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REACTIONS OF O-AMINO-N-(1,1-DIMETHYLPROP-2-YNYL)-BENZAMIDE

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ABSTRACT: *Carbonylation of o-amino-N-(1,1-dimethylprop-2-ynyl)-benzamide **3** with ethyl chloroformate gave 2-carbethoxyamino-N-(1,1-dimethylprop-2-ynyl)-benzamide **6**. Attempted cyclization of **6** under basic conditions did not give the quinazoline **8** but an oxazole **7**. When **3** was also refluxed in triethylorthoformate-acetic anhydride mixture, 2-acetylamino-N-(1,1-dimethylprop-2-ynyl)-benza-mide **4** was formed as the major compound with negligible amount of 3-(1,1-dimethylprop-2-ynyl)-quinazolin-4-(3H)-one **5**.*

INTRODUCTION

The synthesis and biological activities of 3-substituted quinazolinones are well documented[1,3,5]. The carbonylation of the benzamide **3** and other related amides using bis-(trichloromethyl)-carbonate (triphosgene), a substitute for phosgene, have been carried out[5,6]. A search for possible alternative route for the quinazolinone **8** and the avoidance of the probable harzadous effect of phosgene prompted the attempted cyclization to the quinazolinone **8** reported in this paper. Acetic anhydride instead of glacial acetic acid has been ultilised in the synthesis of **5** and an N-acetylated derivative was reported but not characterised[7]. Isatoic anhydride is useful in the synthesis of heterocyclic compounds[8]. The condensation of isatoic anhydride with primary or secondary amines gives rise to substituted anthranilamides. Benzamides like o-amino-N-(1,1-dimethylprop-2-ynyl)-benzamide and 2-carbethoxyamino-N-(1,1-dimethylprop-2-ynyl)-benzamide could be biologically useful, since related amides have been employed as potential muscle relaxant and anticonvulsant[9]. Acetylenic amines have been used in the synthesis of potential biologically active heterocyclic compounds. Recently the anticonvulsant activity of some acetylenic quinazolinone derivatives have been evaluated and most of them exhibited significant activity in the seizure threshold test with subcutaneous pentylenetetrazole (ScMet test) and in the maximal electroschock test (MES test)[10]. The cyclisation of N- propynyl amides to oxazoles have been executed with acid and metallic catalysts.However base induced ring closures are not frequently encountered[5,...]

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and were uncorrected. The ^{1}H and ^{13}C nmr spectra were recorded in appropriate solvent at 200 MHz and 50 MHz respectively with tetramethylsilane as internal reference on a Bruker WM 300 spectrometer. Mass spectra were obtained on a Varian MAT 44S Instrument at 70 ev. The ir spectra were recorded on a Pye Unicam SP3-200 ir spectrophotometer. Silica gel 60 F_{254} (precoated aluminium sheets, 0.2mm thickness; Merck 5549) were used for analytical tlc.

o-Amino-N-(1,1-dimethylprop-2-ynyl)-benzamide 3

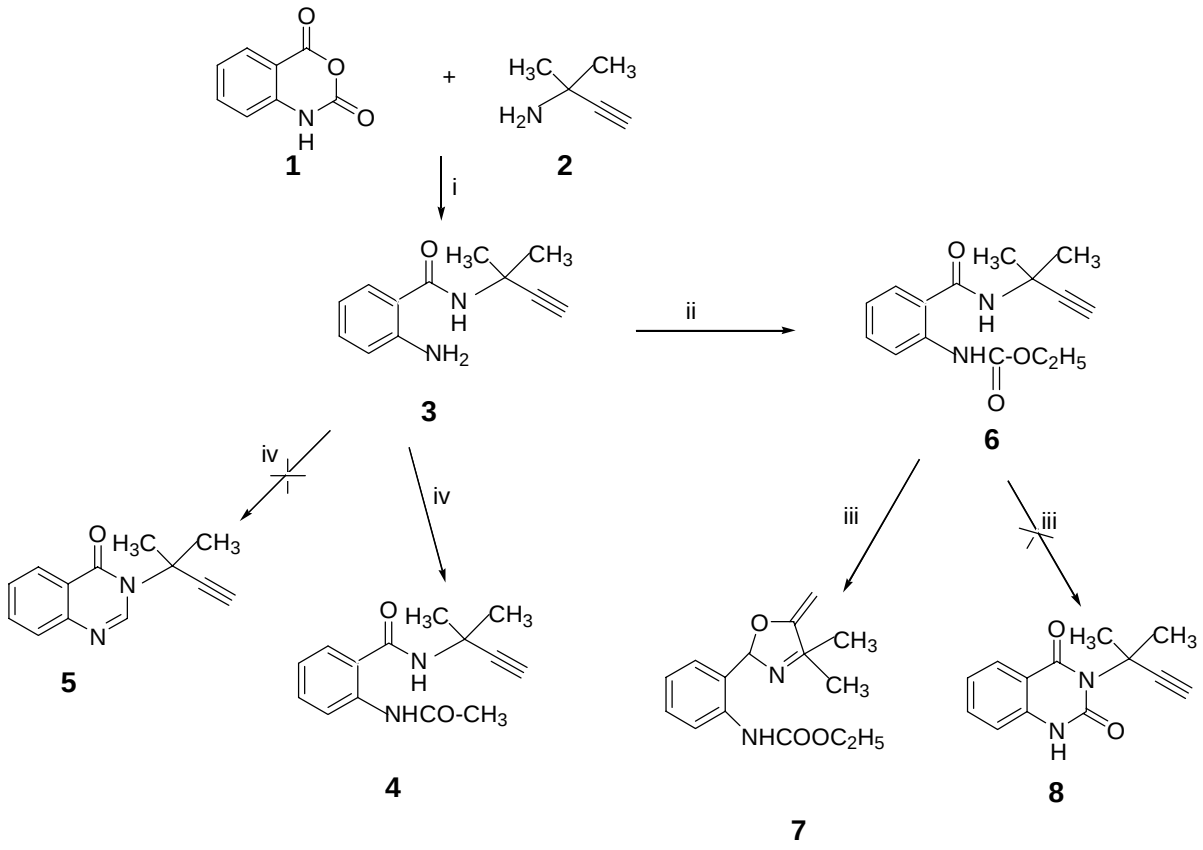
1,1-Dimethylprop-2-ynylamine 2.49g (0.03 mol) was added to isatoic anhydride 3.26 g (0.02 mol) in 20 ml DMF dropwisely over a period of 30 minutes. The reaction mixture was maintained at 50°C for 4 hours until tlc indicated disappearance of isatoic anhydride. The reaction mixture was poured into 200 ml of water and adjusted to pH 9 with 50% NaOH. The solid precipitate obtained was filtered, washed free of base with 3 x 20 ml portions of water, dried and purified through column chromatography (dichloromethane). Recrystallisation from dichloromethane-petroleum ether (30-40°C) gave colourless needles; 2.62 g (65%) mp. 121-122°C [Litt[5]; 121-123°C]. IR (KBr): 3490, 3400, 3390 (NH_2, NH), 3000, 1645 (C=O), 1600, 1260, 760, 700 cm^{-1}. ^{1}H NMR: ($CDCl_3$) δ = 1.72 (s, 6H, 2 x CH_3), 2.38 (s, 1H, 3'-H), 5.34 (brs, 2H, NH_2), 6.14 (brs, 1H, NH), 6.61 (t, J=7.9 Hz, 1H, 5-H), 6.67 (d, J=8.0 Hz, 1H, 3-H), 7.18 (ddd, J=1.2, 7.1, 7.4 Hz, 1H, 4-H), 7.77 (dd, J=1.6, 7.9 Hz, 6-H). ^{13}C NMR: ($CDCl_3$) δ =

29.3, 47.9, 69.5, 87.6, 116.6, 116.8, 117.8, 127.6, 132.7, 149.3, 169.4. MS: m/z = 202 [M^+](55), 174 (13), 136 (20), 119 (100), 105 (30), 92 (50), 65 (42).

2-Carbethoxyamino-N-(1,1-dimethylprop-2-ynyl)-benzamide 6

To o-amino-N-(1,1-dimethylprop-2-ynyl)-benzamide 0.6g (0.3 mmol) and 0.034 g (0.4 mmol) $NaHCO_3$ in 20 ml dichloromethane was added at room temperature 0.033 g (0.3 mmol) ethyl chloroformate. The reaction temperature was then maintained at 40°C with stirring for 3 hours. 50ml of water was added and extraction carried out using (3x20 ml) dichloromethane. The combined organic phase was dried over anhydrous Na_2SO_4 and the removal of solvent *in vacuo* gave **6** which was recrystallised from methanol as colourless plates; 1.01 g (74%); mp = 182 - 183 °C; IR (KBr): = 3360, 3280 (NH), 2995 (ArH), 1710 (C=O), 1640 (C=O), 1590 (C=O), 1530, 760 cm^{-1}. ^{1}H NMR (DMSO-d_6): d = 1.32 (t, J = 7.1Hz, 3H, $OCH_2C\underline{H}_3$), 1.68 (s, 6H, $2xCH_3$), 2.61 (s, 1H, 3^1-H), 4.17 (q, J = 7.1Hz, 2H, $OC\underline{H}_2CH_3$), 7.0 (t, J = 7.0Hz, 1H, 5-H), 7.43 (ddd, J = 1.0, 7.2, 7.7Hz, 1H, 4-H), 7.68 (dd, J = 1.5, 8.0Hz, 1H, 3-H), 8.24 (brs, 1H, $N\underline{H}$-$COCH_2CH_3$), 8.29 (d, J = 8.6Hz, 1H, 6-H), 10.5 (brs, 1H, $N\underline{H}(CH_3)_2$). ^{13}C NMR (DMSO-d_6): d = 14.5 ($OCH_2\underline{C}H_3$), 29.2 ($2xCH_3$), 47.4 (C-1^1), 60.8 ($OC\underline{H}_2CH_3$), 69.8 (C-3^1), 89.6 (C-2^1), 119.3 (C-3), 120.7 (C-1), 121.6 (C-5), 129.0 (C-6), 132.3 (C-4), 140.0 (C-2), 153.8 (Ph-$\underline{C}$=O), 168.9 (O=$\underline{C}$-OCH_2CH_3). MS: m/z (%) = 274 (7) [M^+], 259 (2), 228 (4), 202 (20),162 (16), 146 (100), 119 (52), 90 (18), 65 (60), 41 (75); Elemental Analysis: $C_{15}H_{18}N_2O_3$; Calculated: C, 65.44 H, 6.91 N, 10.18; Found : C, 65.24 H, 6.61 N, 10.22.

SCHEME



i: DMF, 50°C
ii: Ethylchloroformate, CH_2Cl_2, RT
iii: KOH/ethanol, reflux
iv: Triethylorthoformate, Acetic anhydride, reflux

2-(o-Carboethoxyaminophenyl)-4,4-dimethyl-5-methylene-4H-oxazole 7

KOH 0.18g (0.3 mmol) was added to 2-carbethoxy-amino-N-(1,1-dimethylprop-2-ynyl)-benzamide 0.5g (0.2 mmol) in 15ml ethanol. The mixture was stirred and gently heated to reflux and maintained at reflux for 3 hours afterwhich it was cooled, adjusted to pH 7 with acetic acid and extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed *in vacuo* to give a yellow oil; 0.375 g (75%); IR: (NaCl) = 3250 (NH), 2900 (ArH), 1710 (C=CH_2), 1695 (C=O), 1640, 1600, 1590, 1240, 850, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$): d = 1.33 (t, J = 7.1Hz, 3H, OCH_2CH_3), 1.48 (s, 6H, 2xCH_3), (q, J = 7.1Hz, 2H, O$\underline{CH_2}CH_3$), 4.27 (d, J = 3.0Hz, 1H, =CH*trans*), 4.76 (d, J = 3.0Hz,1H, =CH*cis*), 7.05 (ddd, J=1.1, 7.3, 7.4, Hz, 1H, 5-H), 7.48 (ddd, J = 1.7, 7.3, 8.6, Hz, 1H, 4-H), 7.88 (dd, J=1.7, 8.0 Hz, 1H, 3-H), 8.48 (d, J = 8.5Hz, 1H, 6-H), 11.35 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$): d = 14.7 ($OCH_2\underline{C}H_3$), 30.0 (2xCH_3), 61.2 (OCH_2CH_3), 69.6 (C-4), 82.9(C-CH_2), 112.2 (C-1^1), 118.8 (C-3^1), 121.7 (C-5^1), 129.6 (C-6^1), 133.2 (C-4^1), 141.0 (C-2^1), 154.5 (C-5), 160.2 (C-2), 166.6 (C=O); MS: m/z (%) = 274 (28) [M^+], 259 (7), 231 (16), 203 (12),163 (22), 145 (100), 118 (96), 90 (68), 77 (22); High resolution MS: for $C_{15}H_{18}N_2O_3$: Calculated : 274.1302; Found: 274.1317; Elemental Analysis: $C_{15}H_{18}N_2O_3$ Calculated : C, 65.71 H, 6.57 N, 10.22; Found : C, 65.66 H, 6.51 N, 10.09.

2-Acetylamino-N-(1,1-dimethylprop-2-ynyl)-benzamide 4

The condensation of o-amino-N-(1,1-dimethylprop-2-ynyl)-benzamide **3** 1.0 g (0.005 mol) with triethylorthofomate 1.10 ml (0.006 mol) in acetic anhydride (10 ml) after 3 hrs gave a crude product which on column chromatography yielded 2-acetylamino-N-(1,1-dimethylprop-2-ynyl)-benzamide **4** as colourless needles from dichloromethane/hexane; 0.98 g (80%); mp = 140-142 ^{o}C; IR (KBr): = 3360, 3280 (NH), 2995 (ArH), 1710 (C=O), 1640 (C=O), 1530, 760 cm^{-1}. ^{1}H NMR($CDCl_3$): d = 1.77 (s,, 6H, 2xCH_3), 2.16 (s, 3H, -$COCH_3$), 2.44 (s, 1H, =CH), 6.59 (brs, 1H, NH), 6.99-7.07 (ddd, J = 1.9, 7.12 8.0Hz, 1H, Ar-H), 7.28-7.49 (m, 2H, Ar-H), 8.49-8.50 (dd, J = 1.5, 8.0Hz, 1H, Ar-H), 10.87 (brs, 1H, NH). ^{13}C NMR ($CDCl_3$): d = 25.4, 29.2, 48.3, 69.9, 86.9, 121.2, 121.9, 122.9, 127.1, 132.9, 139.9, 168.9, 169.6. MS: m/z (%) = 244 (30) [M^+], 202 (38), 162(36), 136 (32), 119 (100), 92 (60), 82 (26), 65 (52); Elemental Analysis: $C_{14}H_{16}N_2O_2$; Calculated: C, 68.83 H, 6.60 N, 11.47; Found : C, 68.70 H, 6.50 N, 11.42.

DISCUSSION

Quinazolinone can be synthesised by carbonylation of N-substituted anthranilamide with ethylchloroformate and subsequent cyclization under basic conditions[2]. Attempted cyclization of **6** to the quinazolinone **8** was carried out using ethanolic potassium hydroxide and the oxazole **7** formed was as a result of angular cyclization of the side chain. It has however been reported that under basic conditions, the side chain rearranges to the respective oxazole[4]. This shows that angular cyclization is favoured to the elimination of the ethoxy group which should have led to the formation of the expected quinazolinone **8**. When **6** was refluxed in high boiling solvents like chlorobenzene, the oxazole was obtained in lower yield. Cyclocondensation reaction of **3** using the appropriate orthoester in the presence of acetic anhydride gave mainly N-acetylated product **4** and negligible yields of envisaged 3-propynylqunazolinone **5**. The product obtained was different from that earlier reported[7] in which the orthoesters were refluxed in ethanol and equimolar amount of glacial acetic acid, the major product obtained was 3-propynylqunazolinone **5**. The compounds were characterised by their spectroscopic data and elemental analysis.

Compound **6** was essentially spectroscopically similar to compound **5** except for the carbethoxy group which was clearly shown in the ^{1}HNMR as a triplet and quartet. A broad siglet at 8.24ppm also confirm the presence of NH of the carbethoxy amine group. Attempted cyclization of **6** to **8** was not possible rather the oxazole **7** was obtainted. The mass spectra clearly confirmed the formatoin of the oxazole **7**. The presence of two doublet (^{1}HNMR) between **4** and **5**ppm attributable to the exocyclic methylene proton (cis and trans) in addition to the presence of the carbethoxy moiety support the oxazole structure.

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