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Microwave-Mediated Heterocyclization to Benzimidazo[2,1-*b*]quinazolin-12(5*H*)-ones

Richard D. Carpenter,[†] Kit S. Lam,[‡] and Mark J. Kurth[†]*

Department of Chemistry, University of California, Davis, One Shields Ave., Davis, California 95616, and Division of Hematology and Oncology, UC Davis Cancer Center, University of California, Davis, California

mjkurth@ucdavis.edu

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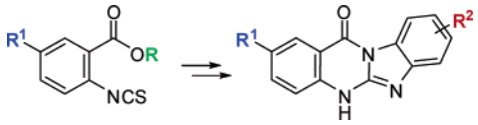
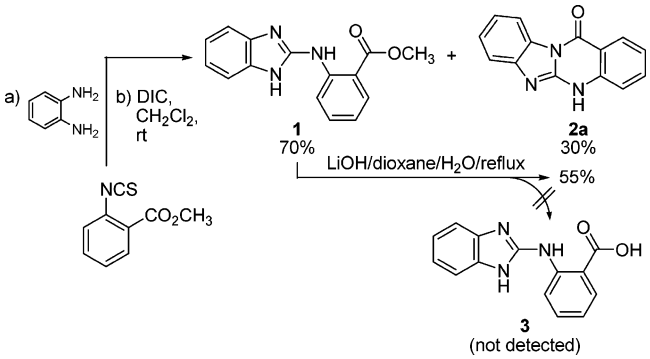


An effective route to benzimidazo[2,1-*b*]quinazolin-12(5*H*)-ones from commercially available *o*-aryl isothiocyanate esters and *o*-phenylenediamines is reported. This method accommodates a variety of substituents on either starting material and proceeds under microwave irradiation in the presence of barium hydroxide, conditions that do not hydrolyze methyl ester substituents. The pharmacologically pertinent benzimidazoquinazolinone heterocycle is delivered in excellent yield and purity via both solution- and solid-phase protocols, the latter involving traceless release from the resin.

Benzimidazo[2,1-*b*]quinazoline-12(5*H*)-ones are potent immunosuppressors in doses as low as 0.1 mg/kg.[1] This class of compounds has also recently been found to present promising antitumor activity with the benzimidazole and quinazolinone moieties serving to intercalate DNA, thereby effectively truncating proliferation of human tumor cell lines.[2] Nearly all existing synthetic routes to this medicinally pertinent heterocycle involve prolonged heating of precursors such as **1** (see Scheme 1), often times resulting in low yield as a result of thermal decomposition. The pioneering work of Giguere and Gedye,[3] coupled with the increased prevalence of microwave (μW) applications in organic synthesis,[4] has allowed for reaction acceleration while minimizing decomposition.[4,5] Indeed, the literature cites an increasing number of examples of μW-mediated heterocyclization,[6] and our reports of carbanilide cyclization employing a barium hydroxide catalyst[7] as well as a thiourea to guanidine cyclization utilizing 1,3-diisopropylcarbodiimide (DIC)[8] are part of this literature. Herein, we report a simple and efficient two-step protocol that delivers benzimidazoquinazolinones in good to excellent yields from aryl isothiocyanate esters. This method has been elaborated to accommodate both solution- and solid-phase methods wherein the last step employs μW irradiation together with stoichiometric barium hydroxide.

SCHEME 1. Initial Experimental Efforts toward Benzimidazoquinazolinones



In earlier work, we reported a mild, one-pot synthesis of *N*-2-arylaminobenzimidazoles from aryl isothiocyanate esters.[9] As shown in Scheme 1, treating aryl isothiocyanate with *o*-phenylenediamine forms an intermediate thiourea and subsequent heterocyclization with DIC delivers the benzimidazole ester. When the isothiocyanate derived from methyl anthranilate was employed in this one-pot procedure, the expected benzimidazole derivative was obtained in 70% yield and the further cyclized benzimidazoquinazolinone **2a** was obtained in a 30% yield. Moveover, attempts to saponify methyl ester **1** to the corresponding acid **3** using 5 equiv of LiOH produced a yellow precipitate that proved to be benzimidazoquinazolinone **2a** (55% yield); none of the benzimidazole acid **3** was detected.

This result with **1** in the formation of **2a** was surprising in light of Lunn and Harper's reported saponification of the methyl ester derived from the corresponding naphthalothiazole sytem where the carboxylic acid was isolated and characterized.[11]

* To whom correspondence should be addressed. Tel: (530) 752-8192. FAX: (530) 752-8995.
[†] Department of Chemistry.
[‡] UC Davis Cancer Center.

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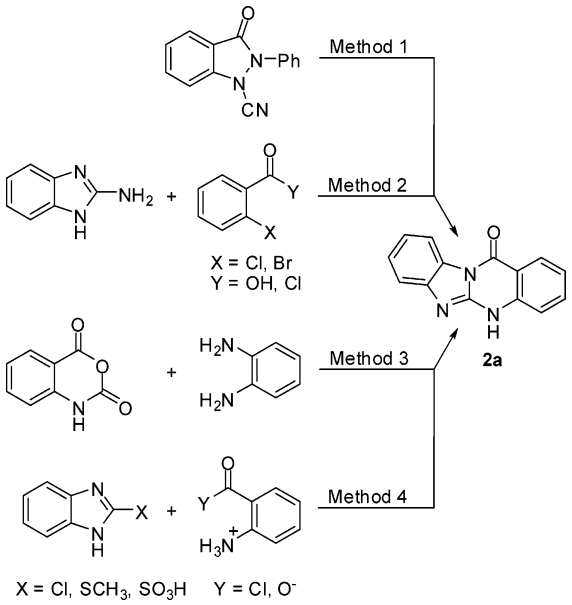
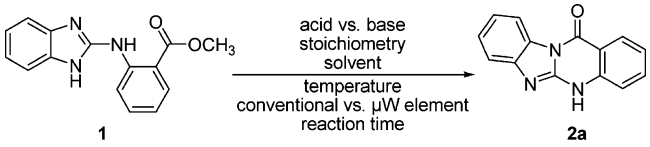
SCHEME 2. Known Routes to Benzimidazo[2,1-*b*]quinazoline-12(5*H*)-one (2a)



SCHEME 3. Optimization Variables of Reaction Conditions[a]



Subsequent in situ acid chloride formation in their work followed by heterocyclization upon heating delivered the napthalothiazoloquinazolinone.[11]

Scheme 2 outlines the most common approaches to benzimdazoquinazolinone **2a**. Review of this literature suggests that none of these methods can accommodate a full spectrum of substituents, both electron-donating and -withdrawing, in both reacting partners.[11] Bird's thermal rearrangement of 3-oxo-2-phenyl-2,3-dihydro-1*H*-indazole-1-carbonitrile at 270 °C (Method 1)[12] gives **2a** in 40% yield. Method 2 illustrates that treatment of 2-aminobenzimidazole with either *o*-bromobenzoic acid under copper-mediated Ullman conditions (170 °C)[2] or Popov's route[13] involving *o*-chlorobenzoyl chloride, which delivers **2a** in moderate yield. Method 3[14] highlights the attack of isatoic anhydride by *o*-phenylenediamine in refluxing acetic acid to afford **2a** in 85% yield together with an aryl benzimidazole byproduct. Finally, refluxing a leaving-group-adorned (R = Cl, SCH_3, SO_3H; Method 4[11,15]) benzimidazole with either the hydrochloride salt of anthranoyl chloride or zwitterionic anthraniloate provides **2a**, but yields are not reported. The relatively uncommon synthetic precursors of some of these methods, in addition to their electronic and temperature demands, provide the impetus for the general and high yielding route to benzimidazoquinazolinones reported here.

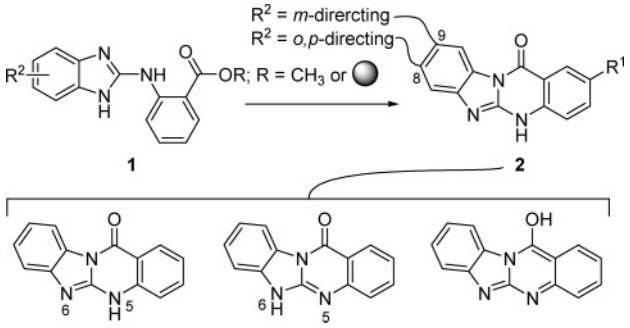
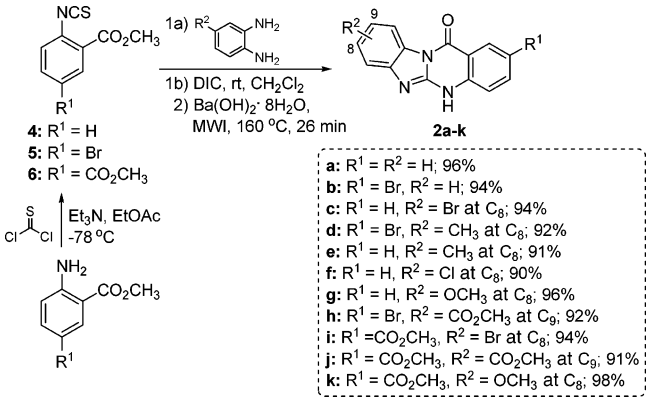


FIGURE 1. Regioselectivity in **1** → **2** and the tautomeric options for **2**.

SCHEME 4. Solution-Phase Synthesis of Benzimidazoquinazolinones 2a−k



To optimize the quinazoline-forming step, we investigated the various parameters detailed in Scheme 3 employing test tubes as reaction vessels. Each test tube was charged with either acid or base in catalytic or stoichiometric quantities together with various solvents. Although all reactions were monitored by TLC, we also noted that successful reactions generated a yellow precipitate that provided a colorimetric indication of success. The best reaction conditions involved heating a dioxane solution of **1** plus $Ba(OH)_2$ to 160 °C under μW irradiation for 26 min, delivering **2a** in 96% yield.

As delineated in Schemes 4 and 5, we established the utility of this method by preparing benzimidazoquinazolinones **2a**−**k** under these optimal conditions with substrates that featured substituents with various electron-donating/-withdrawing properties in both solution and solid phases. Briefly, Scheme 4 shows the thiophosgenation of aniline esters to deliver aryl isothiocyanate esters **4**−**6** in 88−93% yield. These aryl isothiocyanates were then reacted with *o*-phenylenediamines, followed by tandem DIC-mediated benzimidazole cyclization and μW-mediated benzimidazoquinazolinone cyclization with barium hydroxide to deliver derivatives **2a**−**k** in 91−98% overall yield from the starting aryl isothiocyanate. To our surprise, these cyclization conditions were mild enough that saponification of the substituent methyl esters were not observed (e.g., **5**/**6** to **2h**−**k**).

It is noteworthy that all of the 2-(1*H*-benzo[*d*]imidazol-2-ylamino)benzoates (**1**; Figure 1) investigated cyclize to benzimizoquinazolinones **2** with complete regioselectivity relative to the R^2 substituent. Whereas the imidazol-2-ylamino moiety

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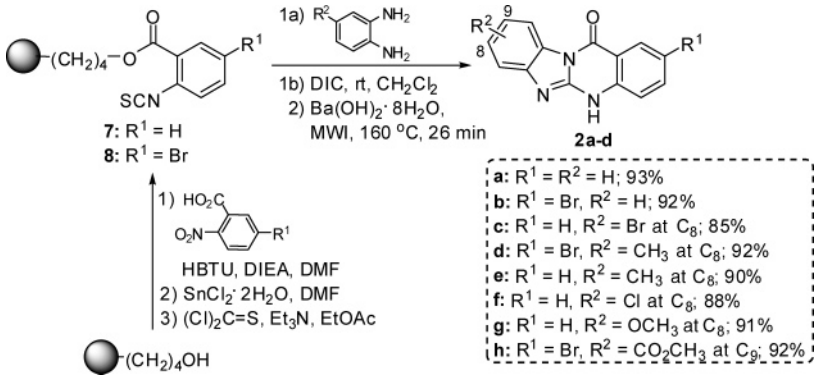
SCHEME 5. Solid-Phase Synthesis of Benzimizoquinazolinones 2a−h



with substituents in the R^2 position exists in tautomeric equilibrium, the deprotonated intermediate cyclizes through the *meta* nitrogen when R^2 is electron-withdrawing (e.g., $R^2 = CO_2CH_3$ at C9) and through the *para* nitrogen when R^2 is electron-donating ($R^2 = OCH_3$, CH_3, Cl, and Br at C8). These R^2 placements derive from comparative melting point analyses with authentic and unambiguous **2e**, **2f**, and **2g**.[12b] Also, although these benzimidazoquinazolinones can potentially exist in three tautomeric forms (see Figure 1), the ^{1}H and ^{13}C NMR data are consistent with one compound on the NMR time scale. Furthermore, the phenolic and the N6^{NH} tautomers can be ruled out as the predominant structures based upon (i) IR data that show a relatively sharp N−H band (∼3300 cm^{-1}) and a strong amide carbonyl band (∼1680 cm^{-1}); (ii) an amide carbonyl carbon (∼160 ppm) in the ^{13}C NMR; and (iii) extensive IR and UV−vis studies by Lunn and Harper that suggest that the N−H should be placed at N5 rather than at N6.[11]

For the solid-phase route shown in Scheme 5, (4-hydroxybutyl)polystyrene resin was first swollen in DMF and then esterified with *o*-nitrobenzoic acid derivatives under HBTU/DIEA conditions. Subsequent tin(II) chloride dihydrate reduction of the aryl nitro group followed by thiophosgenation of the resulting amine delivers the aryl isothiocyanate resins **7** and **8**. These aryl isothiocyanate resins were split into different flasks and treated with *o*-phenylenediamines to give the intermediate thioureas. DIC promoted thiourea to benzimidazole cyclization followed by barium hydroxide/μW-mediated benzimidazoquinazolinone cyclization and concomitant resin release delivered **2a**−**h** in 85−93% overall yield from the starting 4-hydroxybutyl resin. As in the solution phase work, these solid-phase reaction conditions do not hydrolyze esters. This cycloelimination strategy delivered benzimidazoquinazolinones **2a**−**h** in ≥95% purity as determined by LCMS analysis.

The mild, one-pot cyclization effecting aryl isothiocyanate ester → benzimidazole ester and subsequent benzimidazole ester → benzimidazoquinazolinone μW-mediated cyclization delivers the pharmaceutically relevant heterocycle **2** in high yield and purity under either solution- or solid-phase conditions. This generalized method accommodates various substituents and does not result in the hydrolysis of alkyl esters. With the assistance of μW irradiation, the heating time required for the final heterocyclization step is compatible with a resin-supported protocol.

Experimental

General Procedure for Aryl Isothiocyanate Esters. Methyl 2-Isocyanatobenzoate (4). A solution of thiophosgene (30.0 mmol, 2.30 mL) in ethyl acetate (130 mL) was cooled to −78 °C and treated dropwise with a solution of triethylamine (60.1 mmol, 8.37 mL) in ethyl acetate (80 mL) over 30 min. After 10 min of vigorous stirring, a solution of the appropriate anthranilate (e.g., methyl anthranilate; 4.12 g, 27.3 mmol) in ethyl acetate (80 mL) was added over 30 min, followed by stirring at room temperature for 12 h. Workup consisted of dilution with ethyl acetate followed by washing sequentially with water (200 mL × 2) and brine (200 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the crude product was purified via short path column chromatography (hexanes/ethyl acetate, 9:1) to give the aryl isothiocyanate (e.g., **4**; 4.79 g, 91% yield, the analytical data are in accord with literature values).[16]

General Procedure for Aryl Isothiocyanate Ester Resins. (4-Hydroxybutyl)polystyrene *o*-isothiocyanatobenzoate (7). (4-Hydroxybutyl)polystyrene resin (1 g, 3.5 mmol) was swollen in DMF (30 mL) for 16 h, followed by the coupling of the appropriate *o*-nitrobenzoic acid (e.g., *o*-nitrobenzoic acid; 2.92 g, 17.5 mmol) with 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU; 6.64 g, 17.5 mmol) and DIEA (17.5 mmol, 3.09 mL) for 8 h. After filtration and washing, this aryl nitro resin was reduced with $SnCl_2 \cdot 2H_2O$ (23.7 g, 105 mmol) in DMF (30 mL) for 4 h. Following filtration, washing, and a positive chloranil test,[17] this aniline resin was slowly treated with a solution of thiophosgene (10.5 mmol, 804 μL) and Et_3N (23.0 mmol, 3.20 mL) in EtOAc (30 mL). After 16 h, the resin was filtered, washed, and vacuum dried to give the aryl isothiocyanate resin [**7**, IR (neat) 2125, 1740, 688 cm^{-1}].

General Procedure for Solution-Phase Benzimidazoquinazolinones. Benzimidazo[2,1-*b*]quinazoline-12(5*H*)-one (2a). To a solution of an appropriate diamine (e.g., *o*-phenylenediamine; 176 mg, 1.63 mmol) in CH_2Cl_2 (8 mL) was added an appropriate aryl isothiocyanate ester (e.g., **4**; 300 mg, 1.55 mmol) in CH_2Cl_2 (8 mL) dropwise over 30 min. After 16 h, DIC (4.65 mmol, 691 μL) was added, and the reaction was monitored by TLC. In most instances, the reaction was completed in 10 h, although the reaction times ranged between 6 and 18 h. Following completion, the solvent was removed by concentration, and subsequent recrystallization with $CHCl_3$/petroleum ether afforded a mixture of the benzimidazole ester (e.g., **1;** 70%) and the benzimidazoquinazoline (e.g., **2a**; 30%). This mixture (480 mg) was dissolved in dioxane and transferred to a 5 mL round-bottom microwave vial. Barium hydroxide octahydrate (2.57 g, 8.15 mmol) was added, followed by sealing of the vessel and heating to 160 °C for 26 min in a microwave reactor (Personal Chemistry, Emrys Optimizer). The reaction temperature increased from 25 to 160 °C in 155 s and was maintained at 160 °C for the duration. The bright yellow precipitate was filtered and washed with aqueous NH_4Cl, H_2O, dioxane, CH_2Cl_2, and EtOAc to afford **2** (e.g., **2a**; 350 mg, 96% yield, the analytical data are in accord with literature values).[14]

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General Procedure for Solid-Phase Benzimidazoquinazolinones. 8-Bromobenzimidazo[2,1-*b*]quinazoline-12(5*H*)-one (2b). Aryl isothiocyanate resin **7** (1.0 g, 3.5 mmol) was equally divided into two flasks, and each flask received an appropriate *o*-phenylenediamine (4-bromo-*o*-phenylenediamine; 982 mg, 5.25 mmol) and was allowed to react for 16 h. DIC (5.25 mmol, 779 μL) was then added, and the reaction was shaken for an additional 16 h. The resulting benzimidazole resin was transferred to a 5 mL microwave vial to which was added barium hydroxide octahydrate (2.77 g, 8.75 mmol) in DMF (3 mL). The vessel was sealed and heated to 160 °C for 26 min in a microwave reactor (Personal Chemistry, Emrys Optimizer). The reaction temperature increased from 25 to 160 °C in 155 s and was maintained at 160 °C for the remaining heating period, at which point the resin was filtered and washed with warm DMF. The filtrate was diluted with 0.5 M NH_4Cl (15 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with water (3 × 20 mL) and brine (1 × 10 mL) followed by drying ($MgSO_4$) and concentration to afford **2** (e.g., **2b**; 505 mg, 92%) as a yellow solid: mp 368−369 °C; IR (neat) 3331 (sh), 1685, 1050 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.34 (d, 1H, J = 6.3 Hz), 8.23 (dd, 1H, J = 1.0 Hz, J = 5.1 Hz), 7.63−7.58 (m, 1H), 7.56 (d, 1H, J = 1.2 Hz), 7.50 (dd, 1H, J = 2.1 Hz, J = 6.3 Hz), 7.35 (d, 1H, J = 6.3 Hz), 7.18 (dd, 1H, J = 1.5 Hz, J = 6.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.9, 155.2, 151.0, 145.4, 134.6, 128.3, 127.9, 127.2, 124.1, 116.5, 114.6, 114.4, 113.9, 107.7; ESI MS m/z 314, 316 $(M + H)^+$. Anal. Calcd for $C_{14}H_8BrN_3O$: C, 53.53; H, 2.57; N, 13.38. Found: C, 53.39; H, 2.56; N, 13.35. Purity of the crude product was determined to be 97% by HPLC analysis on the basis of absorption at 220 nm.

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Supporting Information Available: Experimental procedures as well as NMR spectra for aryl isothiocyanates (**5**, **6**, and **8**) and benzimidazoquinazolinones (**2c**−**j**). This material is available free of charge via the Internet at http://pubs.acs.org.

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