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Chemical oxidation of an anticonvulsant *N*-(5′-methylisoxazol-3-yl)-2,6-dimethylbenzamide (D2916)

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Abstract

The new anticonvulsant *N*-(5′-methylisoxazol-3-yl)-2,6-dimethylbenzamide (D2916), which presents two kinds of methyl groups which could be oxidized, was submitted to various chemical oxidizing agents. Several sites and degrees of oxidation were observed. The main oxidized site was the arylmethyl group without cleavage of the isoxazole ring, leading via carboxylic acid and primary alcohol intermediates to phthalimide and lactame derivatives. In no case was the methyl group of the isoxazole moiety hydroxylated.

Keywords: Oxidation; Benzamide; Isoxazole; Regioselectivity

1. Introduction

N-(5-methylisoxazol-3-yl)-2,6-dimethylbenzamide (D2916) **1** has been shown to possess an anticonvulsant activity in rodents [1,2]. Its protection effect, specifically in the MES (maximal electroshock seizure), lasted longer in females than in males, this sex difference being due to the time course of an active hydroxylated metabolite, resulting from the biological oxidation of the methyl group of the isoxazole moiety [3–6]. This methyl group is not the only one of D2916 which also presents two methyl groups on the phenyl nucleus.

The regioselectivity in the biological oxidation pathway prompted us to study the reactivity of D2916, **1**, towards various oxidizing agents in order to compare the reactivity of the various sorts of methyl groups.

Several chemical oxidants and conditions were tested here with the benzamide **1** as substrate: chromium (VI) reagents, persulfate and permanganate ions.

In this work we describe several oxidation pathways observed under various conditions:

- oxidation of the arylmethyl group to a carboxylic function;
- oxidation of the arylmethyl group to an alcoholic function;
- oxidative cleavage of the isoxazole ring;

followed in all cases by molecular rearrangements.

In order to support the interpretation of the regioselectivity, the oxidation of various isoxazole models is also reported.

2. Results

2.1. Oxidation of methyl groups on various isoxazole models

Very few examples of oxidation of methyl groups into carboxylic groups were described in the substituted isoxazoles [7].

The first attempt to oxidize 5-methylisoxazole **4** by chromic acid gave the corresponding 5-isoxazole carboxylic acid **5** with moderate yield (52%).

In the case of 3,5-dimethylisoxazole **6**, it was the methyl group in position 3 which was preferentially converted into a carboxylic group, **7**.

Another regioselectivity had been observed by other authors in the case of 3,4,5-trimethylisoxazole **8**, which led to a carboxylic acid in position 4, **9** [8] (Table 1).

These results show that the methyl group in position 5 is only oxidized when there is no other methyl group on the ring.

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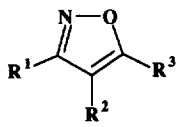
Table 1
Oxidation of methyl groups on the isoxazole ring



Methylisoxazoles	Oxidation products
4: $R^1=H, R^2=H, R^3=CH_3$	**5**: $R^1=H, R^2=H, R^3=COOH$
6: $R^1=CH_3, R^2=H, R^3=CH_3$	**7**: $R^1=COOH, R^2=H, R^3=CH_3$
8: $R^1=CH_3, R^2=CH_3, R^3=CH_3$	**9**: $R^1=CH_3, R^2=COOH, R_3=CH_3$

2.2. Oxidation of the arylmethyl group into a carboxylic acid

Hexavalent chromium oxidized selectively one methyl group of the benzamide **1**, the aryl moiety leading to an acidic intermediate **10**, which could not be isolated because this oxidation was immediately followed by an intramolecular amidification, which led to *N*-substituted-*o*-methylphthalimide **11** (Scheme 2) in good yields, 45% with Fieser's reagent (CrO_3/CH_3COOH) and 77% with Thiele's reagent ($CrO_3/Ac_2O/H_2SO_4$). When water or sulfuric acid together with acetic anhydride were added to the medium, the yield fell to 24%.

By-products such as *o*-methylphthalimide **12** (5%) or *o*-methylphthalic anhydride **13** (1.5%) were obtained when chromic anhydride was used alone in acetic acid, and identified by comparison with samples synthesized by other methods (Scheme 1).

The hypothesis that *N*-(5′-methylisoxazol-3-yl)-3-methylphthalimide **11** was the precursor of the corresponding non-substituted 3-methyl derivative **12** was confirmed by conversion of the more easily available *N*-(5′-methylisoxazol-3-yl)phthalimide **14** to phthalimide **15** under the Fieser condition (Scheme 2).

2.3. Oxidation of the arylmethyl group to a primary alcohol

Persulfate oxidation of the benzamide **1** in the presence of copper(II) acetate and sodium acetate mainly gave the *N*-isoxazolylisoindolone **17**.

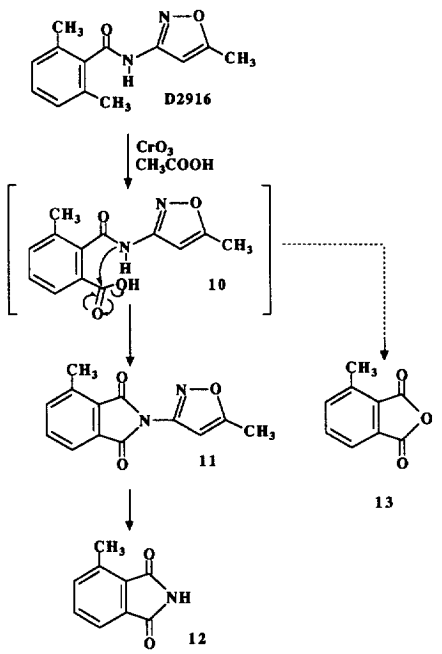
Two by-products were also identified, a lactame **18** and the lactone **3** (Scheme 3) together with traces of a dimethylbenzamide **19**.

The formation of **17** can be explained via the oxidation of the arylmethyl group of **1** into an alcoholic function, leading to the non-isolated intermediate **16** which in turn underwent an intramolecular substitution.

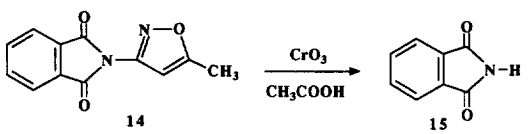
This *N*-isoxazolylisoindolinone **17** was also obtained with low yields when **1** was treated both with chromyl chloride in carbon tetrachloride or ammonium cerium(IV) nitrate in acetic acid.

The role of the substituted lactame **17** as a potential precursor of the lactame **18** was confirmed by direct treatment of pure **17** under the same oxidative conditions.

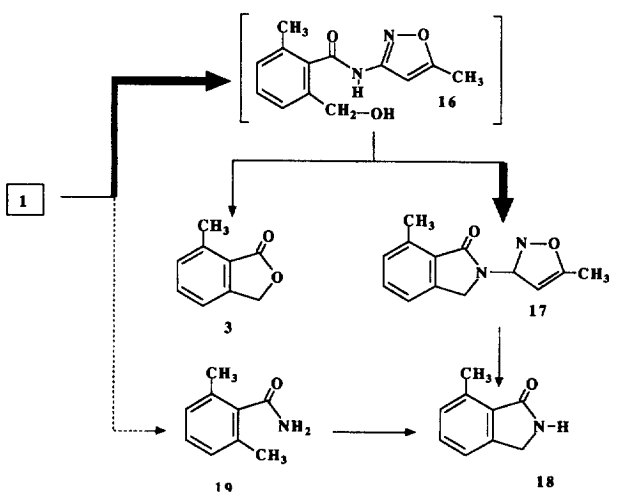
The formation of the other by-product, lactone **3**, resulted from another evolution of the primary alcohol **16**, via a nucleophilic attack of the carbonyl group of the amide function by elimination of the isoxazolyl moiety.



Scheme 1. Chromic oxidation of the D2916 arylmethyl group and formation of a phthalimide structure.



Scheme 2. Oxidation of *N*-substituted **14** in phthalimide **15**.



Scheme 3. Persulfate oxidation of the arylmethyl group into a primary alcohol.

The isolation of traces of the dimethylbenzamide **19** prompted us to verify if it could also be a precursor of the lactame **18**, under the same persulfate oxidation conditions (Scheme 3).

Small amounts of the same lactone **3** were also obtained as a by-product in the case of nitric acid oxidation of D2916 **1**, leading mainly to a nitro compound **20** resulting from an electrophilic substitution of the phenyl ring (Scheme 4).

2.4. Oxidative cleavage of the isoxazole ring

The hypothesis that permanganate oxidation could lead to isoxazole ring opening was based upon previous observations.

Under alkaline conditions, it has been shown that an isoxazole benzamide could undergo a rearrangement into an oxadiazole derivative [9].

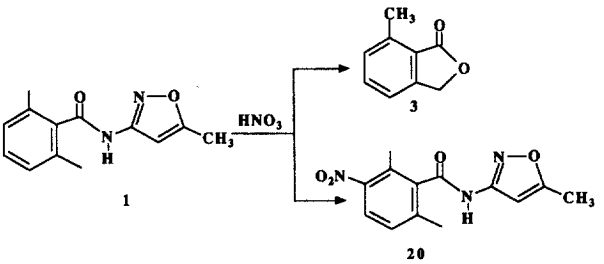
Sodium carbonate in aqueous solution is the medium used for permanganate oxidation and we checked that, even under these weak alkaline conditions, the same type of rearrangement of the benzamide **1** to the oxadiazole **22** occurred (Scheme 5).

Permanganate oxidation under the same alkaline conditions of the oxadiazole **22** did not give the expected compounds **21** or **19**, but only the 3-methylphthalic anhydride **13** already observed in chromic conditions and resulting from the oxidation of an arylmethyl group (Scheme 5).

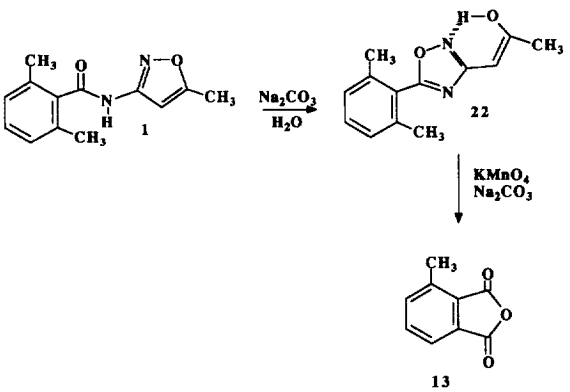
Permanganate oxidation of the benzamide **1** in alkaline conditions led effectively to the destruction of the isoxazole ring with no oxidation of the arylmethyl groups but it did not generate either the oxadiazole **22** or the anhydride **13**.

The 2,6-dimethylbenzoylurea **21** was obtained in 26% yield, similar to an authentic sample prepared from 2,6-dimethylbenzoyl chloride and urea. The 2,6-dimethylbenzamide **19** was obtained as a by-product and proved to be identical to the derivative hydrolysed in basic conditions obtained from **21** (Scheme 6).

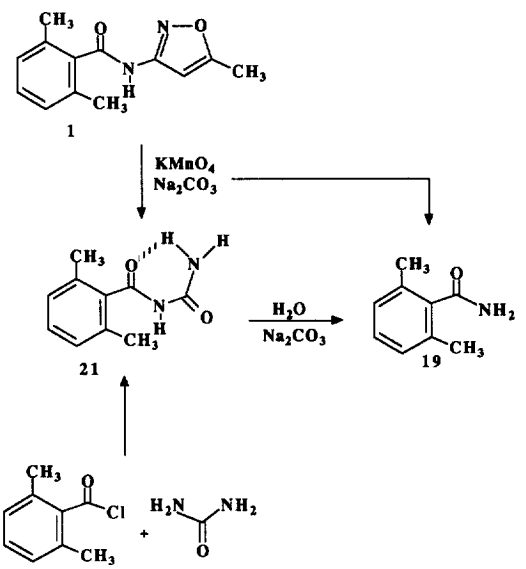
The substituted urea **21** was then formed by direct oxidation of **1** and not via an alkaline degradation of **1**, and the dimethylbenzamide **19** can be considered as the ultimate oxidation product under these conditions.



Scheme 4. Nitric acid oxidation of D2916.



Scheme 5. Passage of benzamide **1** to 3-methylphthalic anhydride **13**.



Scheme 6. Isoxazole ring opening in the course of permanganate oxidation.

3. Conclusions

In conclusion, regioselectivity of oxidation was observed; the main site of oxidation was a methyl group on the phenyl nucleus, leading either to a carboxylic acid or to a primary alcohol.

These intermediates were too reactive to be isolated and yielded phthalimide or lactame derivatives, respectively.

None of the chemical oxidizing agents used in this study led to a selective oxidation of the methyl group of the isoxazole moiety of the benzamide **1**. Oxidative cleavage of the isoxazole ring was also observed under alkaline permanganate conditions.

4. Experimental

Melting points: Kofler apparatus (uncorrected). Elemental analyses: within $\pm 0.4\%$ of calculated values. ^{1}H NMR spectra: Jeol PMX 60Si (60 MHz) or Hitachi R1200 (60 MHz) spectrometers, chemical shifts are reported as δ (ppm) relative to tetramethylsilane (TMS). Mass spectra: GC-MS system; a Hewlett Packard 5970 MSD spectrometer was operated in electron impact mode and directly interfaced with a Hewlett Packard 5890 GC gas chromatograph. Silica (Kieselgel, 0.015–0.040 mm, Merck) was used for flash column

chromatography (column length 30 cm; column diameter 3 cm).

4.1. Oxidation of methyl groups of various isoxazole models

4.1.1. Chromic oxidation of 5-methylisoxazole 4

Potassium dichromate (60 g, 20 mmol) was added portionwise over a 30 min period to a cooled (0°C) solution of 5-methylisoxazole **4** (15 g, 18 mmol) in concentrated sulfuric acid (220 ml). The dark-brown mixture was stirred at 0°C for 2 h and then carefully poured into ice water (500 ml) to precipitate a crude material which was dissolved in ethyl acetate (300 ml). The organic layer was then washed with cold brine, dried over magnesium sulfate and concentrated under vacuum.

5: 5-isoxazolecarboxylic acid. Yield 2.8 g (50%); m.p. 138–140°C with decomposition. ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 7.0 (s, 1H, =CH isoxazole), 8.4 (d, 1H, =CH isoxazole), 9.8 (s, 1H, COOH).

4.1.2. Chromic oxidation of 3,5-dimethylisoxazole 6

The 5-methyl-3-isoxazoloic acid **7** was prepared by chromic oxidation according to the procedure described below for synthesis of **11**.

7: 5-methyl-3-isoxazoloic acid. Yield 0.22 g (17%); m.p. 182°C. ^{1}H NMR (DMSO-d_6): δ 2.3 (s, 3H, CH_3), 6.9 (s, 1H, =CH isoxazole), 8.4 (s, 1H, COOH).

4.2. Oxidation of the arylmethyl group into a carboxylic acid

4.2.1. Oxidation of N-(5-methyl-3-isoxazolyl)-2,6-dimethylbenzamide 1 by Fieser's reagent

4.2.1.1. Synthesis of N-(5-methylisoxazol-3-yl)-3-methylphthalimide 11

D2916 **1** (1.00 g, 4.35 mmol) was added to a solution of chromium (VI) oxide (3.0 g, 30.0 mmol) in acetic acid (25 ml). The mixture was stirred at 45°C for 2 h. After cooling, the solution was poured into 100 ml of diethylether. The organic phase was washed with water and dried with sodium sulfate. The solvent was evaporated under reduced pressure. The crude product was recrystallized from ethanol.

11: *N*-(5-methylisoxazol-3-yl)-3-methylphthalimide. Yield: 0.473 g (45%); m.p. 183°C (ethanol). ^{1}H NMR ($CDCl_3$): δ 2.6 (s, 3H, CH_3 Ph), 2.8 (s, 3H, CH_3 isoxazole), 6.6 (s, 1H, =CH isoxazole), 7.1 (m, 3H, Ar). MS (70 eV): *m/z* (%) 242 (100) [M^+], 199 (14), 172 (48), 160 (12), 118 (98), 89 (78), 77 (11), 63 (37), 51 (11).

By-products: 3-methylphthalimide **12** (5%) and *o*-methylphthalic anhydride **13** (1.5%) were identified in extracts by GC-MS and comparison with standards synthesized by other methods.

4.2.1.2. Synthesis of 3-methylphthalimide 12

This compound, **12**, was prepared by chromic oxidation of 2,6-dimethylbenzamide **19** (1 g, 6.7 mmol) by the same procedure described in the chromic oxidation of *N*-(5-methylisoxazol-3-yl)-2,6-dimethylbenzamide **1**; the temperature was 20°C.

12: 3-methylphthalimide. Yield 0.39 g (36%); m.p. 192°C (Ref. [10], m.p. = 186–188°C). ^{1}H NMR ($CDCl_3$): δ 2.7 (s, 3H, CH_3), 7.6 (m, 3H, Ar), 8.2 (s, 1H, NH, exch D_2O) MS (70 eV): *m/z* (%) 161 (100) [M^+], 143 (36), 133 (16), 115 (34), 104 (16), 90 (54), 77 (10), 63 (42), 51 (13).

4.2.1.3. Synthesis of o-methylphthalic anhydride 13

Sodium carbonate (0.5 g, 4.7 mmol) and potassium permanganate (4.00 g, 25 mmol) were added to a hot (95°C) solution of 3-(2-hydroxyl-1-propen-1-yl)-5-(dimethylphenyl)-1,2,4-oxadiazole **22** (1.00 g, 4.35 mmol) in 80 ml of distilled water. The mixture was refluxed until the purple color disappeared. After cooling, hydrochloric acid was added to the mixture until pH 1 and the latter was refluxed for 30 min. Then the manganese(IV) oxide suspension was neutralized with sodium bisulfite and extracted with diethylether. The solvent was evaporated under reduced pressure. The solid residue was purified by flash chromatography using dichloromethane/methanol (99:1) as eluent.

13: *o*-methylphthalic anhydride. Yield 0.40 g (57%); m.p. 118°C (Ref. [11], m.p. = 115–116°C). ^{1}H NMR ($CDCl_3$): δ 2.74 (s, 3H, CH_3), 7.8 (m, 3H, Ar).

4.2.2. Oxidation of N-(5-methylisoxazol-3-yl)-2,6-dimethylbenzamide 1 by Thiele's reagent

D2916 **1** (1 g, 4.35 mmol) was added to acetic anhydride (5 ml). Sulfuric acid (1 ml) was added dropwise at 0°C to this mixture. A solution of chromium (VI) oxide (1.2 g, 12 mmol) and acetic anhydride (5 ml) was added over a period of 90 min. The mixture was stirred at 0°C for 30 min, then it was poured into 40 ml of cool water. After 12 h at room temperature a precipitate formed. The solid was filtered and washed with water, then with 5% hydrogen carbonate aqueous solution. The solid was dried under vacuum.

11. Yield 0.814 g (77%).

4.2.3. Oxidation of N-(5-methylisoxazol-3-yl)-2,6-dimethylbenzamide 1 by chromyl acetate (chromic oxide, acetic acid, acetic anhydride and sulfuric acid)

Acetic anhydride (5 ml) was added to a cooled (0°C) solution of D2916 **1** (1 g, 4.35 mmol) in acetic acid (6 ml). A solution of chromic oxide (1 g, 10 mmol) in acetic anhydride (3 ml) was added over a period of 45 min. The mixture was stirred at 0°C for 30 min, then it was poured into 40 ml of cold water. After 12 h at room temperature a precipitate formed. The solid was filtered and washed with cold water, then with 5% hydrogen carbonate aqueous solution. The solid was dried under vacuum.

11. Yield 0.255 g (24%).

4.2.4. Oxidation of N-(5-methyl-3-isoxazolyl)phthalimide 14 by CrO_3 in acetic acid

The phthalimide **15** was obtained from **14** (yield 1%) according to the same procedure as described above for the synthesis of *N*-(5-methyl-3-isoxazolyl)-3-methylphthalimide **11**.

4.3. Oxidation of the arylmethyl group to a primary alcohol

4.3.1. Oxidation of D2916 1 by sodium persulfate

D2916 **1** (1 g, 4.35 mmol), sodium persulfate (1.1 g, 4.62 mmol), sodium acetate (0.8 g, 9.75 mmol) and copper(II) acetate monohydrate (0.45 g, 2.25 mmol) were introduced into acetic acid (20 ml). The mixture was refluxed under nitrogen for 4 h. After the medium was cooled to 50°C, sodium persulfate (1.1 g, 4.62 mmol) and sodium acetate (0.8 g, 9.75 mmol) were added. The reflux was continued for another 4 h under nitrogen atmosphere. After cooling, the medium was poured into 30 ml of water. Then the medium was extracted with diethylether. The organic layer was washed with a saturated solution of sodium hydrogen carbonate and dried. The solvent was evaporated under reduced pressure. The crude residue was recrystallized from ethanol.

17: *N*-(5-methylisoxazol-3-yl)-7-methylisoindolinone. Yield 0.21 g (21%); m.p. 170°C. ^{1}H NMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3 Ar), 2.6 (s, 3H, CH_3 isoxazole), 4.7 (s, 2H, CH_2), 6.8 (s, 1H, H isoxazole), 7.3 (m, 3H, Ar). MS (70 eV): *m/z* (%) 228 (60) [M^+], 185 (12), 158 (11), 146 (100), 132 (17), 118 (14), 103 (27), 91 (13), 77 (19), 63 (11), 51 (10).

By-products: 7-methylisoindolinone **18** and 7-methylphthalide **3** [12] were identified in extracts by GC-MS and compared with standards synthesized by other methods.

4.3.2. Oxidation of D2916 1 by chromyl chloride (Etard's reagent)

Chromyl chloride (1.5 g, 9.7 mmol) in carbon tetrachloride (3 ml) was added to a cooled suspension of D2916 **1** (1.00 g, 4.35 mmol) in carbon tetrachloride (3 ml). The mixture was stirred for 1 h at room temperature then refluxed for 20 h. After cooling, the mixture was poured into a solution of sodium sulfite (1.4 g) in water (6 ml) and ice (6 g). Then hydrochloric acid (17%, 2 ml) was added in order to dissolve chromic salts. The aqueous mixture was extracted with carbon tetrachloride. The organic layer was washed with water, dried over sodium sulfate and evaporated under reduced pressure to give **17**.

17. Yield 0.035 g (3.5%).

4.3.3. Oxidation of D2916 1 by ammonium and cerium nitrate in acetic acid

D2916 **1** (1 g, 4.35 mmol) was added to a solution of ammonium cerium nitrate (12 g, 22 mmol) in acetic acid (44 ml). The mixture was refluxed until the color of the solid became yellow. After cooling, the mixture was diluted in 50 ml of distilled water, and extracted with diethylether. The organic layer was washed with a solution of 1.5 N potassium hydroxide then evaporated under reduced pressure to give **17**.

17. Yield: 0.125 g (12.6%).

4.3.4. Persulfate oxidation of N-(5-methylisoxazol-3-yl)-7-methylisoindolinone 17

The lactame **18** was prepared by persulfate oxidation of **17** according to the procedure described for D2916 **1**.

18: 7-methylindolinone. Yield 0.09 g (14%). MS (70 eV): *m/z* (%) 147 (100) [M^+], 132 (49), 118 (53), 91 (39), 77 (9), 65 (22), 51 (15). On the basis of MS findings the substance corresponds in all respects to the description of **18** in Ref. [11].

4.3.5. Persulfate oxidation of 2,6-dimethylbenzamide 19

The lactame **18** was prepared by persulfate oxidation of 2,6-dimethylbenzamide (0.745 g, 5 mmol) according to the procedure described above for D2916 **1**.

18. Yield 0.12 g (12%).

4.3.6. Nitric acid oxidation of N-(5-methylisoxazol-3-yl)-2,6-dimethylbenzamide D2916 1

D2916 **1** (1 g, 4.35 mmol) was added to nitric acid (7 ml) and water (1 ml). The mixture was stirred at 70°C for 55 h. After cooling, the mixture was poured into distilled water (100 ml), then extracted with diethylether. The organic layer was washed with water and dried with sodium sulfate. The solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography using cyclohexane/ethyl acetate (75:25) as eluent.

20: *N*-(5-methylisoxazol-3-yl)-3-nitro-2,6-dimethylbenzamide. Yield 0.873 g (73%); m.p. 148°C. ^{1}H NMR (acetone-d_6): δ 2.42 (s, 3H, CH_3 isoxazole), 2.45 (s, 6H, $2CH_3$ Ph), 6.87 (s, 1H, =CH isoxazole), 7.38 (d, 1H, Ar), 7.89 (d, 1H, Ar), 10.4 (s, 1H, exch D_2O, NH). MS (70 eV): *m/z* (%) 275 (29) [M^+], 233 (63), 178 (66), 160 (20), 147 (25), 133 (30), 119 (36), 104 (61), 91 (33), 77 (100), 63 (42), 51 (63).

By-products: 7-methylphthalide **3** was identified in extracts by GC-MS and compared with a standard reference.

4.4. Oxidative cleavage of the isoxazole ring

4.4.1. Alkaline hydrolysis of N-(5-methylisoxazol-3-yl)-2,6-dimethylbenzamide D2916

Sodium carbonate (0.5 g, 4.7 mmol) was added to a solution of D2916 **1** (1 g, 4.35 mmol) in boiling distilled water (100 ml). The mixture was refluxed for 4 h. After cooling, diluted hydrochloric acid was added to the mixture until pH 1. The precipitate was filtered and dried under vacuum. The solid was purified by flash chromatography using dichloromethane as eluent.

22: 3-(2-hydroxy-1-propen-1-yl)-5-(2,6-dimethylphenyl)-1,2,4-oxadiazole. Yield 0.3 g (30%); m.p. 218°C. ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 3H, CH_3–C–OH), 2.35 (s, 6H,

Ph), 5.3 (s, 1H, CH=C–CH_3), 7.1 (m, 3H, Ar), 12.34 (m, 1H, exch D_2O, OH). MS (70 eV): m/z (%) 230 (4) [M^{+}], 133 (100), 105 (36), 77 (17).

4.4.2. Permanganate oxidation of 3-(2-hydroxy-1-propen-1-yl)-5-(2,6-dimethylphenyl)-1,2,4-oxadiazole 22

This oxidation was described above in the synthesis of *o*-methylphthalic anhydride **13**.

4.4.3. Permanganate oxidation of N-(5-methylisoxazol-3-yl)-2,6-dimethylbenzamide 1

D2916 **1** (1.00 g, 4.35 mmol) was added to a boiling solution of distilled water (80 ml) and sodium carbonate (0.5 g, 4.7 mmol). Then potassium permanganate (4 g, 25 mmol) was added. The mixture was refluxed until the purple color disappeared. After cooling, hydrochloric acid was added to the mixture until pH 1. The mixture was refluxed for 30 min. The manganese(IV) oxide suspension was neutralized with sodium bisulfite. The aqueous layer was extracted with diethylether. The solid residue was purified by flash chromatography using dichloromethane/methanol (99:1) as eluent.

21: 2,6-dimethylbenzoylurea. Yield 0.22 g (26%); m.p. 22°C. ^{1}H NMR (DMSO-d_6): δ 2.22 (s, 6H, $2CH_3$), 7.1 (m, 3H, Ar), 7.5 (s, 1H, exch D_2O, NH_2), 10.5 (s, 1H exch D_2O, CO–NH–CO). MS (70 eV): m/z (%) 192 (17) [M^{+}], 175 (13), 149 (19), 132 (100), 105 (56), 77 (40), 65 (10), 51 (25).

4.4.4. Alkaline hydrolysis of 2,6-dimethylbenzoylurea 21

This hydrolysis, leading to **19**, was carried out in the presence of sodium carbonate according to the procedure described for the alkaline hydrolysis of D2916 **1**, leading to the oxadiazole **22**.

19: 2,6-dimethylbenzamide. Yield 0.768 g (99%); m.p.: 136°C. ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 6H, $2CH_3$), 5.9 (s, 1H, exch D_2O, NH), 6.39 (s, 1H, exch D_2O, NH), 7.0 (m, 3H, Ar). MS (70 eV): m/z (%) = 149 (86) [M^{+}], 132 (100), 105 (85), 91 (26), 77 (36), 63 (26), 51 (48).

4.4.5. Synthesis of 2,6-dimethylbenzoylurea 21

Two drops of concentrated sulfuric acid were added to a suspension of urea (1.21 g, 20 mmol) in toluene (3 ml). The mixture was warmed at 60°C and then 2,6-dimethylbenzoyl chloride (3.4 g, 20 mmol) was added dropwise. The mixture was refluxed for 4 h. After cooling, the solid was filtered and washed with a solution of sodium hydrogen carbonate. The crude solid was dried under vacuum without further purification.

21. Yield 3.4 g (98%).

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