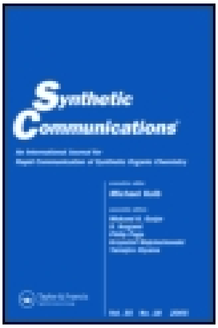

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Synthesis of Quinazolinedione Using Triphosgene

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SYNTHESIS OF QUINAZOLINEDIONE USING TRIPHOSGENE

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Abstract: O-aminobenzamides are easily ring closed to Quinazolinediones using triphosgene.

Pelanserin (1a)[1], has proven to have excellent antihypertensive properties like many other Quinazolinediones[1-6] and recently we have been interested in a pilot scale synthesis of this compound. The key steps in our synthesis is the ring closure of o-aminobenzamide (2) to Quinazolinedione (1) by bubbling phosgene gas through the solution. Although this method works excellent in a bench scale operation, in a pilot

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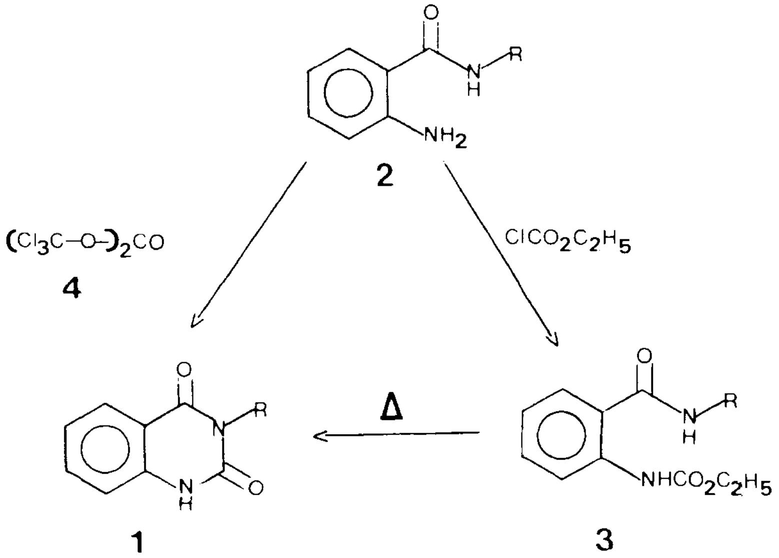
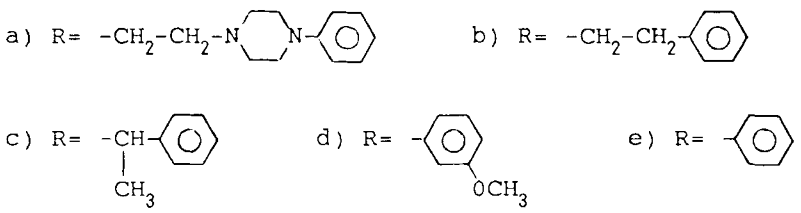
scale, one faces the potential hazard of handling large quantities of phosgene gas. Hence we were exploring other alternative methods of efficient ring closure to the quinazolinedione. One such method was the use of ethylchloroformate to make the O-carboethoxybenzamide derivative (3) and pyrolyse at 200°C (or at its melting point) to bring about the ring closure.





As expected the ring closure on a pilot scale experiment, invariably led to many side products and often needed extensive purification by chromatography and crystallization. Furthermore the yields were often not reproducible. An excellent substitute to the phosgene gas was the recent Aldrich product triphosgene (4)[7], which gave good yields of the final ring closed products (1a-e). Triphosgene (4) was easily weighed out and using large quantities did not pose any poblems. Here we wish to report the synthesis of some quinazolinediones using triphosgene.

Experimental. Melting points were obtained on a Gallenkamp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer FT-IR 1750 spectrophotometer. The proton nuclear magnetic resonance spectra were recorder on a Chemagnetic 200 MHz and Varian EM-390 90 MHz spectrometer. Mass spectra were obteined on a Finnigan 3000 at 70 ev by direct insertion and data processed using the Teknivent system.

GENERAL METHOD FOR MAKING O-AMINOBENZAMIDE.

A solution of 1-(3-aminopropyl)-4-phenylpiperazine (5.0 g, 23 mmoles) in DMF (50 ml) was stirred and isatoic anhydride (4.09 g, 25 mmoles) was added portion wise over a period of 30 min., and the temperature was maintained ~50°C, CO_2 gas was envolved. Stirred at room temperature for additional 2 hrs, added water and the solid collected by filtration.

<u>1-(3-O-Aminobenzamido)propyl-4-phenylpiperazine</u> (2a): mp 119-122°C, yield 85 %, IR (KBr): 3447, 3329, 3062, 2928, 2825, 1640, 1614, 1598, 1582, 1523, 1264, 1237, 1166, 1032, 759, 746 cm^{-1}. ^1H-NMR ($CDCl_3$/DMSO-D_6,90MHz): 7.8 (m,1H), 7.2 (m,5H), 6.8 (d,2H), 6.4 (m,2H), 5.2 (m,2H), 3.5 (m,2H), 3.1 (m,2H), 2.5 (m,8H), 1.8 (m,2H). MS: m/e 337 (M^+).

<u>1-(2-O-Aminobenzamido) 2-phenylethane</u> (2b): mp 80-85°C, yield 60 %, IR (KBr): 3300, 3000, 1620, 1580 cm^{-1}. ^1H-NMR ($CDCl_3$/DMSO-D_6,200 MHz): 7.25 (m,7H, ArH), 6.65 (d,2H, J= 9Hz,ArH), 6.10 (br.S,2H, NH_2), 5.5 (br.S,1H, NH), 3.75 (q,2H, J=6Hz, N-CH_2), 2.95 (t,2H, J=6Hz, CH_2). MS: m/e 240(M^+).

<u>1-(O-Aminobenzamido)-1-phenylethane</u> (2c): mp 100-102°C, yield 62%, IR (KBr): 3470, 1630, 1590 cm^{-1}. ^1H-NMR ($CDCl_3$/DMSO-D_6 200 MHz): 7.35 (m,7H, ArH), 6.60 (d,2H, J= 9Hz, ArH), 6.35 (br.S,1H, NH), 5.25 (q,1H, J=6Hz, CH), 1.55 (d,3H, J=6Hz, CH_3). MS: m/e 240 (M^+).

O-Amino-N-(3-methoxyphenyl)-benzamide (2d): mp 112-114^{0}C, yield 82%, IR (KBr): 3240, 3180,3010,2930, 1640 cm^{-1}. ^{1}H-NMR (CDCl$_3$/DMSO-D$_6$): 9.74 (br.S,1H,NH), 7.60 (m,5H, ArH), 7.15 (t,1H,J=8.1Hz, ArH), 6.84, 6.73 (dd,3H, J=8.1Hz, ArH), 6.58 (t,1H,J=8.1Hz, ArH) 6.16 (br.S, 2H,NH$_2$), 3.76 (s,3H,OCH$_3$): MS: m/e 242 (M$^+$).

O-Amino-N-Phenylbenzamide (2e): mp 119-121^{0}C, yield 88%, IR (KBr): 3450, 1640, 1600 cm^{-1}. ^{1}H-NMR (CDCl$_3$/CDMSO-D$_6$, 90mHz): 9.90 (br.S,1H, NH), 7.80 (d,t,2H,J=8.00, J=2.00Hz), 7.00-7.50 (m,5H,ArH), 6.7 (d,t,1H,J=8,2Hz ArH). MS: m/e 212 (M$^+$).

GENERAL METHOD FOR MAKING QUINAZOLINEDIONE

A solution of O-aminobenzamida (1.2g, 5 mmoles) in CH_2Cl_2 (50ml) was stirred at room temperature, and to this solution added triphosgene (0.5g, 1.7 mmoles) in CH_2Cl_2 (10 ml), and the mixture was refluxed for 2 h. The organic phase was washed with water, dried over $MgSO_4$ and removal of solvent under reduced pressure gave a solid (1a).

3-(3-Propyl-4-phenylpiperazine)-2-4-quinazolinedione (1a): mp 227-229^{0}C, yield 88%, IR (KBr): 3433, 3193, 3133, 3050, 2997, 2950, 2831, 1713, 1658, 1601, 1494, 1454, 1385 cm^{-1}. ^{1}H-NMR ($CDCl_3$/DMSO-D_6,90MHz): 8.0 (d,1H, J=6Hz), 7.5 (d,1H, J=6Hz), 7.2 (m,5H),6.7 (mm,3H), 4.0 (m,5H), 3.6 (m,6H), 3.2 (m,5H), 2.2 (m,2H). MS: m/e 364 (M^+).

<u>3-(2-Phenylethane)-2.4-quinazolinedione</u> (1b'): mp 178-182^{0}C, yield 78%, IR (KBr): 3189 (NH), 1719 (C=O),1655 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$/DMSO-D_6, 90MHz): 10.70 (br.S,1H, NH), 8.10 (d,1H, J=9Hz, ArH) 7.55 (t,1H, J=9Hz, ArH), 7.20 (m,7H, ArH), 4.25 (t,2H, J=6Hz, CH_2), 2.95 (t,2H, J=6Hz, CH_2). MS: m/e 266 (M^+).

<u>3-(1-Phenylethane)-2,4-quinazolinendione</u> (1c): mp 204-206^{0}C, yield 81%, IR (KBr): 3346, 1720, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$/DMSO-D_6,200MHz) 10.75 (br.S, 1H, NH), 7.35 (d,1H, J=8.2Hz, ArH), 7.00 (t,1H, J=8Hz, ArH), 6.80 (t,1H, J=8.2Hz, ArH), 6.35 (m,6H, ArH), 5.30 (q,1H, J=7Hz, CH-CH_3), 1.60 (d,3h, J=7Hz, CH_3-). MS: m/e 266 (M^+).

<u>3-(3-Methoxyphenyl)-2,4-quinazolinedione</u> (1d): mp 205-207^{0}C, yield 84%, IR (KBr): 3198 (NH), 1733 (C=O), 1654 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$/DMSO-D_6, 90MHz): 10.85 (br.S, 1H, NH), 7.85 (d,1H, J=9Hz, ArH), 7.50 (t,1H, J=9Hz, ArH), 7.30-6.60 (m, 6H, ArH), 3.80 (s, 3H, OCH_3). MS: m/e 268 (M^+).

3-phenyl 2,4-Quinazolinedione (1e): mp 210-2121^{0}C, yield 79%, IR(KBr): 3443, 1731, 1650, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$/DMSO-D_6, 200MHz): 11.50 (br.S, 1H, NH), 8.05 (d,1H, J=8.2Hz, ArH), 7.70-7.10 (m, 8H, ArH). MS: m/e 238 (M^+).

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