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The Use of 4-Cyanoaminomethylene-2-phenyl-5(4h)-oxazolone in the Synthesis of Some Heteroarylaminomethylene Substituted 5(4H)-Oxazolones

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THE USE OF 4-CYANOAMINOMETHYLENE-2-PHENYL-5(4*H*)-OXAZOLONE IN THE SYNTHESIS OF SOME HETEROARYL-AMINOMETHYLENE SUBSTITUTED 5(4*H*)-OXAZOLONES.

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ABSTRACT: The use of 4-cyanoaminomethylene-2-phenyl-5(4*H*)-oxazolone in the synthesis of some 4-heteroarylaminomethylene-2-phenyl-5(4*H*)-oxazolones was studied. Synthesis of 4-(1,2,4-oxadiazol-3-yl)aminomethylene-2-phenyl-5(4*H*)-oxazolone is described.

In the course of our investigations on the *N*-functionalization of 4-aminomethylene-2-phenyl-5(4*H*)-oxazolone we found a new approach to 4-cyanoaminomethylene-2-phenyl-5(4*H*)-oxazolone (**1**),[1] a compound previously mentioned in connection with the use of 5(4*H*)-oxazolones in the penicillin synthesis.[2] Since the cyano group can serve as a one-carbon unit in the formation of other functional groups and

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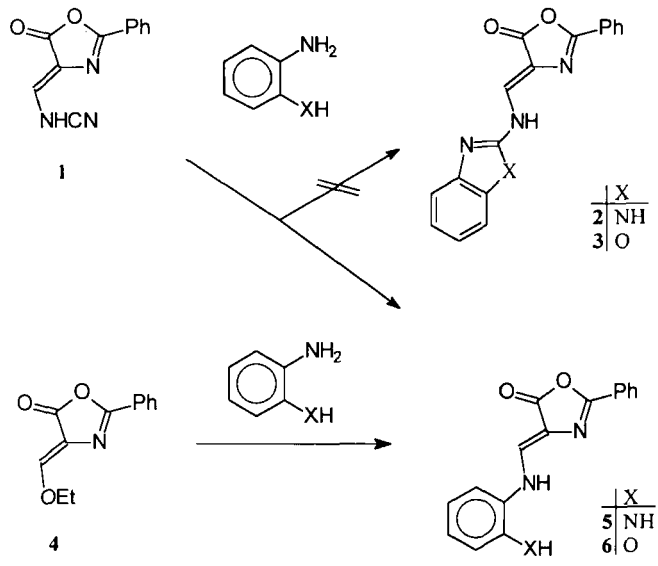
heterocyclic systems,[3] we decided to investigate the utility of compound **1** in the addition reactions leading toward the formation of 4-(2-benzimidazolyl)aminomethylene, 4-(2-benzoxazolyl)aminomethylene and 4-(1,2,4-oxadiazol-3-yl)aminomethylene substituted 2-phenyl-5(4*H*)-oxazolones. Herein we report on the results of these investigations.

Reaction of cyanoamine **1** with o-phenylenediamine gave 4-(2-amino-phenyl)aminomethylene-2-phenyl-5(4*H*)-oxazolone **(5)** (Scheme 1).

Scheme 1



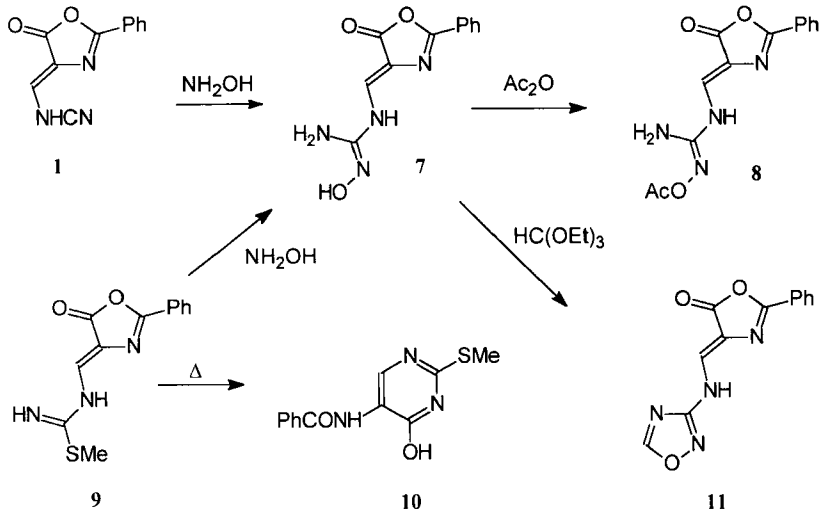
Although the addition of o-phenylenediamine to the cyano group, resulted in the formation of the desired 4-(2-benzimidazolyl)amino-methyleneoxazolone **2**, followed by the substitution of the 2-

benzimidazolylamino group giving product **5** might not be excluded, it seems that direct substitution of the cyanoamino group, which is less common transformation,[4] is more likely to take place. Oxazolone **5** is known to be prepared directly from 4-ethoxymethylene-2-phenyl-5(4*H*)-oxazolone (**4**) and used as a key intermediate in the synthesis of some benzimidazolyl and benzotriazolyl amino acid derivatives.[5] Similarly, reaction between cyanoamine **1** and o-aminophenol gave instead 2-benzoxazolylmethylene derivative **3** compound **6**, which we also prepared from 4-ethoxymethylene oxazolone **4** using the same reagent.

On the other hand, reaction of cyanoamine **1** with hydroxylamine yielded hydroxyguanidine **7**, which on treatment with acetic anhydride afforded *O*-acetyl derivative **8** (Scheme 2). We found that substitution of the methylthio group in isothiourea **9**, which was prepared from ethoxymethylene derivative **4** by described procedure,[2] with hydroxylamine also afforded hydroxyguanidine **7**. This transformation must be carried out at room temperature since at higher temperature competitive cyclization into the pyrimidine derivative **10** could take place, as it was the case in similar reactions of compound **4** with *S*-alkylisothiouronium halides.[6] Treatment of hydroxyguanidine **7** with triethyl orthoformat afforded 4-(1,2,4-oxadiazol-3-yl)aminomethylene-2-phenyl-5(4*H*)-oxazolone (**11**).

Although the stereochemistry of products was not thoroughly studied, we believe that these oxazolones have (*Z*)-configuration on the exocyclic C=C double bond.[1,5,7]

Scheme 2



EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are uncorrected. NMR spectra were recorded on a JEOL JNM FX90Q or Varian EM360L instruments, using TMS as internal standard. Mass spectra were recorded on a CEC-20-110 C instrument. Elemental analyses (C,H,N) were performed on a Perkin-Elmer 240C Analyzer. Compounds **1**,[1,2] **4**,[2] and **9**[2] were prepared as described in literature.

(*Z*)-4-(2-Aminophenyl)aminomethylene-2-phenyl-5(4*H*)-oxazolone (5).

A mixture of compound **1** (165 mg, 0.77 mmol), o-phenylenediamine (84 mg, 0.77 mmol) and ethanol (3 ml) was heated under reflux for

9 h. Upon cooling the separated product was filtered (95 mg, 44%); mp 179-181 ^{0}C (MeOH), mp lit[5] 179-181 ^{0}C.

(*Z*)-4-(2-Hydroxyphenyl)aminomethylene-2-phenyl-5(4*H*)-oxazolone (6).

a) A mixture of compound **1** (170 mg, 0.8 mmol), o-aminophenol (87 mg, 0.8 mmol) and ethanol (4 ml) was heated under reflux for 1.5 h. Upon cooling the separated product was filtered (92 mg, 41%).

b) A mixture of compound **4** (217 mg, 1 mmol), o-aminophenol (109 mg, 1 mmol) and ethanol (4 ml) was stirred for 1.5 h at room temperature. Upon cooling the separated product was filtered (236 mg, 84%). mp 275-278 ^{0}C (acetone); ^{1}H NMR (DMSO-d_6) δ 6.86 (m, 3H, 3'-H, 4'-H, 5'-H), 7.53 (m, 4H, 6'-H, 3H of Ph), 7.91 (m, 2H, Ph), 8.10 (s, 1H, CH), 8.48-10.34 (broad, 2H, NH, OH). Anal. Calcd for $C_{16}H_{12}N_2O_3$ (280.29): C, 68.57; H, 4.32; N, 9.99. Found: C, 68.18; H, 4.56; N, 9.95.

(*Z*)-4-Hydroxyguanidinomethylene-2-phenyl-5(4*H*)-oxazolone (7).

a) To a solution of hydroxylamine hydrochloride (200 mg, 2.9 mmol) in ethanol (5 ml), an ethanolic solution of sodium ethoxide (0.43 N, 6.67 ml) was slowly added, followed by the addition of compound **1** (261 mg, 1 mmol). The reaction mixture was then stirred for 1.5 h at room temperature. Upon cooling the separated product was filtered (195 mg, 79%).

b) To a solution of hydroxylamine hydrochloride (50 mg, 0.72 mmol) in ethanol (2 ml), compound **9** (50 mg, 0.23 mmol) was added. The reaction mixture was then stirred for 4 h, neutralized with ethanolic

sodium ethoxide solution (0.43 N, 0.53 ml), evaporated in vacuo, and the residue was treated with water (2 ml). Upon cooling the separated product was filtered (20 mg, 35%). mp 206-209 ^{0}C (EtOH/DMF). ^{1}H NMR (DMSO-d_6) δ 5.88 (bs, 2H, NH_2), 7.56 (m, 3H, Ph), 7.73 (s, 1H, CH), 7.92 (m, 2H, Ph), 9.39 (broad, 2H, NH and OH). Anal. Calcd for $C_{11}H_{10}N_4O_3$ (246.23): C, 53.66; H, 4.09; N, 22.75. Found: C, 53.67; H, 4.19; N, 22.37.

(*Z*)-4-Acetoxyguanidinomethylene-2-phenyl-5(4*H*)-oxazolone (8).

To a cooled acetanhydride (25 ml) compound **7** (370 mg, 1.5 mmol) was added. The reaction mixture was left for 72 h at -8 ^{0}C. The separated product was filtered (290 mg, 67%). mp 195-197 ^{0}C (DMF/aqueous EtOH). ^{1}H NMR (DMSO-d_6) δ 2.08 (s, 3H, Me), 6.46 (bs, 2H, NH_2), 7.55 (m, 3H, Ph), 7.67 (s, 1H, CH), 7.95 (m, 2H, Ph), 9.86 (bs, 1H, NH). Anal. Calcd for $C_{13}H_{12}N_4O_4$ (288.27): C, 54.17; H, 4.20; N, 19.44. Found: C, 53.83; H, 4.19; N, 19.25.

5-Benzoylamino-4-hydroxy-2-methylthiopyrimidine (10).

A mixture of compound **9** (320 mg, 1.22 mmol) and ethanol (6 ml) was heated under reflux for 7 h. Upon cooling the separated product was filtered (212 mg, 66%). mp 267-270 ^{0}C (i-PrOH), mp lit[8] 268 ^{0}C. ^{1}H NMR (DMSO-d_6) δ 2.53 (s, 3H, Me), 7.57 (m, 3H, Ph), 7.97 (m, 2H, Ph), 8.54 (s, 1H, 6-H), 9.26 (s, 1H, NH). Anal. Calcd for $C_{12}H_{11}N_3O_2S$ (261.31): C, 55.16; H, 4.24; N, 16.08. Found: C, 54.94; H, 4.34; N, 15.90.

(*Z*)-4-(1,2,4-Oxadiazol-3-yl)aminomethylene-2-phenyl-5(4*H*)-oxazolone (11).

A mixture of compound **7** (500 mg, 2.03 mmol) and triethyl orthoformate (5 ml) was heated under reflux for 2 h. Upon cooling the separated product was filtered (431 mg, 83%). mp 219-224 ^{0}C (EtOH/H_2O). ^{1}H NMR (DMSO-d_6) δ 7.61 (m, 3H, Ph), 7.73 (s, 1H, CH), 8.00 (m, 2H, Ph), 9.53 (s, 1H, 5'-H), 11.95 (bs, 1H, NH). Anal. Calcd for $C_{12}H_8N_4O_3$ (256.22) x 1/3H_2O: C, 54.96; H, 3.11; N, 21.37. Found: C, 54.91; H, 3.20; N, 21.34.

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References and notes

1. Dobnikar Tehovnik, M.; Petrič, A. and Verček, B. *Acta Chimica Slovenica,* submitted.
2. Cornforth, J. W. In *The Chemistry of Penicillin*; Clarke, H. T.; Johnson, J. R.; Robinson, R.; Eds.; Princeton University Press: Princeton, **1949**; pp 688-848.
3. Rappoport, Z. In *The Chemistry of the Cyano Group*; Patai, S., Ed.; Interscience, London, **1970**; pp 239-421.
4. Reiter, J. *Org. Prep. Proc. Int.* **1988**, *20*, 465.
5. Dobnikar, M.; Kočevar, M.; Polanc, S.; Tišler, M. and Verček, B. *Heterocycles* **1989**, *29*, 281.
6. Tikdari, A. M.; Tripathy, P. K. and Mukerjee, A. K. *J. Chem. Soc. Perkin Trans. I* **1988**, 1659.
7. The magnitude of the vicinal coupling constant between carbonyl carbon and β-olefinic hydrogen in ^{13}C NMR spectra is smaller than 5 Hz for compounds **4**, **9**, and **11**.

8. Boarland, M. P. V. and McOmie, J. F. W. *J. Chem. Soc.* **1952**, 4942.

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