic of the C-5 methyl of 3-aroylamino compounds (**1**) or 3-alkanoylamino compounds (**5**)] and 2.11-2.25 ppm [characteristic of the

methyl group of the acetylamino moiety in compounds (**2**) or (**6**)], respectively. Compositions at equilibrium are expressed in % of the two isomers (within 1-2%).

3-Aroylamino-5-methyl-1,2,4-oxadiazoles (1): The aroylamino compounds (**1a-c**) have been already described in our previous papers.[19,21,23] Similarly, aroylamino compounds (**1d-h**) have been prepared by reacting 3-amino-5-methyl-1,2,4-oxadiazole (**3**) with the appropriate aroyl chloride according to this previous procedure. Thus, in the cases of **1d-g**, the aroyl chloride (0.012 mol) was added to a solution of the amino compound (**3**) (1 g, 0.01 mol) in anhydrous benzene (150 mL) containing pyridine (0.95 g, 0.012 mol), and the mixture was allowed to stand at rt (with stirring) for about 10 days, following the course of the reaction by TLC analysis. In the case of **1h**, because of the high reactivity of the pentafluorobenzoyl chloride, the reagent was previously diluted in anhydrous benzene (50 mL) and then added to the amino substrate slowly under stirring. The mixture was then allowed to stand for 24 h. For all reactions, the solvent was removed under reduced pressure and the residue was worked up with water and filtered off. The crude material was then suitably purified by column chromatography or by crystallization, affording the aroylamino compounds (**1**) in 75-80% yields. If necessary, analytical sample (checked by NMR spectrometry) was recrystallized. Selected physical and spectral data for compounds (**1d-h**) prepared are reported in Table 2.

Analytical equilibration between the 3-aroylaminooxadiazoles (**1a-c**) and the corresponding 3-acetylamino derivatives (**2a-c**) has been already reported.[21] Similarly, samples of the aroylamino compounds (**1d-h**) (0.018 mmol) in CD_3OD (1 mL) were mantained in NMR tubes at 40 °C until constant mixture composition between the two isomers (Table 1). For preparative purposes, the equilibration can be realized by refluxing the aroylamino compounds in ethanol (see after). In the representative case of **1h**, the equilibration has been also attained by refluxing **2h** in ethanol. Analytical samples of compounds (**2d-h)** have been obtained by acetylation of the corresponding 3-aminooxadiazoles (**4**) with acetyl chloride in pyridine, working up by conventional procedures (Table 2).

Synthesis of 3-Amino-5-aryl-1,2,4-oxadiazoles (4): A sample of the 3-aroylamino compound (**1**) (2.5 mmol) in ethanol (100 mL) was refluxed for 10 h (to reach equilibration between **1** and **2**). Concentrated hydrochloric acid (1 mL) was then added and the mixture was refluxed for additional 8 h (12 h in the cases of **1f** and **1h**), monitoring the hydrolysis by TLC analyses. After neutralization with aqueous (20%) potassium hydroxide, the solvent was removed under reduced pressure and the residue chromatographed to give the 3-aminooxadiazoles (**4**) (see Table 3). To avoid base-induced nuclephilic substitution at the C(5)-polyfluorophenyl moiety, in the case of synthesis of **4h-j** the final hydrolysis mixture was not neutralized.

In a typical one-pot procedure, to a sample of **3** (0.5 g, 5 mmol) in dry benzene (100 mL) containing pyridine (0.45 mL, 5.5 mmol) benzoyl chloride (0.65 mL, 5.5 mmol) was added and the mixture was refluxed for 8 h. The solvent was removed under reduced pressure and then ethanol (100 mL) was added to the residue and boiling continued for an additional 10 h. The hydrolysis step then follows as above: after addition of concentrated hydrochloric acid (1 mL), the mixture was refluxed (8 h) and then neutralized with aqueous (20%) potassium hydroxide; after removal of the solvent, chromatography (eluant: light petroleum/ EtOAc 5:1) of the residue gave 3-amino-5-phenyl-1,2,4-oxadiazole (**4a**) (0.57 g, 70%).

A similar procedure was also representatively tested for the preparation of compounds (**4e**, **4f**) and the pentafluorophenyl derivative (**4h**), and then applied successfully for the preparation of 5-polyfluorophenyl substituted oxadiazoles (**4i,j**) (see Table 1).

3-Alkanoylamino-5-methyl-1,2,4-oxadiazoles (5): To a sample of **3** (0.5 g, 5 mmol) in dry benzene (100 mL) containing pyridine (0.45 mL, 5.5 mmol) the alkanoyl chloride (5.5 mmol) was added and the mixture was refluxed for 8 h. After removal of the solvent under reduced pressure, the residue was worked up with water. In the case of **5c** the product separated was filtered off and crystallized. In the cases of **5a,b** the mixture was neutralized with solid sodium hydrogen carbonate and extracted with EtOAc (3 x 50 mL) which was washed with water and dried (Na_2SO_4). The organic solvent was removed and the residue crystallized. (see Table 2).

The equilibration between 3-alkanoylaminooxadiazoles (**5**) and the corresponding 3-acetylamino derivatives (**6**) was reached by melting compounds (**5**) in an oil-bath at 120 °C for 90 min and cheked by ^{1}H-NMR spectral technique (Table 1). Analytical samples of **6** have been obtained by acetylation of the 3-amino compounds (**7**) (2.5 mmol) with acetyl chloride (0.2 mL, 2.7 mmol) in dry benzene (50 mL) containing pyridine (0.2 mL, 2.7 mmol) under reflux (4 h), by using conventional procedures (Table 2).

Preparative scale equilibration between compounds (**5**) and (**6**) has been achieved by refluxing compounds (**5**) (5 mmol) in ethanol (100 mL) for 12 h. An analytical sample of the resulting equilibration mixture (after removing of the solvent and ^{1}H-NMR spectral analysis of the residue) confirmed the above composition.

Synthesis of 3-Amino-5-alkyl-1,2,4-oxadiazoles (7): To a sample of **3** (0.5 g, 5 mmol) in anhydrous benzene (100 mL) containing pyridine (0.45 mL, 5.5 mmol) suitable alkanoyl chloride (5.5 mmol) was added and the mixture was refluxed for 8 h. The solvent was removed under reduced pressure and then ethanol (100 mL) was added to the residue allowing to reflux for additional 12 h. The hydrolysis step then follows as above: after addition of concentrated hydrochloric acid (1 mL), the mixture was refluxed (4 h) and then neutralized with aqueous (20%) potassium hydroxide; after removing of the solvent,

chromatography (eluant: light petroleum/ EtOAc 1:1) of the residue gave at first the 3-amino-5-alkyl-1,2,4-oxadiazole (**7a-c**) (50%) (see Tables 1 and 3) and then starting amino compound (**3**) (0.2 g, 40%).

3-Perfluorooctanoylamino-5-methyl-1,2,4-oxadiazole (8): To a sample of **3** (0.5 g, 5 mmol) in dry benzene (100 mL) containing pyridine (0.5 mL, 6 mmol) the perfluorooctanoyl chloride (1.5 mL, 6 mmol) diluted in dry benzene (30 mL) was added slowly under stirring, and then the mixture was left at rt for 48 h. After removal of the solvent under reduced presure, the residue was worked-up with water and filtered giving compound (**8**) (2.1 g, 86%), mp 98-100 °C (from benzene). Compound (**8**) had IR cm^{-1} 3250, 3200, 3100, ^{1}H NMR (DMSO-d_6) δ 2.63 (s, 3H), 13.00 (s, 1H). Anal. Calcd for $C_{11}H_4N_3O_2F_{15}$. C, 26.68; H, 0.81; N, 8.49. Found: C, 26.50; H, 0.90; N, 8.30.

Compound (**8**) remained unchanged after: i) refluxing (4 h) in ethanol; ii) melting at 120 °C (2 h). Attempts to intercept compound (**9**) (by ^{1}H-NMR spectral analysis) failed. Treating compound (**10**)[6] (0.15 g) with a slight excess of acetyl chloride (0.2 mL) in pyridine (5 mL) at rt (24 h), removal of the solvent under reduced pressure and chromatography directly gave **8** (60%). Similarly, after refluxing compound (**10**) with a slight excess of acetyl chloride in benzene containing pyridine (16 h), removal of the solvent and chromatography gave **8** (70%).

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