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N-Alkylation and Aminohydroxylation of 2-Azidobenzenesulfonamide Gives a Pyrrolobenzothiadiazepine Precursor Whereas Attempted N-Alkylation of 2-Azidobenzamide Gives Benzotriazinones and Quinazolinones

Muslih S. Hamasharif, Oliver E. P. Smith, Collette J. Curran, and Karl Hemming*

Department of Chemistry, University of Huddersfield, Queensgate, Huddersfield, West Yorkshire HD1 3DH, United Kingdom

ABSTRACT: N-Alkylation of 2-azidobenzenesulfonamide with 5-bromopent-1-ene gave an N-(pentenyl) sulfonamide, which underwent intramolecular aminohydroxylation to give an N-(2-azidoaryl)sulfonyl prolinol, a precursor for the synthesis of a pyrrolobenzothiadiazepine. The attempted N-alkylation of 2-azidobenzamide gave a separable mixture (~1:1) of a benzotriazinone and a quinazolinone in a 72% combined yield. Other primary alkyl halides (3 examples) gave similar mixtures of benzotriazinones and quinazolinones. Benzylic, allylic, and secondary and tertiary alkyl halides (5 examples) gave only benzotriazinones in moderate yields. The results of mechanistic studies show the likely involvement of nitrene intermediates in the quinazolinone pathway and a second pathway involving a dimethylsulfoxide- or dimethylsulfoxide-mediated conversion of 2-azidobenzamide into benzotriazinones.

INTRODUCTION

Pyrrolo[2,1-c][1,4]benzodiazepines (PBDs) 1 are a class of natural products that have attracted a great deal of interest because of their ability to function as sequence-selective DNA-interacting molecules. PBD derivatives have entered phase II clinical trials as antitumor compounds and have also attracted attention as antibiotics with a novel mode of action. Pyrrolo[1,2-b][1,2,5]benzothiadiazepines (PBTDs) 2 are attracting interest as PBD analogues, non-nucleoside reverse transcriptase inhibitors, antischistosomals, and Glut-1 transporter inhibitors and are emerging as a potential treatment for chronic leukemia (compound 4).

Almost all approaches toward the synthesis of PBDs and PBTDs use l-proline-derived starting materials, meaning that the de novo synthesis of the pyrrolidine ring is a rare approach to the PBDs and a very rare approach to the PBTDs. Metathesis, intramolecular lactam formation, reductive cyclization, cyclization—elimination, and ring contraction of 1,2-thiazines are approaches to the PBDs that involve five-membered ring construction. Only the latter has been applied for the synthesis of PBTDs. With this in mind, we became interested in using intramolecular aminohydroxylation to construct a functionalized pyrrolidine derivative, which would then act as a precursor to the PBTDs or PBDs. Intramolecular aminohydroxylation of alkenes is an area of recent interest in heterocyclic synthesis and has been used to access simple prolinol derivatives. Using this, our initial hypothesis (Figure 1) was that the N-(pent-4-en-1-yl)-azidobenzenesulfonamide 5 and N-(pent-4-en-1-yl)azidobenzamide 6 would undergo aminohydroxylation to yield N-arylazido-substituted prolinols 7 and 8, respectively, which could then be used to synthesize PBDs and PBTDs.

RESULTS AND DISCUSSION

We synthesized N-(pent-4-en-1-yl)benzenesulfonamide 5 from the reaction of 2-azidobenzenesulfonamide 9 with 5-bromopentene (21%) or from the reaction of 2-azidobenzenesulfonyl chloride 10 with pent-4-en-1-amine (63%), as shown in Scheme 1. Pent-4-en-1-amine was synthesized from 5-
chloride was prepared in two steps from anthranilic acid\textsuperscript{26–28} and converted into secondary amide 6 by reaction with pent-4-en-1-amine.\textsuperscript{23} Attempted intramolecular aminohydroxylation failed to deliver the desired N-arylazido substituted 8. As shown in Scheme 4, we also attempted to form compound 6 by the reaction of 2-azidobenzamide 20 with 5-bromopentene 19 in DMSO in the presence of a base, a reaction that had worked with 2-azidobenzensulfonamide (Scheme 1). This did not produce N-(pent-4-en-1-yl)benzamide 6 but instead led to some unexpected results (also shown in Scheme 4). Thus, under a variety of conditions, we observed the formation of a mixture of benzotriazinone 21 and quinazolinone 22. The use of anhydrous DMSO as the solvent, sodium carbonate as the base, and a temperature of 95 °C allowed an optimized combined yield of 72\% (isolated yields of 39\% for compound 21 and 33\% for compound 22) with 4% recovery of the starting material 20 and the formation of 15\% of the reduced product, 2-aminobenzamide 23.

We decided to explore this process in more detail (Scheme 5) with respect to the substrate scope of the organohalide. The reaction of 2-azidobenzamide with 4-bromobutene gave benzotriazinone 26 (35\%) and quinazolinone 24 (29\%), whereby the expected quinazolinone 25 underwent a facile double-bond migration to give conjugated 24. The recovered starting material 20 (8\%) and 2-aminobenzamide 23 (14\%) were also present and were also formed in all other reactions shown in Scheme 5. 1-Bromobutane and 1-bromopropane gave benzotriazinones 27 and 28, respectively, again as mixtures with the respective quinazolinones. Benzyl bromide, 2-bromopropane, and bromocyclohexane did not form quinazolinones, giving only benzotriazinones 29–31, respectively. 2-Bromo-2-methylpropane behaved unexpectedly and gave benzotriazinone 32 in a 30\% yield, a reaction that is discussed later. The identical benzotriazinone 32 was formed in a 36\% yield from the reaction of 2-azidobenzamide with 3-bromo-2-methylprop-1-ene. Attempts to optimize these reactions further were unsuccessful: other solvents (see below) did not react; other bases (Et₃N, DBU, DABCO, and pyridine) and/or reduced temperatures gave reduced yields; and increased temperatures gave increased degradation resulting in reduced yields of benzotriazinones and quinazolinones, together with higher yields of the reduced product 2-aminobenzamide 23. (Bromomethylene)dibenzene was unreactive toward the azide but was converted into benzophenone 33, whereas trityl bromide was unreactive and furnished triphenyl methanol 34.

Scheme 6 shows our suggested mechanism for the formation of quinazolinones. We consider that nitrene addition occurred spontaneously to furnish the racemic PBTD Bestmann (96\%), which was converted into alkyne 16 using the Bestmann–Ohira reagent 18. Intramolecular 1,3-dipolar cycloaddition occurred spontaneously to furnish the racemic PBTD derivative 3 in a 70% yield from aldehyde 16.

With a successful PBTD system in hand (Figure 1, X = SO₂), we next attempted to synthesize the analogous PBD system using the same approach (Figure 1, X = CO). 2-Azidobenzoyl bromopentene.\textsuperscript{23} The sulfonyl chloride 10 was synthesized using diazotization and azidation of 2-aminobenzensulfonic acid 11 followed by the treatment of 2-azidobenzensulfonic acid 12 with thionyl chloride.\textsuperscript{10,24} 2-Azidobenzensulfonamide 9 was synthesized by reacting the sulfonyl chloride 10 with ammonia or from the diazotization and azidation of 2-aminobenzensulfonic acid 13 via the sulfonamide 14.\textsuperscript{10,24}

For the intramolecular aminohydroxylation, we found that Oxone in the presence of tosic acid as an electrophilic oxidant, as reported previously by Togo\textsuperscript{20} for nonazido substrates, worked well for our azido substrate using the same approach (Figure 1, X = CO). 2-Azidobenzoyl

an 83–95\% yield. As far as we are aware, this is the first reported example of such a reaction having been performed with an azide group present.

In our previous studies,\textsuperscript{10,25} we reported the synthesis of the Glut-1 transporter-inhibiting triazolo-PBTD as a single enantiomer from the enantiopure version of alcohol 7 (Scheme 2) was produced over repeated attempts in an 83–95\% yield. As far as we are aware, this is the first reported example of such a reaction having been performed with an azide group present.

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with the alkyl halide to form intermediate 36 (path A1), which undergoes hydrogen radical extrusion to form imine 37. Cyclization gives the dihydroquinazoline species 38, and loss of hydrogen would form the final quinazolinone. This pathway also explains the formation of 2-aminobenzamide due to nitrene 35 abstracting hydrogen from the reaction medium (path A2). Generation of nitrenes from aryl azides in solvents at temperatures below 100 °C 29,30 including DMSO 31 is known. There is an alternative route whereby nitrene formation is preceded by N-alkylation of the amide nitrogen to give compound 6 (see earlier for structure and synthesis). However, we saw no evidence for the formation of compound 6 using thin-layer chromatography (TLC). Compound 6 also failed to give quinazolinones under our reaction conditions. Quinazolinones are important and well-known heterocycles 32–36 that are synthesized by a variety of routes including an iron-catalyzed intramolecular C–N bond formation from N,N-disubstituted 2-azidobenzamides 36 and from dihydroquinazolinones formed from 2-aminobenzamides and aldehydes using DMSO as a mild oxidant, 37,38 providing some precedent for our suggested mechanism. We speculated that our process may occur via the formation of 2-aminobenzamide 23 from the azide and subsequent reaction with the alkyl halide to give intermediate 39, which could then form species 36. However, when 2-aminobenzamide was used as the starting material in the place of 2-azidobenzamide, the reaction was not seen. We also thought it was possible that DMSO could generate an aldehyde from the alkyl halide and that this aldehyde was reacting with either starting material 20 or with 2-aminobenzamide 23 (paths B and A2b in Scheme 6). We exclude these two paths because (i) the introduction of the relevant aldehyde into the system had no influence and (ii) our reaction was very sensitive to water (anhydrous DMSO was necessary) and the paths B and A2b both generate water. Path B also supposes the formation of an N-acyl imine by the reaction of 2-azidobenzamide with an aldehyde, a conversion that we have been unable to achieve. Thus, it appears that 2-azidobenzamide 20 forms nitrene 35 under our reaction conditions and goes on to form quinazolinones via path A1 and 2-aminobenzamide 23 via path A2. The secondary amide 6 did not react in this way. Interestingly, when we subjected a tertiary amide, compound 40 (Scheme 7), to the same reaction conditions, we isolated the disubstituted dihydroquinazolinone 41, in line with the literature precedent for tertiary amides. 36

Scheme 8 shows our mechanism for the formation of benzotriazinones 26–32. 3-Substituted 1,2,3-benzotriazin-4-ones are useful targets in medicinal chemistry 39–41 and as synthetic intermediates. 42,43 The most common route to 3-substituted 1,2,3-benzotriazin-4-ones is diazotization of the relevant N-substituted anthranilamide. 39–41 For our mechanism, we suggest that compound 42 (Scheme 8) is an intermediate. When this readily available 44 compound was used as the starting material in our reaction, the same benzotriazinones could be isolated. N-Alkylation of benzotriazinone 42 is a known route to N-alkyl benzotriazinones. 45 2-Azidobenzamide 20 has an azide group, which can be stabilized by an intramolecular hydrogen bond that renders the azide susceptible to nucleophilic attack followed by alkylation.
processes have precedent in azide chemistry.\textsuperscript{46–49} Loss of the azide terminal nitrogen is then facilitated, allowing the formation of a diazonium species, which can cyclize to give intermediate 42. As discussed previously, we were able to isolate significant quantities of benzophenone 33 from the reaction mixture when (bromomethylene)dibenzene was used as the alkyl halide. We also isolated triphenyl methanol when (bromomethylene)dibenzene was used.

![Scheme 8. Proposed Mechanism for Benzotriazinone Formation](image)

\[ \text{Me}^+ \text{SMe} \text{Br} \rightarrow \text{Me}^+ \text{SMe} \text{Br}^- \rightarrow \text{Me}^+ \text{SMe} \text{Br}^- \]

\[ \text{Me}^+ \text{SMe} \text{Br}^- + \text{RBr} \rightarrow \text{Me}^+ \text{SMe} \text{R}^- + \text{HBr} \]

* where, for example:

\[ \text{Me}^+ \text{SMe} \text{R}^- + \text{Nu} \rightarrow \text{Me}^+ \text{SMe} \text{Nu}^- + \text{R}^- \]

and elimination would generate 2-methylpropene, a process that has precedent.\textsuperscript{51,52} The interception of a free radical species by benzotriazinone 42 would generate the free radical intermediate 43, which could then react with 2-methylpropene to form intermediate 44, which would yield benzotriazinone 32 after the loss of a hydrogen radical.

**CONCLUSIONS**

A new approach to the synthesis of pyrrolobenzothiadiazepine nucleus has been presented that relies upon the formation of a racemic proline derivative using the previously unreported intramolecular aminohydroxylation of an N-alkylated 2-azidobenzenesulfonamide. We are currently working to expand the scope of this process by applying it to other N-alkylated 2-azidobenzenesulfonamide substrates. Attempts to form the corresponding N-alkylated 2-azidobenzenamides led to mixtures of benzotriazinones and benzoquinazolines, which were formed from an unusual process that allowed us to hypothesize a nitrene-based pathway to the benzoquinazolines and a pathway to the benzotriazinones that involves the conversion of an azide into a diazonium via nucleophilic attack on the azide. Our work offers some useful and interesting mechanistic insights into organoazide chemistry and organosulfur chemistry.

**EXPERIMENTAL SECTION**

Compounds (9) to (15)\textsuperscript{10,24,53} and (20)\textsuperscript{24,27,28} were synthesized as described in the literature. The methods that we used to access racemic (16) and (3) are methods that we developed previously to produce enantiopure (16) and (3).\textsuperscript{10,25} Enantiopure compound (7) is also known but was previously accessed using chemistry different from the new method that is reported for racemic (7) below. The synthesis of benzotriazinones (28),\textsuperscript{34} (29),\textsuperscript{44} and (30)\textsuperscript{44} have been reported previously but with no data and via a different route. Other routes to 2-ethylquinazolin-4(3H)-one,\textsuperscript{54} 2-propylquinazolin-4(3H)-one,\textsuperscript{55} and 2-(1’-propen-1-yl)quinazoline (24)\textsuperscript{16} have been reported.

**2-Azido-N-(pent-4-en-1-yl)benzamide (6)**, 2-Azidobenzoic acid (717 mg, 4.4 mmol) was heated at reflux in a 2 M solution of (COCl), in dichloromethane (5.0 mL, 10.0 mmol) with a drop of DMF under an inert atmosphere of nitrogen for 5 h. The reaction mixture was stirred at room temperature. The crude acid chloride was concentrated, and the residue was washed with dichloromethane (2 × 20 mL) to give crude 2-azidobenzoyl chloride as a brown solid. One portion of a solution of potassium carbonate (1.10 g, 8.00 mmol) in water (10 mL) was added to the stirred solution of 5-aminopent-4-ene (170 mg, 2.0 mmol) in dichloromethane (10 mL). 2-Azidobenzoyl chloride was dissolved in dichloromethane (2 × 20 mL) to give crude 2-azidobenzoyl chloride as a brown solid. One portion of a solution of potassium carbonate (1.10 g, 8.00 mmol) in water (10 mL) was added to the stirred solution of 5-aminopent-4-ene (170 mg, 2.0 mmol) in dichloromethane (10 mL). 2-Azidobenzoyl chloride was dissolved in dichloromethane (5 mL) and was added slowly to this solution. The reaction mixture was stirred at room temperature for 18 h before the organic layer was separated, and the aqueous layer was washed with dichloromethane (2 × 20 mL). The combined organic phases were dried (MgSO4), filtered, concentrated, and purified using silica column chromatography (petroleum ether/ethyl acetate 1:4). The product was obtained as a white solid (320 mg, 72%). IR (neat, ν\textsubscript{max}) cm\textsuperscript{-1}: 1164, 1294, 1445, 1480, 1536, 1577, 1638, 1712, 2125, 2864, 2930, 3076, 3294. 1H NMR (400 MHz, CDCl3): δ 1.66 (2H, tt, J = 7.4, 7.4 Hz, −CH2−CH=CH2−), 2.09 (2H, dt, J = 7.4, 7.8 Hz, CH=CH−CH2−), 3.37−3.42 (2H, m, NHCH2), 4.88−4.97 (2H, m, CH−CH2−), 5.72−5.82 (1H, m, CH=N=CH2−), 7.10 (1H, dd, J = 7.8 Hz, J′ = 0.8 Hz, ArH), 7.14 (1H, dd, J = 7.8 Hz, J′ = 7.4 Hz, J′ = 7.4 Hz, J′ = 1.6 Hz, ArH), 7.39−7.41 (2H, m, NH + ArH), 8.04 (1H, dd, J = 7.8 Hz, J′ = 1.6 Hz, ArH).13C NMR (100 MHz, CDCl3): δ 28.64 (CH3), 31.25 (CH3), 39.54 (CH2), 115.22 (CH=CH2), 118.37 (CH), 125.17 (CH), 125.26 (qC), 132.17 (CH), 132.19 (CH), 136.82 (qC), 137.79 (CH), 164.58 (C=...
The reaction was quenched with a mixture of diethyl ether (5 mL = 7.8, 7.7, 1.3 Hz, Ar) and alcohol (0.015 mmol). The whole mixture was heated at reflux temperature for 12 h, while being monitored using TLC. To this solution, saturated aqueous NaHCO₃ solution (15 mL) was added, and the product was extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with brine (15 mL) and dried over anhydrous MgSO₄, and the solvent was removed under vacuum. Purification using silica chromatography (eluent: petroleum ether/ethyl acetate 1:10, Rf = 0.2) yielded the product as a yellow oil (20 mg, 20% yield) as a yellow oil (20 mg, 95%). IR (neat, νmax) cm⁻¹: 2870, 2992, 3108. 1H NMR (400 MHz, CDCl₃): δ 1.52 – 1.72 (2H, t, J = 7.1, 1.3 Hz, CH₂), 2.00 (2H, dt, J = 7.1, 1.3 Hz, CH₂), 2.83 (2H, dt, J = 6.8, 1.3 Hz, CH₂), 4.88 – 4.96 (3H, N – H = CH₂), 5.59 – 5.70 (1H, m = CH), 7.18 – 7.23 (2H, m, Ar). Residue was filtered, and concentrated in vacuo to yield an orange solid. The reaction was quenched with saturated aqueous ammonium chloride (10 mL). The organic phase was separated, and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried (MgSO₄), filtered, and concentrated in vacuo to yield an orange solid. Purification using thin layer chromatography (eluent: petroleum ether/ethyl acetate 1:3, Rf = 0.22) yielded the product as a yellow solid (207 mg, 70%, mp = 208 – 210 °C). Crude yield was 287.0754 mg [M + Na]⁺. C₁₃H₁₄N₂O₄S requires 287.0703.

**Pyrrrolo[1,2-b][1,2,3]triazolo[5,1-d][1,2,5]benzothiadiazepine, 8,8-dioxide (3).** Aldehyde (16) (300 mg, 1.07 mmol) was dissolved in dry methanol (5 mL); potassium carbonate (296 mg, 2.14 mmol) and the Bestmann–Ohira reagent (209 µL, 247 mg, 1.29 mmol) were added, and the whole mixture was stirred for 22 h under nitrogen. The reaction was quenched with saturated aqueous ammonium chloride (10 mL). The organic phase was separated, and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried (MgSO₄), filtered, and concentrated in vacuo to yield an orange solid. Purification using silica chromatography (eluent: petroleum ether/ethyl acetate 1:3, Rf = 0.22) yielded the product as a yellow solid (207 mg, 70%, mp = 208 – 210 °C). Crude yield was 287.0754 mg [M + Na]⁺. C₁₃H₁₄N₂O₄S requires 287.0703.
3-Butylbenzo[d][1,2,3]triazin-4(3H)-one (27) and 2-(1′-Propen-1′-yl)-quinazoline-4(3H)-one (24) To a solution of 2-azidobenzamide (200 mg, 1.23 mmol) and sodium carbonate (392 mg, 3.70 mmol) in anhydrous DMSO (10 mL), 1-bromobutane (338 mg, 2.47 mmol) was added. The solution was heated at 95 °C for 48 h under a nitrogen atmosphere, and after completion of the reaction, which was monitored using TLC, the resultant mixture was diluted with dichloromethane (30 mL) and washed with 0.1 M NaCl and water many times to remove DMSO. The mixture was dried with anhydrous magnesium sulfate and filtered under vacuum, and the solvent was removed under vacuum. The residue was purified using column chromatography to give 3-butylbenzo[d][1,2,3]triazin-4(3H)-one (27) (eluent: petroleum ether/ethyl acetate 4:1, Rf = 0.21) as a light yellow oil (85% mg, 35%). IR (neat, v_max) cm⁻¹: 1043, 1105, 1165, 1280, 1296, 1346, 1668, 1602, 1681, 2840, 2954, 3075. ¹H NMR (400 MHz, CDCl₃): δ 2.61 (2H, d, f = 7.1, 7.1 Hz, CH₂), 4.47 (2H, t, j = 7.1 Hz, CH₂), 4.95–5.00 (2H, m, =CH₂), 5.71–5.84 (1H, m, =CH), 7.72 (1H, dd, J = 7.7 Hz, J = 7.4 Hz, ArH), 8.76 (1H, dd, J = 8.1 Hz, J = 8.0 Hz, ArH), 8.06 (1H, d, J = 8.1 Hz, ArH), 8.27 (1H, d, J = 7.7 Hz, ArH). ¹³C NMR (100 MHz, CDCl₃): δ 33.15 (CH₂), 49.03 (CH₃), 117.78 (CH₂), 119.77 (qC), 125.07 (CH), 128.24 (CH), 132.27 (CH), 133.97 (CH), 134.73 (CH), 144.27 (qC), 155.50 (C═O) ppm. HRMS (ESI⁺) m/z: found 202.0970 [M + H⁺], C₁₂H₁₃N₂O requires 202.0975. Also isolated was 2-(1′-propen-1′-yl)-quinazoline-4(3H)-one (24) (eluent: petroleum ether/ethyl acetate 1:1, Rf = 0.29) as a yellow solid (65 mg, 29%, mp = 167–169 °C). IR (neat, v_max) cm⁻¹: 1105, 1144, 1252, 1296, 1343, 1468, 1562, 1607, 1659, 2924, 3003, 3182. ¹H NMR (400 MHz, CDCl₃): δ 2.08 (3H, dd, J = 6.8 Hz, f = 1.1 Hz, CH₃), 6.40 (1H, dd, J = 15.9 Hz, J = 1.3 Hz, =CH), 7.19–7.26 (1H, m, =CH), 7.47 (1H, dd, J = 7.6 Hz, J = 7.3 Hz, ArH), 7.72 (1H, d, J = 7.8 Hz, ArH), 7.80 (1H, dd, J = 7.8 Hz, J = 7.6 Hz, ArH), 8.30 (1H, d, J = 7.6 Hz, ArH), 11.98 (1H, s, NH). ¹³C NMR (100 MHz, CDCl₃): δ 18.77 (CH₃), 120.75 (qC), 125.32 (CH), 126.28 (CH), 126.36 (CH), 127.51 (CH), 134.83 (CH), 138.47 (CH), 149.67 (qC), 150.89 (qC), 164.12 (C═O). HRMS (ESI⁺) m/z: found 187.0860 [M + H⁺], C₁₀H₁₃N₂O requires 187.0793. The data recorded for compound (24) are consistent with those published elsewhere.⁵⁰

3-Butylbenzo[d][1,2,3]triazin-4(3H)-one (27) and 2-Propylquinazolin-4(3H)-one. To a solution of 2-azidobenzamide (200 mg, 1.23 mmol) and sodium carbonate (392 mg, 3.70 mmol) in anhydrous DMSO (10 mL), 1-bromobutane (338 mg, 2.47 mmol) was added. The solution was heated at 95 °C for 48 h under a nitrogen atmosphere, and after completion of the reaction, which was monitored using TLC, the resultant mixture was diluted with dichloromethane (30 mL) and washed with 0.1 M NaCl and water many times to remove DMSO. The mixture was dried with anhydrous magnesium sulfate and filtered under vacuum, and the solvent was removed under vacuum. The residue was purified using column chromatography to give 3-butylbenzo[d][1,2,3]triazin-4(3H)-one (27) (eluent: petroleum ether/ethyl acetate 4:1, Rf = 0.2) as a light yellow oil (92 mg, 37%). IR (neat, v_max) cm⁻¹: 1032, 1164, 1294, 1320, 1380, 1429, 1463, 1607, 1678, 2873, 2960. ¹H NMR (400 MHz, CDCl₃): δ 0.91 (3H, t, J = 7.4 Hz, CH₂), 1.37 (2H, app. sextet, J = 7.6 Hz, CH₂), 1.86 (2H, app. pentet, J = 7.5 Hz, CH₂), 4.40 (2H, t, J = 7.1 Hz, CH₂), 7.71 (1H, d, J = 7.9 Hz), 7.52 (1H, d, J = 7.5 Hz, ArH), 7.86 (1H, dd, J = 7.9 Hz, J = 7.5 Hz, ArH), 8.07 (1H, d, J = 8.1 Hz, ArH), 8.28 (1H, d, J = 8.1 Hz, ArH). ¹³C NMR (100 MHz, CDCl₃): δ 13.66 (CH₃), 19.89 (CH₂), 50.94 (CH₂), 46.97 (CH), 119.33 (qC), 125.05 (CH), 128.18 (CH), 132.20 (CH), 134.66 (CH), 144.33 (qC), 155.50 (C═O). HRMS (ESI⁺) m/z: found 204.1127 [M + H⁺], C₁₂H₁₄N₂O requires 204.1131. Also formed was 2-propylquinazolin-4(3H)-one (eluent: petroleum ether/ethyl acetate 1:1, Rf = 0.22) as a light yellow oil (~20% by NMR), which could not be obtained free of 2-amino benzamide. IR (neat, v_max) cm⁻¹: 1082, 1161, 1265, 1293, 1394, 1449, 1478, 1565, 1615, 1650, 2926, 3173. ¹H NMR (400 MHz, CDCl₃): δ 0.98 (3H, t, J = 7.5 Hz, CH₂), 1.69 (2H, app. sextet, J = 7.4 Hz, CH₂), 2.68 (2H, t, J = 7.8 Hz, CH₂), 3.77 (1H, dd, J = 8.0 Hz, J = 7.0 Hz, HAr), 6.71 (1H, d, J = 8.0 Hz, HAr), 7.68 (1H, dd, J = 8.0 Hz, J = 7.0 Hz, HAr), 8.17 (1H, d, J = 8.0 Hz, HAr), 11.12 (1H, s, NH). ¹³C NMR (100 MHz, CDCl₃): δ 18.37 (CH₃), 40.47 (CH₂), 121.46 (qC), 122.46 (CH), 125.18 (CH), 127.35 (CH), 132.96 (CH), 149.47 (qC), 157.17 (qC), 164.25 (C═O). HRMS (ESI⁺) m/z: found 189.1023 [M + H⁺], C₁₂H₁₄N₂O requires 189.1022. The data recorded for 2-propylquinazolin-4(3H)-one are consistent with those published elsewhere.⁵⁰
128.20 (CH), 132.21 (CH), 134.68 (CH), 144.33 (qC), 155.54 (C=O). HRMS (ESI) m/z: found 190.0973 [M + H]+, C8H12N2O requires 190.0975. Also present was 2-ethylquinazolin-4-one (eluent: petroleum ether/ethyl acetate 1:1, Rf = 0.28) as a light yellow solid (23% by NMR), which could not be obtained free of 2-aminobenzamide. IR (neat, νmax) cm⁻¹: 1139, 1201, 1251, 1341, 1373, 1467, 1504, 1608, 1619, 1674, 2835, 2922, 3044, 3163. ¹H NMR (400 MHz, CDCl₃): δ 1.17–1.38 (2H, m, CH₂), 2.78 (2H, d, J = 6.9 Hz, CH₂), 7.18 (1H, bs, ArH), 7.38–7.40 (1H, m, ArH), 7.64–7.68 (2H, m, 2 × ArH), 8.22 (1H, d, J = 6.8 Hz, ArH), 12.17 (1H, s, NH). ¹³C NMR (100 MHz, CDCl₃): δ 11.57 (CH₃), 29.71 (CH₃), 120.50 (qC), 126.23 (CH), 126.33 (CH), 127.22 (CH), 134.78 (CH), 149.54 (qC), 156.78 (qC), 164.57 (C=O). HRMS (ESI) m/z: found 175.0869 [M + H]+, C₁₀H₁₂N₂O requires 175.0866. The data recorded for 2-ethylquinazolin-4(3H)-one are consistent with those published elsewhere.⁵⁵

3-Benzylbenzod[1,2,3]triazin-4-one (29). To a solution of 2-azidobenzamide (200 mg, 1.23 mmol) and sodium carbonate (392 mg, 3.70 mmol) in anhydrous DMSO (10 mL), benzyl bromide (422 mg, 2.47 mmol) was added. The solution was heated at 95 °C for 48 h under a nitrogen atmosphere, and after completion of the reaction, which was monitored using TLC, the resultant mixture was diluted with dichloromethane (30 mL) and washed with 0.1 M NaCl and water many times to remove DMSO. The mixture was dried with anhydrous magnesium sulfate and filtered under gravity, and the solvent was removed under vacuum. The residue was purified using column chromatography (eluent: petroleum ether/ethyl acetate 4:1, Rf = 0.2) to yield the product as a light yellow solid (85 mg, 30%, mp = 137–139 °C). IR (neat, νmax) cm⁻¹: 1046, 1164, 1161, 1181, 1221, 1267, 1292, 1331, 1376, 1460, 1607, 1681, 2851, 2928, 3073. ¹H NMR (400 MHz, CDCl₃): δ 1.17–1.38 (1H, m, CH₂), 1.39–1.50 (2H, m, CH₂), 1.68–2.72 (1H, m, CH), 1.86–2.01 (6H, m, 3 × ArH), 4.96 (1H, p, J = 7.6 Hz, CH), 7.70 (1H, dd, J₁ = 8.0 Hz, J₂ = 7.3 Hz, ArH), 7.85 (1H, ddd, J₁ = 8.1 Hz, J₂ = 8.0 Hz, J₃ = 1.1 Hz, ArH), 8.06 (1H, d, J = 8.0 Hz, ArH), 8.28 (1H, d, J = 8.1 Hz, ArH). ¹³C NMR (100 MHz, CDCl₃): δ 32.59 (CH₃), 25.80 (2 × CH₃), 56.64 (2 × CH₂), 119.60 (qC), 123.01 (qC), 125.27 (CH), 128.02 (CH), 132.00 (CH), 134.62 (CH), 134.88 (qC), 155.12 (C=O). HRMS (ESI) m/z: found 230.1285 [M + H]+, C₁₂H₁₀N₂O requires 230.1288.

3-(2-Methylallyl)benzod[1,2,3]triazin-4-one (30). To a solution of 2-azidobenzamide (200 mg, 1.23 mmol) and sodium carbonate (392 mg, 3.70 mmol) in anhydrous DMSO (10 mL), 3-bromo-2-methylpropene (333 mg, 2.47 mmol) was added. The solution was heated at 95 °C for 48 h under a nitrogen atmosphere, and after completion of the reaction, which was monitored using TLC, the resultant mixture was diluted with dichloromethane (30 mL) and washed with 0.1 M NaCl and water many times to remove DMSO. The mixture was dried with anhydrous magnesium sulfate and filtered under gravity, and the solvent was removed under vacuum. The residue was purified using column chromatography (eluent: petroleum ether/ethyl acetate 4:1, Rf = 0.21) to yield the product as a light orange solid (90 mg, 36%, mp = 69–71 °C). IR (neat, νmax) cm⁻¹: 1089, 1153, 1223, 1276, 1297, 1333, 1463, 1580, 1609, 1684, 2930, 2973, 3083. ¹H NMR (400 MHz, CDCl₃): δ 1.84 (3H, s, CH₃), 4.85 (1H, s, ≈CH(CH₃)), 5.00 (H, s, ≈CH₂), 5.03 (2H, s, CH₂), 7.83 (1H, ddd, J₁ = 8.1 Hz, J₂ = 8.0 Hz, J₃ = 1.1 Hz, ArH), 7.97 (1H, ddd, J₁ = 8.1 Hz, J₂ = 8.0 Hz, J₃ = 1.1 Hz, ArH), 8.18 (1H, d, J = 8.1 Hz, ArH), 8.38 (1H, dd, J₁ = 8.1 Hz, J₂ = 1.0 Hz, ArH). ¹³C NMR (100 MHz, CDCl₃): δ 20.45 (CH₃), 54.77 (CH₂), 113.54 (CH₃), 119.88 (qC), 125.22 (CH), 128.33 (CH), 132.38 (CH), 134.84 (CH), 139.51 (qC), 144.29 (qC), 155.43 (C=O). HRMS (ESI) m/z: found 202.0975 [M + H]+, C₁₁H₁₂N₂O requires 202.0975.

3-(2-Methylyl)benzod[1,2,3]triazin-4-one (31). To a solution of 2-azidobenzamide (250 mg, 1.54 mmol) and sodium carbonate (490 mg, 4.63 mmol) in anhydrous DMSO (15 mL), 2-bromo-2-methylpropane (425 mg, 3.10 mmol) was added. The solution was heated at 95 °C for 48 h under a nitrogen atmosphere, and the resultant mixture was diluted with dichloromethane (50 mL) and washed with 0.1 M NaCl
and water many times to remove DMSO. The mixture was dried with anhydrous magnesium sulfate and filtered under gravity, and the solvent was removed under vacuum. The residue was purified using column chromatography (eluent: petroleum ether/ethyl acetate 4:1, Rf = 0.21) to yield the product as a light yellow oil (94 mg, 30%) with identical spectroscopic data to those reported above.

2-Azido-N,N-dibutylbenzamide (40). 2-Azobenzamide (98 mg, 0.60 mmol), KOH (50 mg, 0.90 mmol), and TBAB (58 mg, 0.18 mmol) were mixed and stirred for 15 min at room temperature, and then, 1-bromobutane (102 mg, 0.75 mmol) was added. The mixture was heated at 80 °C in an oil bath for 15 min. The crude mixture was diluted with water (10 mL) and then extracted with dichloromethane (3 × 10 mL). The organic layer was dried with anhydrous magnesium sulfate and filtered, and the solvent was removed in vacuo. Purification using silica chromatography (eluent: petroleum ether/ethyl acetate 2:1, Rf = 0.25) yielded the product as a yellow oil (115 mg, 70%). IR (neat, νmax cm−1): 1081, 1118, 1201, 1425, 1444, 1577, 1598, 1633, 2091, 2873, 2931, 2957. 1H NMR (400 MHz, CDCl3): δ 6.58 (3H, t, J = 7.3 Hz, CH3), 1.04 (2H, app. Sextet, J = 7.6 Hz, CH2), 2.96–2.98 (2H, m, CH2), 3.24 (1H, br s, CHH), 3.54 (1H, br s, CHH), 7.06–7.14 (3H, m, 3 × ArH), 7.31 (1H, ddd, J1 = 8.2 Hz, J2 = 8.0 Hz, J3 = 1.4 Hz, ArH). 13C NMR (100 MHz, CDCl3): δ 13.56 (CH3), 13.93 (CH3), 19.70 (CH3), 20.25 (CH2), 29.51 (CH2), 30.55 (CH2), 44.22 (CH2), 48.18 (CH2), 118.41 (CH), 124.93 (CH), 127.87 (CH), 129.44 (qC), 129.95 (CH), 136.17 (qC), 168.19 (C=O). HRMS (ESI+) m/z: found 275.1860 [M + H]+, C16H13N3O requires 275.1866.

3-Butyl-2-propyl-2,3-dihydroquinazolin-4-one (41). To a solution of 2-azido-N,N-dibutylbenzamide (98 mg, 0.36 mmol) and sodium carbonate (114 mg, 1.07 mmol) in anhydrous DMSO (8 mL), 2-bromopropane (88 mg, 67 μL, 0.72 mmol) was added. The solution was heated at 95 °C for 15 min. The crude mixture was diluted with water (10 mL) and washed with 0.1 M NaCl and water many times to remove DMSO. The mixture was dried with anhydrous magnesium sulfate and filtered under gravity, and the solvent was removed under vacuum. The residue was purified using column chromatography (eluent: petroleum ether/ethyl acetate 2:1, Rf = 0.21) to yield the product as a yellow oil (55 mg, 63%). IR (neat, νmax cm−1): 1028, 1153, 1169, 1322, 1464, 1509, 1580, 1610, 2872, 2930, 2957, 3284. 1H NMR (400 MHz, CDCl3): δ 0.84 (6H, 2 × CH3, J = 7.2 Hz, 2 × CH2), 1.15–1.24 (1H, m, CHH), 1.29–1.36 (3H, m, CH3 + CHH), 1.50–1.59 (3H, m, CH2 + CHH), 1.74–1.84 (1H, m, CHH), 2.76 (1H, dd, J = 13.7, 7.5 Hz, NCHH), 4.48–4.50 (2H, m, CH + NH), 6.55 (1H, d, J = 8.0 Hz, ArH), 7.65 (1H, ddd, J1 = 7.6 Hz, J2 = 7.6 Hz, J3 = 1.2 Hz, ArH), 7.16–7.20 (1H, m, ArH), 7.81 (1H, dd, J1 = 7.8 Hz, J2 = 1.2 Hz, ArH). 13C NMR (100 MHz, CDCl3): δ 13.68 (CH3), 13.89 (CH3), 18.64 (CH2), 20.15 (CH3), 30.48 (CH2), 35.48 (CH2), 44.88 (CH3), 69.25 (CH), 114.81 (CH), 117.14 (qC), 118.41 (CH), 128.41 (CH), 133.06 (CH), 145.06 (qC), 162.34 (C=O). HRMS (ESI+) m/z: found 247.1802 [M + H]+, C13H12N2O requires 247.1805.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00211.

Copies of 1H and 13C NMR spectra for the compounds 5, 6, 7, 16, 3, 21, 22, 24, 26–33, 40, and 41 (PDF)

AUTHOR INFORMATION

Corresponding Author
E-mail: k.hemming@hud.ac.uk (K.H.).

ORCID

Karl Hemming: 0000-0002-1368-366X

Notes

The authors declare no competing financial interest.

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REFERENCES

Intramolecular Aminohydroxylation of
1337. Synthesize β-activity study of the cyclization of N-unprotected amino olefins.
catalyzed hydroamination. A kinetic, mechanistic, and diastereoselective studies of the formation of the tetracyclic framework.

Pyrrolo[1,2-b]benzothiadiazepines (PBTDs) exert their anti-proliferative activity by interfering with Akt-mTOR signaling and bax:bid ratio modulation. Benzothiadiazepines (PBTDs) exert their anti-proliferative activity by interfering with Akt-mTOR signaling and bax:bid ratio modulation.

b-dipolar cycloaddition as a route to triazolobenzodiazepines and 1,1-Dioxides via a Tandem Aza-Wittig/Heterocumulene Annulation. Harriman, G.; Jones, M. Synthesis of 3-Amino-1,2,4-benzothiadiazine-2(1H)-ones with 1,3-Dienes and Alkenes. Tetrahedron Lett. 2004, 45, 7553.

b-functionalization and therapeutic potential of quinazoline and anthranilamides and aldehydes via metal-free aerobic oxidation in DMSO. Tetrahedron Lett. 2015, 56, 6433.

b-Reddy, C. M.; Misra, P.; Pal, M. Cu-mediated N-arylation of 1,2,3-triazole-4-ones with 1,3-Dienes and Alkenes. Tetrahedron Lett. 2011, 52, 1337.


b-Molecules

b-Di Stefano, C.; Marfe, G.; Trawinska, M. M.; Sinibaldi-Salimei, P.; Silvestri, R.; Amadori, S.; Abruzzese, E. Pyrrolo[1,2-b][1,2,5]-benzothiadiazepines (PBTDs) exert their anti-proliferative activity by interfering with Akt-mTOR signaling and bax:bid ratio modulation in cells from chronic myeloid leukemia patients. Cancer Sci. 2010, 101, 991.


b-Mair, A. C.; Stevens, M. F. G. Triazines and Related Products. Part VIII. Potential Irreversible Chymotrypsin Inhibitors: 3-Alkyl-1,2,3-benzotriazin-4(3H)-ones and 1,3-Dienes and Alkenes. J. Org. Chem. 2005, 70, 10206.


