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A CONVENIENT SYNTHESIS OF 5-AMINO-SUBSTITUTED 1,2,4-OXADIAZOLE DERIVATIVES *VIA* REACTIONS OF AMIDOXIMES WITH CARBODIIMIDES†

Maria Ispikoudi,[a] Konstantinos E. Litinas,[b] and Konstantina C. Fylaktakidou[a,*]

[a]Molecular Biology and Genetics Department, Democritus University of Thrace, 68100 Alexandroupolis, Greece; E-mail: kfylakta@mbg.duth.gr

[b]Laboratory of Organic Chemistry, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece

Abstract - 5-Amino substituted 1,2,4-oxadiazole derivatives were easily prepared, in one step and in high yields, via reactions of a variety of aryl, benzyl, cycloalkyl and alkyl amidoximes with commercially available carbodiimides. Alkyl carbodiimides reacted with amidoximes in toluene to give 5-alkylamino-1,2,4-oxadiazoles, whereas aromatic carbodiimide reacted in DMF to give initially the intermediate *O*-amidoxime adducts, which were further cyclized to the corresponding 5-arylamino-1,2,4-oxadiazoles.

1,2,4-Oxadiazoles[1-3] and specifically their *N*-substituted (on the 3-, or 5-, or 3,5-positions) derivatives is a class of heterocyclic compounds evaluated in numerous therapeutic areas. They were found to be potent antiviral agents,[4] muscarinic receptor antagonists,[5,6] histamine H2 receptor antagonists,[7,8] hypocholesterolemic agents[9] and anti-inflammatories.[10,11] The variety of their biological activities was ascribed to the bioisosteric replacement[12,13] of an ester or amide functionality and the electronic effects of the main heterocyclic ring. The latter was interpreted in terms of the hydrogen bonding capacity of the pharmacophore. A number of structure-activity relationship studies revealed that the attachment of an additional amine functional group to the heterocyclic core increased the efficacy of the compound, by increasing the hydrogen bonding capacity of the pharmacophore.[5,6] Furthermore, changes in hydrophilicity by introduction of side chains on the nitrogen atom also affected the biological activity.[4-6,10,11]

† Dedicated to Prof. Emeritus Demetrios N. Nicolaides on the occasion of his 70th birthday

For the synthesis of *N*-substituted 1,2,4-oxadiazole derivatives Eloy and Lenaers[14-16] have reported a two step procedure: initially, formation of the 5-trichloromethyl- or 5-chloro-1,2,4-oxadiazole derivatives from a proper amidoxime and then, nucleophilic substitution of the trichloromethyl or chloro substituent by the desired amine. The same team discovered[14,15] the formation of primary or secondary amine derivatives upon the reaction of hydroximoyl chlorides with guanidine derivatives. These are widely used methodologies for the synthesis of the above mentioned heterocycles in the area of medicinal chemistry, though, in most of the cases, the first step is usually low to moderate yielded.

A straightforward formation of 5-amino-substituted 1,2,4-oxadiazoles from amidoximes, relies on condensation with cyanoguanidine,[17] *N,N*-dialkylcyanamides,[18] diphenyl cyanocarbonimidate,[11] phosphorous ylides,[19] and *N,N′*-dicyclohexylcarbodiimide (DCC),[20] methodologies which suffer generality or provide the products in low yields. Interestingly, to the best of our knowledge, the procedure involving the DCC was demonstrated only with the reaction with benzamidoxime, under dry conditions and the yield did not exceeded 54%, even when a biequimolar quantity of the carbodiimide was employed.[20]

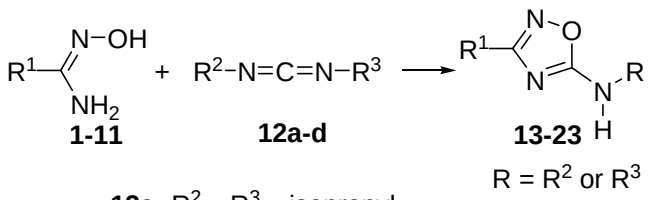
Our interest in the chemistry and biology of amidoximes[19,21-24] has prompted us to investigate thoroughly this reaction, taking into account that a relatively large number of carbodiimides, as well as amidoximes (or their precursors, nitriles) are nowadays commercially available. We envisaged that the construction in a single step of the 1,2,4-oxadiazole heterocyclic ring bearing an *N*-substituent at position 5 and a variety of alkyl or aryl substituents at position 3, could be a useful synthetic tool in the area of medicinal chemistry.

To our delight, when aryl-, benzyl-, cycloalkyl- and alkyl- amidoximes **1-11**[25] reacted, in each case, with diisopropylcarbodiimide (DIC, **12a**), DCC (**12b**) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC, **12c**), in refluxing toluene and under air (instead of dry $CHCl_3$[20]), the heterocycles **13-23** were smoothly obtained,[26,27] as exemplified in Table 1. For solubility reasons the reaction of bis(4-nitro-phenyl)-carbodiimide (NPC, **12d**) was performed in DMF at 120 ^oC.[28] Under these simple and direct conditions, the previously reported[20] 5-cyclohexylamino-3-phenyl-1,2,4-oxadiazole derivative **13b** was formed in an optimized yield (81%), whereas in general, all combinations of amidoximes and carbodiimides examined showed a rather fast conversion of the reactants, leading to the desired products in very good yields (>65%).

An exception was observed regarding the reaction of amidoxime **1** with **12d** (Entry 24). In this case **13d**

was obtained in a low yield although some starting amidoxime remained unreacted. This event is probably a result of the sensitivity of aromatic carbodiimides, which are vulnerable to polymerization when an electron withdrawing group is attached on them.[29]

Table. Reactions of amidoximes with carbodiimides



1-11 **12a-d** **13-23**

R = R^2 or R^3

12a: R^2 = R^3 = isopropyl
12b: R^2 = R^3 = cyclohexyl
12c: R^2 = ethyl, R^3 = 3-(dimethylamino)propyl
12d: R^2 = R^3 = *p*-nitrophenyl

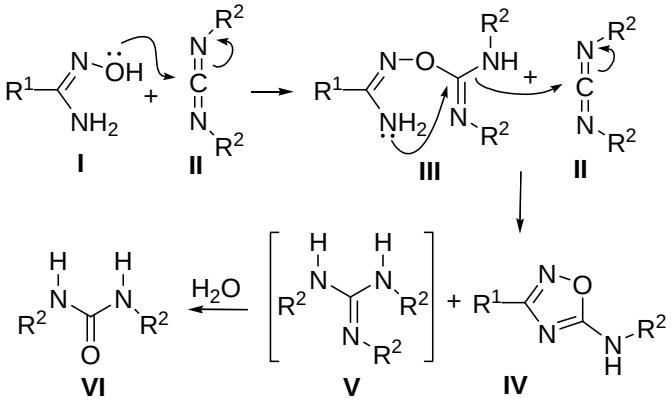
1: R^1 = phenyl
2: R^1 = *p*-methoxyphenyl
3: R^1 = *p*-methylphenyl
4: R^1 = *p*-nitrophenyl
5: R^1 = *m*-nitrophenyl
6: R^1 = *o*-nitrophenyl
7: R^1 = benzyl
8: R^1 = *p*-chlorobenzyl
9: R^1 = *p*-nitrobenzyl
10: R^1 = cyclohexyl
11: R^1 = propyl

Entry	Amidoxime	Carbodiimide	Product	Reaction Time (h)	Yield %[a]
1	**1**	**DIC (12a)**	**13a**	6	81
2	**2**	"	**14a**	6	74
3	**3**	"	**15a**	6	78
4	**4**	"	**16a**	6	80
5	**5**	"	**17a**	7	72
6	**6**	"	**18a**	8	67
7	**7**	"	**19a**	7	75
8	**8**	"	**20a**	7	72
9	**9**	"	**21a**	7	68
10	**10**	"	**22a**	10	65
11	**11**	"	**23a**	10	65
12	**1**	**DCC (12b)**	**13b**	7	81
13	**2**	"	**14b**	7	89
14	**3**	"	**15b**	7	85
15	**4**	"	**16b**	7	97
16	**5**	"	**17b**	9	84
17	**7**	"	**19b**	8	65
18	**8**	"	**20b**	8	68
19	**9**	"	**21b**	8	72
20	**10**	"	**22b**	8	65
21	**1**	**EDC (12c)**	**13c** ($R = R^2$)	4	60
			13c´ ($R = R^3$)		31
22	**2**	"	**14c** ($R = R^2$)	4	55
			14c´ ($R = R^3$)		25
23	**3**	"	**15c** ($R = R^2$)	4	61
			15c´ ($R = R^3$)		27
24	**1**	**NPC (12d)**	**13d**	24	14 (35)[b]

[a] Yields obtained after column chromatography purification.

[b] Yield in parenthesis is based on the reacted starting material.

We have observed that all reactions required two equivalents of carbodiimide in order to achieve the complete consumption of starting amidoxime. This fact is easily explained by accepting the mechanistic pathway proposed earlier.[20] A nucleophilic attack, Scheme 1, of the hydroxyl group of amidoxime (**I**) to the electrophilic centre of carbodiimide (**II**) occurs initially, leading to the *O*-amidoxime adducts (**III**), which subsequently undergo an intramolecular attack by the amino group attached to the parent amidoxime. A second molecule of carbodiimide facilitates the latter transformation by abstracting the remaining alkyl- or aryl-amino moiety of carbodiimide. Thus, the 1,2,4-oxadiazole derivative (**IV**) is produced along with a guanidine type intermediate (**V**), which under air is hydrolyzed and delivers the corresponding urea derivative (**VI**).



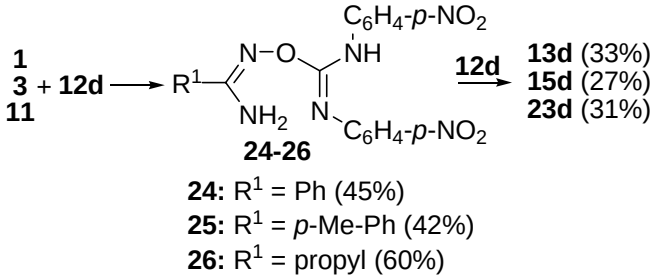
Scheme 1. Mechanistic pathway for the formation of 5-amino substituted 1,2,4-oxadiazole derivatives.

A two step procedure, was adopted in order to verify the mechanism of the reaction. We first examined the reaction of benzamidoxime **1** with an equimolar amount of DCC (**12b**) in toluene at room temperature. The reaction mixture was stirred for a longer period (24 h), to give only product **13b** in 42% yield, whereas almost half of **1** remained unreacted. However, when DMF was used as the solvent under the same reaction conditions, the isolated products were **13b** and the intermediate *O*-adduct (**III**, R^2 = cyclohexyl, Scheme 1) in 20% and 45% yields, respectively. The isolation of the intermediate *O*-adducts in DMF is probably due to the stabilization of the polar intermediates by the more polar solvent.

Similarly, when NPC (**12d**) reacted with amidoximes (**1**, **3** and **11**) in DMF at rt, all *O*-amidoxime adducts **24**-**26**[30] were isolated in 42-60% yields (Scheme 2). These derivatives having an extensive conjugation and, thus, a less nucleophilic secondary amino group were rather reluctant to react further at room temperature with another molecule of carbodiimide and deliver the corresponding 1,2,4-oxadiazole ring. Nevertheless, upon heating at 120 ^{o}C in the presence of **12d**, all three oxadiazoles **13d**, **15d** and **23d** were obtained in 27-33% yield.

Another point of interest was the observed preference for the formation of one of the *N*-substituted

oxadiazole derivatives when a non symmetrical carbodiimide was used (e.g. EDC, Entries 21-23). These reactions afforded in all cases the two possible products in a ratio of *ca* 2:1, favoring the ethyl one. A result like this could be explained accepting a stabilization of one of the two equilibrated tautomers of type **III** (Scheme 1) through an intramolecular hydrogen bond, (Figure 1), an event which again supports the proposed mechanistic pathway.



Scheme 2. Formation of the intermediate *O*-amidoxime adducts **24-26** and the 1,2,4-oxadiazoles **13d**, **15d** and **23d**.

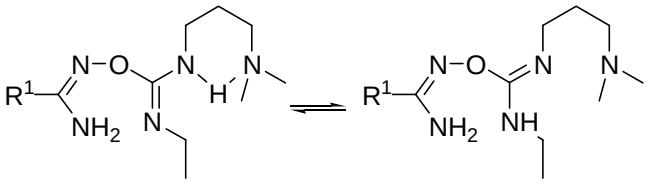


Figure 1. Structures of the intermediate *O*-amidoxime adducts related to EDC.

As a conclusion, we provide a facile and convenient methodology for the preparation in one step and in very good yields of 3-substituted-5-alkyl-, cycloalkyl- or aryl- amino-1,2,4-oxadiazoles. Clarification of the proposed mechanism was achieved with the isolation of some initially formed aducts. Furthermore, the obtained compounds bearing a secondary amino group maybe be used as key synthons to reach the corresponding *N,N*-bis-substituted derivatives, as it had been earlier demonstrated by us.[19]

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25. All amidoximes were prepared according to procedures described in: F. Eloy and R. Lenaers, *Chem. Rev.,* 1962, **62**, 153.
26. General procedure for the reactions of amidoximes with carbodiimides **12a,b**: Amidoxime was

dissolved in toluene (0.15 M) and 2.1 equivalents of DIC or DCC were added in one portion. The mixture was refluxed for 6-10 h, cooled to rt, concentrated and the residue was subjected to column chromatography with hexanes/EtOAc. **16a**: pale yellow crystals, mp 183.5-184 °C (hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (d, J = 6.7 Hz, 6H), 4.05 (m, 1H), 5.12 (bd, J = 7.9 Hz, 1H, NH), 8.18 (d, J = 8.5 Hz, 2H), 8.31 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 46.6, 123.8, 128.1, 151.2, 153.8, 159.6, 160.8; IR (neat): 3316, 2978, 2939, 1632, 1610; HRMS: calcd for $C_{11}H_{12}N_4NaO_3$ *m/z*: $(M+Na)^+$ 271.0802, found 271.0803. **15b**: white crystals, mp 146-147 °C ($CHCl_3$/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20-1.49 (m, 5H), 1.60-1.68 (m, 1H), 1.75-1.80 (m, 2H), 2.10 (bd, J = 11.8 Hz, 2H), 2.39 (s, 3H), 3.63-3.74 (m, 1H), 5.12 (bd, J = 8.2 Hz, 1H, NH), 7.25 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 24.6, 25.3, 33.2, 52.8, 124.8, 127.1, 129.3, 140.9, 163.7, 170.4; IR (neat): 3285, 3235, 2938, 2913, 2853, 1641, 1613; HRMS: calcd for $C_{15}H_{19}N_3NaO$ *m/z*: $(M+Na)^+$ 280.1420, found 280.1402.

27. General procedure for the reactions of amidoximes with carbodiimide **12c**: EDC·HCl and an equimolar amount of Na_2CO_3 were added in water and an equal volume of toluene was added. This biphasial system was stirred vigorously for 5 min, then the two phases were separated, the aqueous phase was washed with toluene, the combined organic phases were dried with Na_2SO_4 and the filtrate was added to a flask containing the amidoxime (concentration approximately 0.15 M). The mixture was heated at reflux for 4 h, concentrated and the residue was subjected to column chromatography with hexanes/EtOAc for the elution of the ethyl derivative. The 3-dimethylaminopropyl product was eluted with CH_2Cl_2/MeOH/Et_3N (90/5/5). **13c**: white crystals, mp 74-75 °C (heptanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 3.48 (dq, J = 7.2, 5.6 Hz, 2H), 6.95 (bs, 1H, NH), 7.43-7.50 (m, 3H), 8.01 (dd, J = 7.9, 1.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 38.2, 127.0, 127.5, 128.5, 130.6, 168.1, 171.2; IR (neat): 3198, 3073, 2980, 2934, 1654, 1629; HRMS: calcd for $C_{10}H_{11}N_3NaO$ *m/z*: $(M+Na)^+$ 212.0794, found 212.0810. **13c′**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (quintet, J = 6.3 Hz, 2H), 2.24 (s, 6H), 2.46 (t, J = 6.3 Hz, 2H), 3.52 (t, J = 6.3 Hz, 2H), 7.35-7.48 (m, 3H), 7.63 (bs, 1H, NH), 7.95 (dd, J = 7.8, 2.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 43.6, 45.0, 58.2, 127.0, 127.7, 128.5, 130.5, 168.3, 171.2; IR (neat): 3229, 2946, 2819, 1635; HRMS: calcd for $C_{13}H_{19}N_4O$ *m/z*: $(M+H)^+$: 247.1553, found 247.1565.

28. Amidoxime **1** was dissolved in DMF (0.15 M) and 2.1 equivalents of NPC **12d** were added in one portion. The mixture was stirred at 120 °C for 24 h, concentrated and the residue subjected to column chromatography with hexanes/EtOAc. **13d**: yellow crystals, mp 226-227 °C (hexanes/EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54-7.60 (m, 3H), 7.80 (d, J = 8.7 Hz, 2H), 8.03 (d, J = 6.4 Hz, 2H), 8.31 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 118.1, 125.9, 127.1, 127.4, 129.6, 131.9, 142.5, 144.5, 167.9, 168.0; IR (neat): 3359, 3117, 1629, 1583; HRMS: calcd for $C_{14}H_9N_4O_3$ *m/z*: (M-

H)$^+$ 281.0669, found 281.0681.

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30. General procedure for the synthesis of the intermediate *O*-substituted amidoxime derivatives: Amidoxime was dissolved in DMF (0.15 M) and 2.1 equivalents of NPC **12d** were added in one portion. The mixture was stirred at rt for 24 h, concentrated and the residue was subjected to column chromatography with hexanes/EtOAc. **26**: yellow crystals, mp 189-190 ^{o}C (hexanes/EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.82 (t, J = 7.4 Hz, 3H), 1.46 (sixtet, J = 7.6 Hz, 2H), 1.97 (t, J = 7.6 Hz, 2H), 7.19 (d, J = 8.9 Hz, 2H), 7.99 (d, J = 9.2 Hz, 2H), 8.11 (d, J = 8.9 Hz, 2H), 8.21 (d, J = 9.2 Hz, 2H), 9.69 (bs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.3, 19.6, 31.9, 118.9, 123.4, 124.3, 124.6, 141.5, 145.4, 148.1, 154.2, 158.4; IR (neat): 3497, 3380, 3319, 2966, 1654, 1609, 1595; HRMS: calcd for $C_{17}H_{18}LiN_6O_5$ *m/z*: (M+Li)$^+$ 393.1493, found 393.1492.