Bisheterocycles: Synthesis of some novel 1,2,3-triazolyl oxadiazole and 4(3H)-quinazolinones *via* azide cycloaddition reaction

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Abstract

2,5-Bis[2-(4,5-dimethoxycarbonyl)1,2,3-triazol-1-yl)acetylaminophenyl]-1,3,4-oxadiazole (**4**) and dimethyl 1-(2-{[(3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl) methyl]anilino}-2-oxoethyl)-1H-1,2,3-triazole-4,5-dicarboxylate (**6**) are prepared by cycloaddition of dimethyl acetylenedicarboxylate to the oxadiazolyl azide **3** and the quinazolinone azide **5**, respectively.

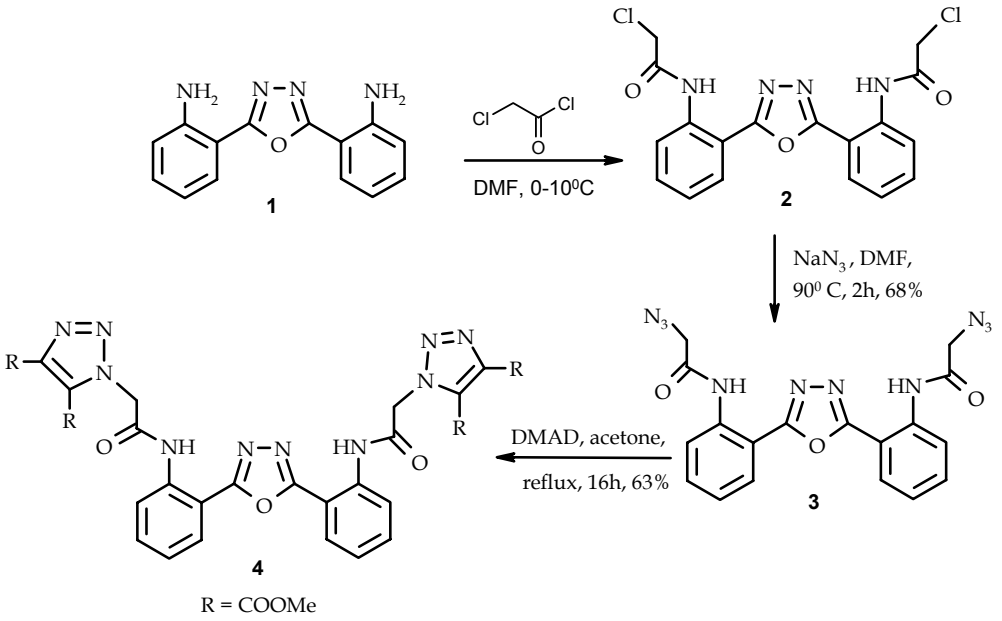
Keywords: Bistriazolyloxadiazole, Bistriazolylquinazolinones, Azide cycloaddition reactions

Introduction

Many 2-heteryl/heteroalkyl-4(3H)-quinazolinones exhibit a wide range of pharmacological activity such as antihistaminic, anticonvulsant, hypnotic, anti-inflammatory, CCK antagonists, antiulcer and muscle relaxant.[1] Similarly, several 1,2,3-triazole derivatives have received much attention because of their wide range of applications as light stabilizers, fluorescent whiteners, optical brightening agents, corrosion retardants, dyestuffs, asymmetric dihydroxylation catalysts, photosensitizers,[2-7] fungicidal, herbicidal, cytostatic, virostatic, antiinflammatory,[3] anti-HIV,[8] antimicrobial[9] and β-adrenergic receptor agonists.[10] The most popular method for the construction of 1,2,3-triazole framework is the 1,3-dipolar cycloaddition reactions of azides with alkynes[11]. Thorson and his coworkers[12] have recently utilized the 1,3-dipolar cycloaddition of azide and acetylenes to generate fifty triazole analogs of the antibiotic vancomycin. In the above context, we report here a convenient route to some new bisazaheterocycles *viz* bistriazolyloxadiazole (**4**) and bistriazolylquinazolinones (**6**) starting from 2,5-bis(2-aminophenyl)-1,3,4-oxadiazole (**1**) and the azidoacetyl arylaminomethyl quinazolinone **5,** whose synthesis were reported earlier [13,14].

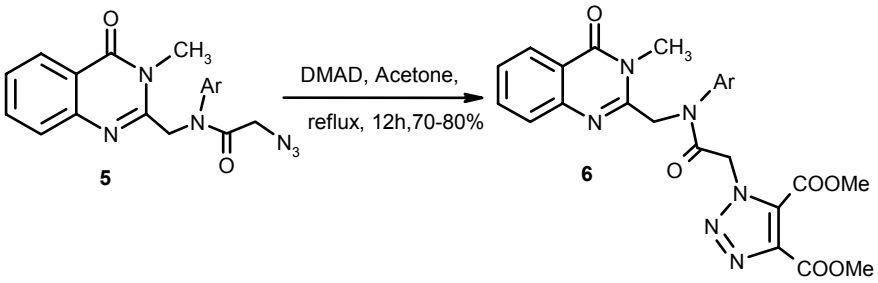
Results and Discussion

2,5-Bis[2-(2-azidoacetylamino)phenyl]-1,3,4-oxadiazole (**3**) was prepared in 68 per cent yield by reacting 2,5-bis[2-(2-chloroacetamido)phenyl]-1,3,4-oxadiazole (**2)** with sodium azide in DMF. The product tested negative for chlorine (Lassaigne's and flame tests). The molecular weight of the bisazido-1,3,4-oxadiazole **3** has been confirmed as 418 by the appearance of ion peaks at m/z 419 ($M^{+\cdot}$+1) and m/z 441 ($M^{+\cdot}$+23) in its LC-MSD-Trap-SL mass spectrum. The presence of azide groups is evident in the IR spectrum (strong peak at 2096 cm^{-1}). The ^1H NMR spectrum is simple and suggestive of C_2-symmetry in the molecule. The singlet peak at δ 4.2 (4H) is due to methylene groups (2 x CH_2), each flanked by CO and N_3. The aromatic protons have resolved into four peaks - δ 7.3 (2H), δ 7.6 (2H), δ 8.1 (2H) and δ 8.7 (2H). The amide NH protons appeared at δ 11.3 (2H). Being a dipole, the azide group undergoes 1,3-cycloaddition reaction with dimethyl acetylenedicarboxylate (DMAD) to form a 1,2,3-triazole ring. We extended this customary reaction to **3,** which contained two azido groups, and isolated the title compound 2,5-bis[2-(4,5-bis(methoxycarbonyl)-1,2,3-triazol-1-yl)acetylaminophenyl]-1,3,4-oxadiazole (**4**) in 63 per cent yield (**Scheme 1**). The expected molecular weight is 702, which is confirmed by the appearance of ion peaks at m/z 705 ($M^{+\cdot}$+3) and m/z 704 ($M^{+\cdot}$+2) in the FAB mass spectrum. The IR spectrum is devoid of the azide peaks (~2100 cm^{-1}). Instead, it indicated ester carbonyls (b, 1731 cm^{-1}). In the ^1H NMR spectrum, the four ester methyls appeared as two singlets [at δ 3.82 (6H) and δ 3.9 (6H)], and the two methylenes as one singlet at δ 5.8 (4H). The electronic environment of the two CO_2CH_3 groups at C_4 and C_5 of the triazole ring are not identical, and therefore a difference in their chemical shift is not surprising. The two singlet peaks at δ 160.4 and δ 163.7 in its ^{13}C NMR spectrum provides proof for this assumption. The aromatic protons were recorded at δ 7.4 (t, 2H), δ 7.7 (t, 2H) and δ 8.2 (m, 4H). The two amide NH protons resonated at δ 10.8 (s).



Scheme 1

Quinazolinone based bisazaheterocycles containing a 1,2,3-triazole ring are not so far known in literature. In view of the excellent paharmacological activity associated with 1,2,3-triazole derivatives[15-17], we sought to synthesize 1,2,3-triazolylquinazolinones by extending 1,3-cycloaddition reaction to the azide intermediate **5** that was earlier prepared in our laboratory[14]. For example, reflux of **5a** with DMAD in dry acetone for 12h yielded a novel heterocycle named dimethyl 1-(2-{[(3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl)methyl]anilino}-2-oxoethyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (**6a**) in 74 per cent yield. This reaction has been extended to four other derivatives of **5** and, in each case, the corresponding **6** was isolated in 70 – 80 per cent yield (**Scheme 2**). The FAB mass spectrum of **6a** (MNBA matrix) recorded the $M^{+\cdot}$+1 ion peak at 491. The IR spectrum was devoid of the azide absorption. The triazole ester carbonyls appeared at 1763 cm^{-1}, 1732 cm^{-1} and the quinazolinone carbonyl at 1681 cm^{-1}. In the ^{1}H NMR spectrum, singlet peaks appeared at δ 3.6, δ 3.8 and δ 3.9, each integrating for three protons, corresponding to one N-CH_3 and two triazole ester methyls (2 x O$\underline{CH_3}$), respectively. Besides these, two singlet peaks at δ 5.0 and δ 5.3, each integrating for two protons, correspond to methylenes attached to quinazolinone and triazole rings, respectively. The aromatic region showed peaks between δ 7.3-7.5 (m, 4H, Ar-H), and δ 7.6-7.7 (m, 4H, Ar-H). The quinazolinone peri proton appeared as a doublet at δ 8.2. In ^{13}C NMR also, there are four carbonyl carbon signals (δ 164.3, 162.2, 160.2, 159.1) besides other signals.



5, 6	a	b	c	d	e
Ar	C_6H_5	4-$CH_3C_6H_4$	3-$CH_3C_6H_4$	4-ClC_6H_4	3-ClC_6H_4

Scheme 2

Experimental Section

General Procedures. All the melting points were determined in capillaries using Polmon digital melting point apparatus (Model No. MP-96) and reported uncorrected in degree centigrade. CHN analysis was carried out on Thermo Finnigen Flash, E-112 Elemental analyzer. Infrared spectra were recorded in KBr pellets on Shimadzu 435 instrument. The position of absorptions was quoted in ± 2.5 cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on Varian Gemini (200 MHz) with TMS as internal standard. Chemical shift values are given in δ ppm. The solvent in which the NMR spectrum was recorded is indicated at the appropriate places. Mass spectra were recorded on FAB (MNBA matrix) and LC-MSD (Trap-SL). The IUPAC nomenclature of the compounds **1-6** using ACD LAB software, along with the names reflecting the central core of the heterocycle are mentioned at the appropriate places.

2,5-bis[2-(2-chloroacetamido)phenyl]-1,3,4-oxadiazole (2)[18] : 2-(5-(2-Aminophenyl)-1,3,4-oxadiazol-2-yl)benzenamine[13] (**1**, 2.52 g, 10 mmol) was dissolved in DMF (15 mL), and the solution was cooled to 0 ^oC . To this cold solution, chloroacetyl chloride (1.56 mL, 20 mmol) in dioxane (5 mL) was added drop wise during a period of 30 minutes, with vigorous stirring at 0-10^oC. N^1-[2-(5-{2-[(2-Chloroacetyl)amino]phenyl}-1,3,4-oxadiazol-2-yl)phenyl]-2-chloro acetamide (**2**)[18] separated out as a solid from the reaction mixture. It was filtered, washed with water and dried, yield 90%, mp 275 ^oC. IR (KBr): 3254 (amide NH), 1693 (amide CO), 1612 (C=N). ^1H NMR ($CDCl_3$): 4.3 (s, 4H, 2xCH_2), 7.2-7.4 (m, 2H, Ar-H), 7.3-7.6 (t, 2H, Ar-H), 8.1 (d, 2H, J=9.0 Hz, Ar-H), 8.8 (d, 2H, J=9.0 Hz, Ar-H), 11.7 (s, 2H, 2xNH). Mass m/z rel. int (%): 404 (M^+, 23).

2,5-Bis[2-(2-azidoacetylamino)phenyl]-1,3,4-oxadiazole (3): A mixture of N^1-[2-(5-{2-[(2-chloroacetyl)amino]phenyl}-1,3,4-oxadiazol-2-yl)phenyl]-2-chloroacetamide (2, 4.08 g, 10 mmol) and sodium azide (1.95 g, 30 mmol) was stirred in DMF at 90^0C for 2h. The cold reaction mixture was then poured in ice-cold water. The pale yellow amorphous solid, 2-azido-N-(2-{5-[2-(2-azido-acetylamino)-phenyl]-[1,3,4] oxadiazole-2-yl}-phenyl)acetamide (**3**) that separated

out was filtered and recrystallised from 10% aqueous ethanol, yield 68%, mp 190-193 ^{o}C. IR (KBr): 3278 (amide NH), 2096 (azide), 1693 (amide CO), 1614 (CN). ^{1}H NMR (d_6-DMSO): 4.2 (s, 4H, 2x CH_2), 7.3-8.7 (m, 8H, Ar-H), 11.3 (s, 2H, 2 x NH). Mass m/z rel. int (%): 441 ($M^{+\cdot}$+23, 61), 419 ($M^{+\cdot}$+1, 14), 404 (6), 301 (6). Anal. calcd. for $C_{18}H_{14}N_{10}O_3$: C, 51.68; H, 3.37; N, 33.48; Found: C, 51.94; H, 3.64; N, 28.57.

2,5-Bis[2-(4,5-bis(methoxycarbonyl)-1,2,3-triazol-1-yl)acetylaminophenyl]-1,3,4-oxadiazole (4): To a solution of 2-azido-N-(2-{5-[2-(2-azido-acetylamino)-phenyl]-[1,3,4] oxadiazole-2-yl}-phenyl)acetamide (**3**, 2.09 g, 5 mmol) in dry acetone (30 mL) was added dimethyl acetylenedicarboxylate (DMAD, 10 mmol). The reaction mixture was refluxed for 16h, monitored by tlc for completion and cooled. Removal of excess solvent yielded a colorless solid. It was filtered and purified by repeatedly washing with cold methanol, yield 63%, mp 224-226 ^{o}C, and characterised as dimethyl 1-[2-(2-{5-[2-({2-[4,5-di(methoxycarbonyl)-1H-1,2,3-triazol-1-yl]acetyl}amino)phenyl}-1,3,4-oxadiazol-2-yl}anilino)-2-oxoethyl] -1H-1,2,3-triazole-4,5-dicarboxylate (**4**)**.** IR (KBr): 3279 (amide NH), 1731 (ester CO), 1618 (CN), ^{1}H NMR (d_6-DMSO): 3.8 (s, 6H, 2 x OCH_3), 3.9 (s, 6H, 2 x OCH_3), 5.7 (s, 4H, 2 x CH_2), 7.4 (t, 2H, Ar-H), 7.7 (t, 2H, Ar-H), 8.2 (m, 4H, Ar- H), 10.8 (s, 2H, 2 x NH). ^{13}C NMR (d_6-DMSO): 51.1, 51.5, 52.1, 52.3, 118.9, 126.5, 126.8, 127.1, 129.1, 129.9, 133.4, 137.1, 138.1, 138.8, 145.8, 150.8, 157.8, 159.1, 160.4, 163.7. Mass m/z rel. int (%): 705 ($M^{+\cdot}$+3, 11), 704 ($M^{+\cdot}$+2, 27), 231 (5), 147 (17), 145 (100) 122 (8). Anal. calcd. for $C_{30}H_{26}N_{10}O_{11}$: C, 51.29; H, 3.73; N, 19.44; Found: C, 51.72; H, 3.9, N, 18.5.

Dimethyl 1-(2-{[(3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl) methyl] arylamino}-2-oxo-ethyl)-1H-1,2,3-triazole-4,5-dicarboxylate (6)

General Procedure: A solution of the appropriate 1-(2-{[(3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl)methyl]arylamino}-2-oxoethyl)-1,2-triazadien-2-ium[14] (**5**, 10 mmol) in dry acetone (25 mL) was added dimethyl acetylenedicarboxylate (DMAD, 10 mmol). The reaction mixture was refluxed for 12-14h depending on the nature of the azide. The reaction was monitored by tlc for completion. Evaporation of solvent yielded colorless solids that were recrystallised from ethanol.

Dimethyl 1-(2-{[(3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl)methyl]anilino}-2-oxo ethyl)-1H-1,2,3-triazole-4,5-dicarboxylate (6a). Colorless solid, mp 195-197 ^{o}C**,** (74% yield), IR (KBr)**:** 1763(ester CO), 1732 (ester CO), 1681 (quinazolinone CO), 1607 (C=N). ^{1}H NMR(d_6-DMSO): 3.6 (s, 3H, N-CH_3), 3.8 (s, 3H, O-CH_3), 3.9 (s, 3H, O-CH_3), 5.0 (s, 2H, CH_2), 5.3 (s, 2H, CH_2), 7.3-7.5 (m, 4H, Ar-H), 7.6-7.7 (m, 4H, Ar-H), 8.2 (d, 1H, J= 8.2 Hz, periproton). ^{13}C NMR (d_6-DMSO): 29.3, 52.2, 52.3, 52.8, 53.3, 120.3, 126.7, 126.9, 127.4, 128.6, 129.7, 130.4, 130.7, 134.1, 139.9, 146.7, 150.1, 159.1, 160.2, 162.2, 164.3. Mass m/z rel. int (%): 491 ($M^{+\cdot}$+1, 53), 354 (7), 237 (7), 202 (13). Anal. calcd. for $C_{24}H_{23}N_6O_6$: C, 58.65; H, 4.72; N, 17.10; Found: C, 58.29, H, 4.41; N, 16.98.

Dimethyl 1-(2-(4-methyl{[(3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl)methyl] anilino}-2-oxoethyl)-1H-1,2,3-triazole-4,5-dicarboxylate(6b). Colorless solid, mp 168-169 ^{o}C, (79% yield)**,** IR (KBr, cm^{-1})**:** 1740 (ester CO), 1674 (quinazolinone CO), 1599 (C=N). ^{1}H NMR (d_6-

DMSO): 2.4 (s, 3H, Ar-CH_3), 3.6 (s, 3H, N-CH_3), 3.9 (s, 3H, O-CH_3), 3.9 (s, 3H, O-CH_3), 5.0 (s, 2H, CH_2-triazole), 5.3 (s, 2H, CH_2), 7.3-7.7 (m, 7H, Ar-H), 8.1 (d, 1H, J = 8.4 Hz, periproton). ^{13}C NMR (d_6-DMSO): 24.2, 29.8, 52.6, 53.1, 53.4, 53.7, 120.1, 123.2, 124.5, 126.3, 127.2, 128.1, 130.1, 131.2, 132.2, 134.8, 141.1, 146.1, 148.2, 153.1 157.8 160.1, 164.1, 165.1. Mass m/z rel. int (%): 505 ($M^{+\cdot}$+1, 64), 527 (19, $M^{+\cdot}$+23). Anal. calcd. for $C_{25}H_{24}N_6O_6$: C, 59.52; H, 4.80; N, 16.66; Found: C, 59.04, H, 4.81; N, 16.78.

Dimethyl 1-(2-(3-methyl{[(3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl)methyl] anilino}-2-oxoethyl)-1H-1,2,3-triazole-4,5-dicarboxylate (6c). Colorless solid, **m**p 164-165 ^{o}C, (77% yield), **(**IR (KBr)**:** 1734 (ester CO), 1678 (quinazolinone CO), 1607 (C=N). ^{1}H NMR (d_6-DMSO): 2.4 (s, 3H, Ar-CH_3), 3.6 (s, 3H, N-CH_3), 3.9 (s, 3H, O-CH_3), 4.0 (s, 3H, O-CH_3), 5.1 (s, 2H, CH_2-triazole), 5.4 (s, 2H, CH_2), 7.3-7.8 (m, 7H, Ar-H), 8.2 (d, 1H, J = 8.2 Hz, periproton). ^{13}C NMR (d_6-DMSO): 22.1, 29.2, 52.6, 53.5, 54.3, 55.4, 123.1, 124.9, 125.4, 126.6, 128.2, 128.8, 130.1, 131.6, 132.2, 133.2, 134.5, 141.2, 145.1, 147.3, 152.3, 158.2, 161.4, 164.1, 166.1. Mass: m/z rel. int (%): 505 ($M^{+\cdot}$+1, 6), 527 ($M^{+\cdot}$+23, 100). Anal. calcd. for $C_{25}H_{24}N_6O_6$: C, 59.52; H, 4.80; N, 16.66; Found: C, 59.46, H, 4.71; N, 16.89.

Dimethyl 1-(2-(4-chloro{[(3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl)methyl] anilino}-2-oxoethyl)-1H-1,2,3-triazole-4,5-dicarboxylate (6d). Colorless solid, mp 185-187 ^{o}C, (69% yield)**,** IR (KBr)**:** 1731 (ester CO), 1677 (quinazolinone CO), 1603 (C=N), ^{1}H NMR (d_6-DMSO): 3.6 (s, 3H, N-CH_3), 3.8 (s, 3H, O-CH_3), 3.9 (s, 3H, O-CH_3), 5.0 (s, 2H, CH_2-quinazolinone), 5.4 (s, 2H, CH_2-triazole), 7.4-7.8 (m, 7H, Ar-H), 8.2 (d, 1H, J = 7.8 Hz, periproton), ^{13}C NMR (d_6-DMSO): 29.9, 51.2, 52.6, 52.3, 53.4, 119.5, 126.1, 126.7, 126.9, 128.5, 128.9, 129.2, 130.1, 133.8, 134.5, 139.6, 139.4, 146.6, 152.7 157.3, 160.7, 161.4, 164.2. Mass m/z rel. int (%): 525 ($M^{+\cdot}$+1, 100), 527 ($M^{+\cdot}$+2, 35), 547 ($M^{+\cdot}$+23, 6), 74 (10). Anal. calcd. for $C_{24}H_{21}ClN_6O_6$: C, 54.92; H, 4.03; N, 16.01; Found: C, 54.67, H, 4.01; N, 16.12.

Dimethyl 1-(2-(3-chloro{[(3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl)methyl] anilino}-2-oxo ethyl)-1H-1,2,3-triazole-4,5-dicarboxylate (6e). Colorless solid, mp 182-183 ^{o}C, (73% yield), IR (KBr)**:** 1740 (ester CO), 1675 (quinazolinone CO), 1599 (C=N), ^{1}H NMR (d_6-DMSO): 3.6 (s, 3H, N-CH_3), 3.8 (s, 3H, O-CH_3), 3.9 (s, 3H, O-CH_3), 5.1 (s, 2H, CH_2-quinazolinone), 5.4 (s, 2H, CH_2-triazole), 7.5-7.8 (m, 7H, Ar-H), 8.2 (d, 1H, J = 7.2 Hz, periproton). ^{13}C NMR (d_6-DMSO): 27.8, 50.2, 51.5, 52.6, 53.2, 118.4, 125.3, 126.4, 126.8, 127.7, 128.7, 129.3, 130.2, 131.6, 134.7, 138.6, 139.8, 145.4, 152.6, 157.6, 160.6, 162.2, 164.8. Mass m/z rel. int (%): 525 ($M^{+\cdot}$+1, 100), 527.3 ($M^{+\cdot}$+2, 33), 74 (10). Anal. calcd. for $C_{24}H_{21}ClN_6O_6$: C, 54.92; H, 4.03; N, 16.01; Found: C, 54.72, H, 3.97; N, 16.28.

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