The behaviour of 4-alkoxymethylene-2-phenyl-4H-oxazol-5-one and 4-dimethylaminomethylene-2-phenyl-4H-oxazol-5-one toward nitrogen nucleophiles under microwave heating

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The reactivity of 4-ethoxymethylene-2-phenyloxazol-5(4*H*)-one and 4-dimethylaminomethylene-2-phenyloxazol-5(4*H*)-one toward amines and active methylene reagents under microwave heating is reported. A new 3-aroylamino-4-pyridone synthesis is described.

Keywords: oxazoles, oxazol-5-ones, carboxanilides, pyran-2-ones, pyridin-4-ones, benzimidazoles, thiophenes

Some years ago Stanovnik *et al.*[1] reported the ready ring opening of 4-dimethylaminomethylene-2-phenyloxazol-5(4*H*)-ones **1** with methanol in presence of HCl under mild conditions. It occurred to us possible to extend this useful reaction to enable the preparation of the corresponding amides and/or ketones via reaction of **1** with amines and carbon nucleophiles. However, under a variety of conditions we failed to effect this ring opening reaction with amines in refluxing solvents of different polarity (DMF, acetic acid, and dioxan). Since microwave heating has been reported[2-4] greatly to enhance organic reaction rates we thought of using microwave heating to effect this ring opening reaction as a part of our recent interest in the utility of microwave heating in organic synthesis.[5-9]

Results and discussion

On heating 4-dimethylaminomethylene-2-phenyloxazol-5(4*H*)-one **1** with aniline, *p*-nitroaniline, and *p*-chloroaniline in microwave no reaction took place, but with *p*-toluidine a product of condensation *via* dimethylamine elimination was formed. Structures **3** and **4** seemed thus possible. Structure **3** could be ruled out based on the non-identity of the reaction product with the product of reaction of the ethoxymethylene derivative **5** with *p*-toluidine (Scheme 1).

We believe that the stability of **1** toward nucleophiles under these conditions is a result of the existence of **1** as a resonance hybrid with a significant contribution from **1a.** It is possible that the ring opening which occurred with Stanovnik *et al.*[1] in the presence of HCl is the result of a reaction of the hydrochloride **2**, in which the dimethylamino function is protonated.

In order to reduce lone pair resonance into the oxazolone ring in **1** a variety substituted anilinomethyleneoxazolones **3a–h** were prepared by the reaction of **5** with various aromatic amines. The anilinomethylene derivatives formed were found to exist in only one form. An X-ray crystal structure (*cf.* Fig. 1) indicated that these products adopt the *E* form **3**. The predominance of such forms in oxazolones of similar structure was confirmed early by Stanovnik *et al.*[10] from the HMBS coupling values. Compound **3h** having an adjacent ester function was found to exist in two forms, with predominance of the *E* form. Here it is possible that hydrogen bonding with the ester group reduces the energy difference between the *Z* and *E* forms, permitting some *Z* form to exist.

Even compounds **3** with different electron attracting substituents failed to react further with amines. The heterocyclic amines **7**, **9**, and **11** also reacted with **5** to yield either products of amine exchange as with **7** or **11**, or products of ring opening and recyclisation, as with **9**, yielding **10.** ^{13}C NMR of the

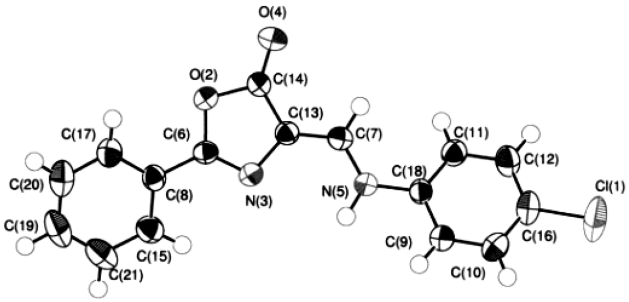
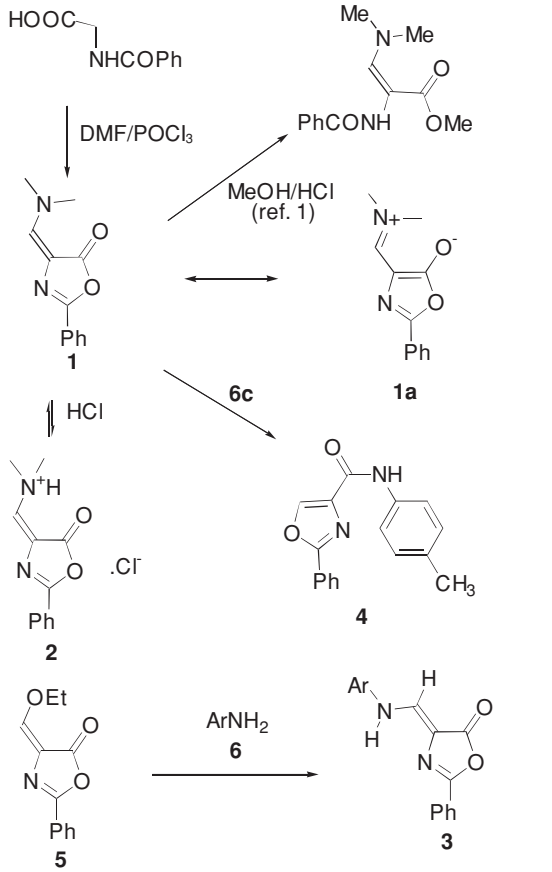


Fig. 1 X-ray structure of compound **3b.**



3,6 **a**, Ar = C_6H_5 **e**, Ar = 4-BrC_6H_4
b, Ar = 4-ClC_6H_4 **f**, Ar = 4-$NO_2C_6H_4$
c, Ar = 4-$CH_3C_6H_4$ **g**, Ar = 2-C_6H_4CN
d, Ar = 4-$CH_3OC_6H_4$ **h**, Ar =2-$C_6H_4CO_2Me$

Scheme 1

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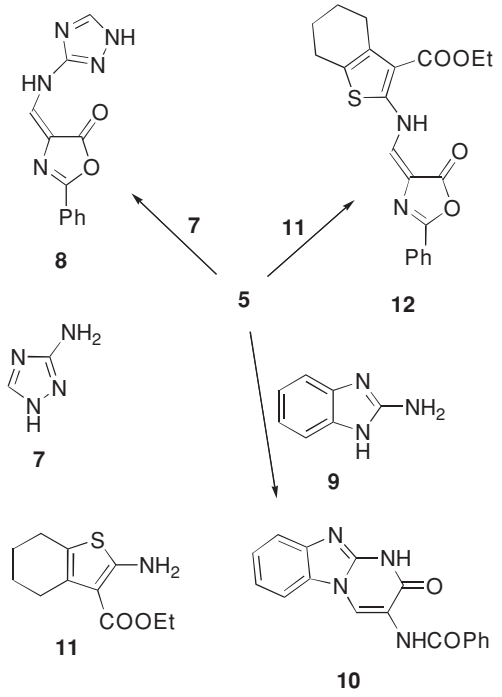
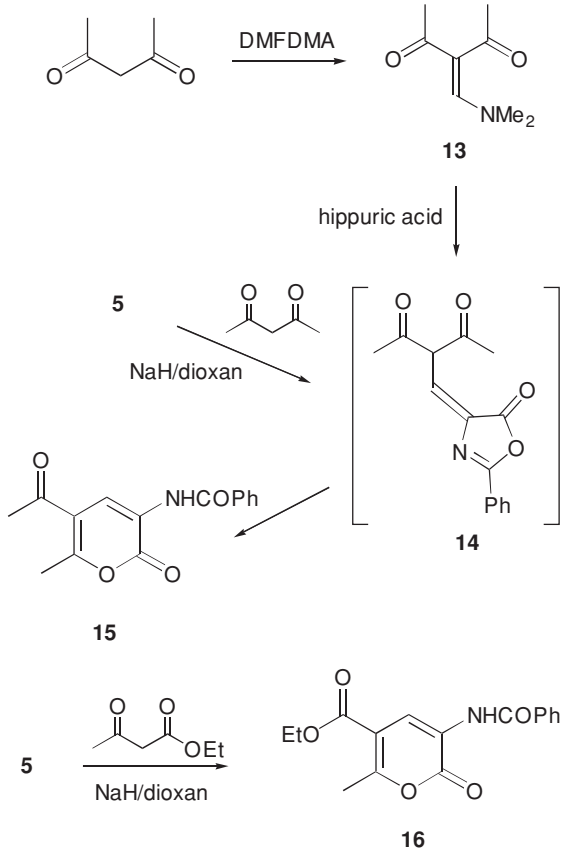
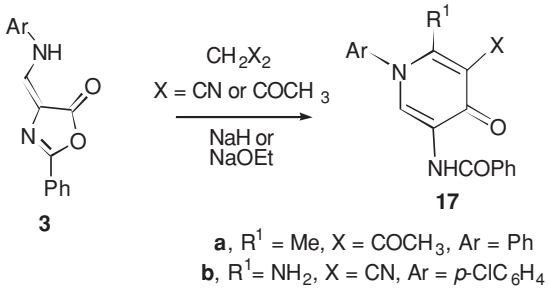


Scheme 2

reaction products could readily be used to assign structures. In the reaction with **7**, to produce **8**, only one carbonyl carbon could be observed (the product, while the product of reaction with **9** showed two carbonyl carbons at δ 164.8 and δ 165.9 ppm. The product of reaction of **11** with **5** showed a signal at δ 161.4 ppm for the ring carbonyl and another at δ 164.5 ppm for the ester function (Scheme 2).



Scheme 3



a, R^1 = Me, X = $COCH_3$, Ar = Ph
b, R^1= NH_2, X = CN, Ar = *p*-ClC_6H_4

Scheme 4

Acetylacetone reacts readily with **5** to yield pyran **15**, previously reported by Kepe *et al.*[11] to be formed by reacting a mixture of acetylacetone, DMFDMA, and hippuric acid. Such reaction in this case may occur *via* intermediate **14**. However the fact that **1** failed to react with acetylacetone under these reaction conditions established that **13** is the reactive species under these reactions and its condensation with oxazolone formed *via* cyclisation of hippuric acid affords **13** which then rearranges to **15**. Compound **5** reacts with ethyl acetoacetate to yield **16**; under similar conditions **1** failed to react (Scheme 3). Compounds **16** was previously reported by Svete *et al.*[12] from the reaction of ethyl 2-benzoyl-3-dimethylaminopropenoate with acetylacetone or ethyl acetoacetate.

Reacting **3a** with acetylacetone in the presence of sodium ethoxide yields pyridinone **17a**, while reaction of **3b** with malononitrile afforded **17b**. To our knowledge this is the first reported synthesis of 3-acylamino-4-pyridinones by oxazolone ring opening (Scheme 4).

Experimental

Melting points were measured on a Gallenkamp electrothermal melting point apparatus. The microwave oven was type SIO 390W. The IR spectra were recorded as KBr disks using a FTIR unit Bruker-Vector 22 spectrophotometer. The ^1H and ^{13}C NMR spectra were measured in DMSO-d_6 at 300/75 MHz on a Varian Gemini with tetramethylsilane (TMS) as internal standard; with exception of that of **8** which was measured in pyridine-d_5; chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GCMS-QP-1000 EX mass spectrometer at 70 eV. Microanalyses were performed at the Microanalytical Center of Cairo University.

4-Dimethylaminomethylene-2-phenyl-oxazol-5(4H)-one (**1**): A mixture of hippuric acid (0.01 mol) and phosphorus oxychloride (0.025 mol) was stirred at 0 °C and *N*,*N*-dimethylformamide (DMF) (0.025 mol) was added dropwise. The mixture was then stirred at 40–45 °C for 1 hr. The volatile compounds were evaporated *in vacuo* and the oily residue was poured into a mixture of aqueous ammonia (25%, 10 ml) and crushed ice (20g). The product was collected by filtration. The organic layer was dried over anhydrous sodium sulfate and evaporated *in vacuo*. The solid residue was recrystallised from ethanol to give **1**.[13] Yield 64% and m.p. 175 °C[lit. 166–167; yield 94.6%].

2-Phenyloxazole-4-carboxylic acid p-tolylamide (**4**): A mixture of **1** (0.01 mol) and *p*-tolylamine (0.01 mol) was irradiated in a microwave oven for 4.5 minutes. The resulting product was washed with ethanol, then recrystallised from ethanol to give red crystals (73%), m.p. 150–152 °C. IR: ν_{max} 3275 (NH), 1722 cm^{-1} (CO). ^1H NMR (d_6-DMSO): δ 2.4 (s, 3H, CH_3), 7.0–7.5 (m, 9H, Ph and aryl-H), 7.8 (s, 1H, oxazole-H), 8.5 (s, 1H, NH). MS (70 eV): *m*/*z* 278 (M^+, 6%). Anal. Calcd. for $C_{17}H_{14}N_2O_2$ (278.31): C, 73.37; H, 5.07; N, 10.7. Found C, 72.89; H, 5.12; N, 9.95 %.

General procedure for the preparation of **3a–h, 8, 10** and **12**: A mixture of **5**[14] (0.01 mol) and the appropriate aromatic amine (0.01 mol) was irradiated in a domestic microwave oven for 3 minutes; the resulting products was washed with ethanol, then recrystallised from ethanol.

2-Phenyl-4-(phenylaminomethylene)oxazol-5(4H)-one (**3a**): Orange crystals (93 %), m.p. 150–152 °C. IR: ν_{max} 3223 (NH), 1720 cm^{-1} (CO). MS: *m*/*z* 264 (M^+, 34%). Anal. Calcd. for $C_{16}H_{12}N_2O_2$ (264.28): C, 72.72; H, 4.58; N, 10.60. Found C, 71.69; H, 4.52; N, 10.46 %.

4-[(4-Chlorophenylamino)methylene]-2-phenyloxazol-5(4H)-one (**3b**): Yellow crystals (80 %), m.p. 205–206 °C. IR: ν_{max} 3197 (NH), 1708 cm^{-1} (CO). MS: *m/z* 298 (M^+, 24%). Anal. Calcd. for $C_{16}H_{11}ClN_2O_2$ (298.72): C, 64.33; H, 3.71; N, 9.38. Found C, 64.38; H, 3.62; N, 9.27 %.

2-Phenyl-4-(p-tolylaminomethylene)oxazol-5(4H)-one (**3c**): Red crystals (78 %), m.p. 160–161 °C. IR: ν_{max} 3321 (NH), 1713 cm^{-1} (CO). MS: *m/z* 278 (M^+, 20%). Anal. Calcd. for $C_{17}H_{14}N_2O_2$ (278.31): C, 73.37; H, 5.07; N, 10.7. Found C, 73.82; H, 4.78; N, 9.83 %.

4-[(4-Methoxyphenylamino)methylene]-2-phenyloxazol-5(4H)-one (**3d**): Yellow crystals (86 %), m.p. 165–167 °C. IR: ν_{max} 3260 (NH), 1710 cm^{-1} (CO). MS: *m/z* 294 (M^+, 20%). Anal. Calcd. for $C_{17}H_{14}N_2O_3$ (294.30): C, 69.38; H, 4.79; N, 9.52. Found C, 69.32; H, 4.74; N, 9.43 %.

4-[(4-Bromophenylamino)methylene]-2-phenyloxazol-5(4H)-one (**3e**); Red crystals (78 %), m.p. 200–202 °C. IR: ν_{max} 3310 (NH), 1715 cm^{-1} (CO). MS: *m/z* 342 (M^+, 14%), (M+2, 13.9%). Anal. Calcd. for $C_{16}H_{11}BrN_2O_2$ (343.17): C, 56.00; H, 3.23; N, 8.16. Found C, 55.69; H, 3.29; N, 8.11 %.

4-[(4-Nitrophenylamino)methylene]-2-phenyloxazol-5(4H)-one (**3f**); Red crystals (71 %), m.p. 260–262 °C. IR: ν_{max} 3448 (NH), 1742 cm^{-1} (CO). ^1H NMR (d_6-DMSO): δ = 7.5–7.7 (m, 5H, Ph), 7.9 (d, 2H, aryl-H), 8 (s, 1H, CH) 8.1 (d, 2H, aryl-H), 11 (br, 1H, NH). ^{13}C NMR (d_6-DMSO): δ_C = 167.0, 156.1, 146.0, 142.3, 133.3, 131.9, 129.2, 126.8, 126.1, 125.4, 116.8, 114.1. MS: *m/z* 309 (M^+, 38%). Anal. Calcd. for $C_{16}H_{11}N_3O_4$ (309.28): C, 62.14; H, 3.58; N, 13.59. Found C, 62.04; H, 3.59; N, 13.48 %.

2-[(5-Oxo-2-phenyl-4,5-dihydrooxazol-4-ylidenemethyl)amino]-benzonitrile (**3g**); Pale yellow crystals (75 %), m.p. 200–202 °C. IR: ν_{max} 3351 (NH), 2221 (CN), 1776 cm^{-1} (CO). ^1H NMR (d_6-DMSO): δ = 7.4–8 (m, 10H, Ph, aryl and CH), 10.5 (br, 1H, NH). ^{13}C NMR (d_6-DMSO): δ_C = 166.9, 155.5, 142.4, 139.0, 136.7, 134.8, 134.5, 133.8, 131.7, 129.1, 126.6, 125.2, 121.4, 116.9, 112.7. MS: *m/z* 289 (M^+, 30%). Anal. Calcd. for $C_{17}H_{11}N_3O_2$ (289.29): C, 70.58; H, 3.83; N, 14.53. Found C, 70.55; H, 3.72; N, 14.48 %.

Methyl 2-[(5-oxo-2-phenyl-4,5-dihydrooxazol-4-ylidenemethyl)-amino]benzoate (**3h**); Orange crystals (85 %), m.p. 125–127 °C. IR: ν_{max} 3237 (NH), 1775 (CO), 1703 cm^{-1} (CO). MS: *m/z* 322 (M^+, 50%); ^1H NMR (d_6-DMSO): δ = 3.8 (s, 3H, CH_3), 7–7.9 (m, 9H, Ph and benzoate), 8.2 (s, 1H, CH), 11.3 (br, 1H, NH). ^{13}C NMR (d_6-DMSO): δ_C = 167.7, 166.2, 155.9, 141.0, 140.8, 135.0, 132.8, 131.2, 129.1, 126.6, 126.1, 125.9, 122.7, 115.2, 114.4, 52.7. MS: *m/z* 322 (M^+, 50%). Anal. Calcd. for $C_{18}H_{14}N_2O_4$ (322.31): C, 67.07; H, 4.38; N, 8.69. Found C, 67.04; H, 4.36; N, 8.60 %.

2-Phenyl-4-[(1H-1,2,4-triazol-3-ylamino)methylene]oxazol-5(4H)-one (**8**); Brown crystals (60 %), m.p. 220–222 °C. IR: ν_{max} 3237 (NH), 1775 (CO), 1703 cm^{-1} (CO). ^1H NMR (pyridine-d_5): δ = 7.5–8.3 (m, 5H, Ph), 9.2 (s, 1H, CH), 9.35 (s, 1H, triazole), 9.47 (br, 1H, NH), 10.4 (br, 1H, NH).^{13}C NMR (pyridine-d_5): δ_C = 166.8, 153.1, 152.2, 146.5, 132.1, 131.5, 128.7, 128.5, 127.9, 127.6. MS: *m/z* 255 (M^+, 45%). Anal. Calcd. for $C_{12}H_9N_5O_2$ (255.23): C, 56.47; H, 3.55; N, 27.44. Found C, 56.39; H, 3.50; N, 27.38 %.

N-(3-Oxo-3,4-dihydropyrimido[1,2-a]benzimidazol-2-yl) benzamide (**10**); Yellow crystals (75 %), m.p. 287–300 °C. IR: ν_{max} 3398 (NH), 3364.9 (NH), 1775.9 (CO). ^1H NMR (d_6-DMSO): δ = 7.4–7.6 (m, 5H, Ph), 8.0 (m, 4H, benzimidazole), 8.45 (s, 1H, pyrimidine), 9.4 (s, 1H, NH), 9.6 (s, 1H, NH). ^{13}C NMR (d_6-DMSO): δ_C = 165.9, 164.8, 156.3, 147.4, 147.1, 134.0, 131.6, 128.9, 128.4, 127.5, 127.2, 126.4, 121.1, 115.6, 112.0. MS: *m/z* 304 (M^+, 60%). Anal. Calcd. for $C_{17}H_{12}N_4O_2$ (304.30): C, 67.10; H, 3.97; N, 18.41. Found C, 67.3; H, 3.91; N, 18.38 %.

Ethyl 2-[(5-oxo-2-phenyl-4,5-dihydrooxazol-4-ylidenemethyl)-amino]-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**12**); Orange crystals (90 %), m.p. 180–182 °C. ^1H NMR (d_6-DMSO): δ = 1.3 (t, *J* = 8 Hz, 3H, CH_3), 1.8–3 (m, 8H, $(CH_2)_4$), 4.3 (q, *J* = 8 Hz, 2H, OCH_2), 7.8–8.0 (m, 6H, Ph and CH), 11.0 (br, 1H, NH). ^{13}C NMR (d_6-DMSO): δ_C = 164.5, 161.4, 152.3, 143.4, 142.1, 138.2, 135.2, 132.5, 129.2, 126.7, 125.0, 106, 60.7, 26.0, 23.4, 22.1, 21.9, 14.0. MS: *m/z* 396 (M^+, 25%). Anal. Calcd. for $C_{21}H_{20}N_2O_4S$ (396.46): C, 63.62; H, 5.08; N, 7.07; S, 8.09. Found C, 63.61; H, 5.08; N, 7.02; S, 7.86 %.

Pyran derivatives **15** *and* **16**

A mixture of **5** (0.01 mol), acetylacetone or ethyl acetoacetate (0.01 mol), and NaH (0.01mol) in dioxan (15 ml) was refluxed for 2 h. The solvent was then evaporated under reduced pressure and the residue poured into water and neutralised with HCl. The product was collected by filtration and crystallised from ethanol.

N-(5-Acetyl-6-methyl-2-oxo-2H-pyran-3-yl)benzamide (**15**) formed pale brown crystals (86 %), m.p. 130–132 °C (lit.[11] mp. 139–140 °C).

Ethyl 5-benzoylamino-2-methyl-6-oxo-6H-pyran-3-carboxylate (**16**); formed yellow crystals (88 %), m.p. 128–130 °C (lit.[12] m.p. 135–138 °C).

N-(5-Acetyl-6-methyl-4-oxo-1-phenyl-1,4-dihydropyridin-3-yl) benzamide (**17a**): The anilinomethyleneoxazolone **3a** (0.01 mol), and acetylacetone (0.01 mol) were dissolved in a solution of NaOEt, prepared from sodium (2.3 mg) and absolute EtOH (20 ml). The mixture was refluxed for 4h, cooled to room temperature, and neutralised with HCl. The product was collected by filtration and crystallised from ethanol to give whitish crystals (73 %), m.p. 186–188 °C. IR: ν_{max} 3345.3 (NH), 1672 cm^{-1} (CO). ^1H NMR (d_6-DMSO): δ = 2.0 (s, 3H, CH_3), 3.1 (s, 3H, OCH_3), 7.5–7.9 (m, 10H, phenyl H), 8.75 (s, 1H, pyridine H), 9.42 (s, 1H, NH). MS: *m/z* 346 (M^+, 89%). Anal. Calcd. for $C_{21}H_{18}N_2O_3$ (346.38): C, 72.82; H, 5.24; N, 8.09. Found C, 72.75; H, 5.12; N, 8.02 %.

N-[6-Amino-1-(4-chlorophenyl)-5-cyano-4-oxo-1,4-dihydropyridin-3-yl]benzamide (**17b**): A mixture of **3b** (0.01 mol), malononitrile (0.01 mol), and NaH (0.01mol) in dioxan (15 ml) was refluxed for 3 h. The solvent was then evaporated under reduced pressure and the residue poured into water and neutralised by HCl. The product was collected by filtration and crystallised from ethanol and dioxan (1:1) to give brown crystals (78 %), m.p. 300–301 °C. IR: ν_{max} 3371, 3317.9 (NH_2), 3217.9 (NH), 2211.9 (CN), 1715, 1657 cm^{-1} (CO). ^1H NMR (d_6-DMSO): δ = 7.1 (s, 2H, NH_2), 7.5–7.8 (m, 9H, phenyl-H and aryl-H), 8.29 (s, 1H, pyridinyl-H), 9.17 (s, 1H, NH). MS: *m/z* 364 (M^+, 21%). Anal. Calcd. for $C_{19}H_{13}ClN_4O_2$ (364.79): C, 62.59; H, 3.59; N, 15.36. Found C, 62.48; H, 3.59; N, 15.27 %.

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