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One-Pot, Two-Step Cascade Synthesis of Quinazolinotriazolobenzodiazepines

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ABSTRACT

An operationally simple, one-pot, two-step cascade method has been developed to afford quinazolino[1,2,3]triazolo[1,4]benzodiazepines. This unique, atom-economical transformation engages five reactive centers (amide, aniline, carbonyl, azide, and alkyne) and employs environmentally benign iodine as a catalyst. The method proceeds via sequential quinazolinone-forming condensation and intramolecular azide–alkyne 1,3-dipolar cycloaddition reactions. Substrate scope, multicomponent examples, and mechanistic insights are discussed.

Quinazolinones, benzodiazepines, and triazoles are considered privileged heterocycles and are found in many bioactive compounds.[1−3] The quinazolinone core is a ubiquitous pharmacophore appearing in natural and synthetic products.[1a] Natural products (Figure 1) with the quinazolinone moiety include rutaecarpine (**1**,[1a−c] a Chinese herbal medication isolated from the fruit of *Evodia rutaecarpa* with applications in the treatment of headache, cholera, and dysentery) and febrifugine (**2**,[1a] a Chinese herb used in the treatment of malaria). Methaqualone (**3**, Figure 1) was once a commonly prescribed synthetic drug (on the market in the U.S. since the 1960s) that exhibits hypnotic and sedative effects.[1a,d] Pharmaceuticals derived from the benzodiazepine core, binding to $GABA_A$ receptors at the benzodiazepine site,[2a] emerged in many marketed drugs during the 1970s. Two of these are alprazolam (**4**, Xanax)[2b] and diazepam (**5**, Figure 1, Valium),[2c] which continue to be prescribed today for the treatment of anxiety and insomnia. Compounds such as **6** (plus analogues, Figure 1), derived from the further elaborated [1,2,3]triazolo[1,4]benzodiazepine skeleton, display activity as protease inhibitors.[3]

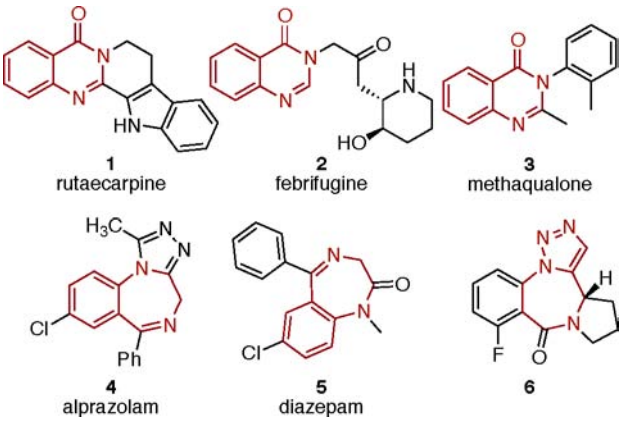

Figure 1. Natural and synthetic examples of bioactive quinazolinones, benzodiazepines, and triazoles.

The pharmacological records of these privileged motifs prompted us to develop an atom-economical, one-pot, two-step cascade method for the production of compounds incorporating the three aforementioned heterocycles. Many procedures have appeared in the literature for the synthesis of quinazolinones; these generally utilize

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(2) (a) Sigel, E. *Med. Chem. Rev.—Online* **2005**, *2*, 251–56. (b) Hester, J. B., Jr. U.S. Patent No. 3,987,052, 1969. (c) Keller, O.; Steiger, N.; Sternbach, L. H. U.S. Patent No. 3,442,946, 1969.

(3) (a) Sharpless, K. B.; Manetsch, R. *Expert Opin. Drug Discovery* **2006**, *1*, 525–38. (b) Mohapatra, D. K.; Maity, P. K.; Shabab, M.; Khan, M. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5241–45.

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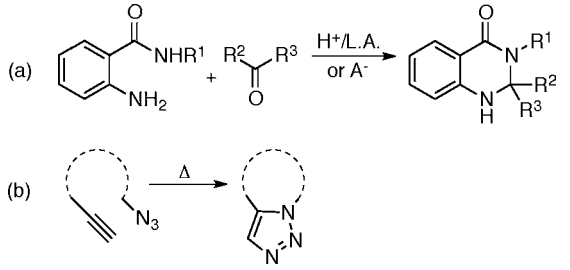
o-aminobenzamides and aldehydes or ketones as starting materials and Bronsted/Lewis acids or Bronsted bases as catalysts to effect imine formation and subsequent ring closure (Scheme 1a).[4a−i] The quinazolinone synthesis methodology developed by Wang et al. is attractive because it is environmentally benign, and inexpensive molecular iodine is used catalytically (5 mol %) at 50 °C to promote product formation.[4d] Furthermore, the thermally driven intramolecular azide−alkyne 1,3-dipolar cycloaddition is well-documented, usually employing elevated temperatures (80−120 °C is common) to afford the 1,5-fused-1,2,3-triazole (Scheme 1b).[1c,3,5]

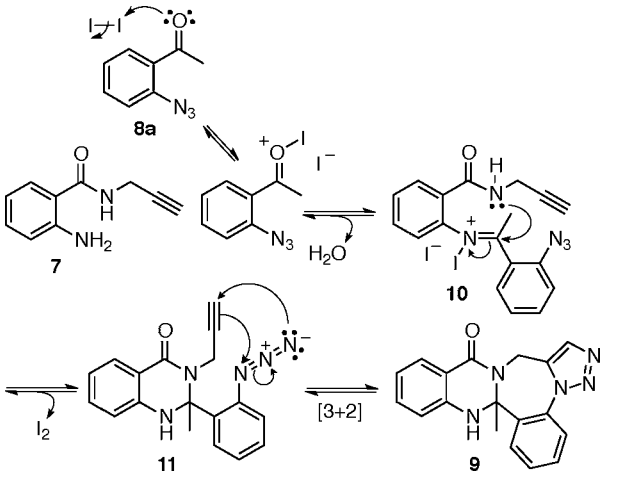
Scheme 1. Classic Methods for the Synthesis of Quinazolinones (a) and 1,5-Fused 1,2,3-Triazoles (b)



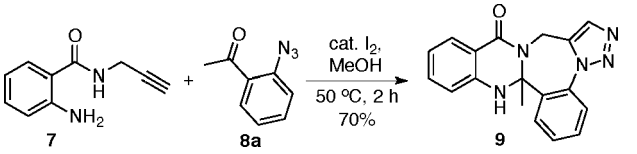
The method described herein (Scheme 2) draws on these ideas to explore the use of molecular iodine to promote a cascade sequence of reactions. Step one consists of anilino−keto condensation to form Schiff base **10** and subsequent nucleophilic attack by the amide nitrogen onto the imine to form an aminal (quinazolinone **11**). These two iodine-promoted condensations preorganize the alkyne and azide for an intramolecular 1,3-dipolar cycloaddition (step two) to form the complex pentacyclic system **9**.[6]

These transformations were demonstrated by reacting *o*-amino-*N*-(prop-2-yn-1-yl)benzamide (**7**) with *o*-azidoacetophenone (**8a**) in MeOH using 10 mol % of I_2 at 50 °C (open to the atmosphere). This one-pot, two-step cascade reaction delivered pure quinazolino[1,2,3]triazolo[1,4]-benzodiazepine **9**, which precipitated from the reaction mixture in 70% isolated yield (Scheme 3).

Scheme 2. Proposed Mechanism



Scheme 3. One-Pot Cascade Synthesis of Quinazolino-[1,2,3]triazolo[1,4]benzodiazepine **9**[a]



[a] Product characterized by ^{1}H and ^{13}C NMR, IR, and HRMS.

This method affords many advantageous features. For instance, exploiting inexpensive, nontoxic, air-stable iodine as catalyst[4h] in a one-pot, two-step cascade process characterizes this as an operationally simple procedure. Additionally, this is a highly atom-economical reaction engaging five reactive centers (aniline, amide, carbonyl, azide, and alkyne) spanning two starting materials. Another attractive aspect is that each starting material can be accessed in one straightforward step from commercial reagents. *o*-Amino-*N*-(prop-2-yn-1-yl)benzamide (**7**) was prepared by the chemoselective nucleophilic opening of isatoic anhydride (**12**) with propargylamine and subsequent decarboxylation of the in situ formed carbamic acid, providing the propargylated amide/free aniline in 88% yield in pure form (Scheme 4a; no column chromatography necessary).[7] The second starting material, *o*-azidoacetophenone (**8a**: R^2 = Me; R^3 = H), was obtained in one pot by diazotization of *o*-aminoacetophenone (**13a**) and subsequent displacement with sodium azide in high yield (Scheme 4b; **8b**−**d** were also prepared in this fashion; **8b**: R^2 = Me; R^3 = [3,4]dioxole; **8c**: R^2 = Ph; R^3 = H; **8d**: R^2 = Ph; R^3 = *p*-Cl).[8] Substituted isatoic anhydrides are an ideal starting point for this method but, unfortunately,

(4) (a) Shaabani, A.; Maleki, A.; Mofakham, H. *Synth. Commun.* **2008**, *38*, 3751–59. (b) Wang, M.; Dou, G.; Shi, D. *J. Comb. Chem.* **2010**, *12*, 582–86. (c) Roy, A. D.; Jayalakshmi, K.; Dasgupta, S.; Roy, R.; Mukhopadhyay, B. *Magn. Reson. Chem.* **2008**, *46*, 1119–26. (d) Wang, X.-S.; Yang, K.; Zhou, J.; Tu, S.-J. *J. Comb. Chem.* **2010**, *12*, 417–21. (e) Cheng, X.; Vellalath, S.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786–87. (f) Miklós, F.; Fülöp, F. *Eur. J. Org. Chem.* **2010**, *5*, 959–65. (g) Mohiuddin, G.; Reddy, P. S.; Ahmed, K.; Ratnam, C. V. *J. Chem. Res., Synop.* **1987**, 224–25. (h) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *Chem.—Eur. J.* **2012**, *18*, 5460–89. (i) Xu, W.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. *Org. Lett.* **2011**, *13*, 1274–77.

(5) (a) Majumdar, K. C.; Ray, K. *Synthesis* **2011**, *23*, 3767–83. (b) Donald, J. R.; Martin, S. F. *Org. Lett.* **2011**, *13*, 852–55. (c) Arigela, R. K.; Mandadapu, A. K.; Sharma, S. K.; Kumar, B.; Kundu, B. *Org. Lett.* **2012**, *14*, 1804–07.

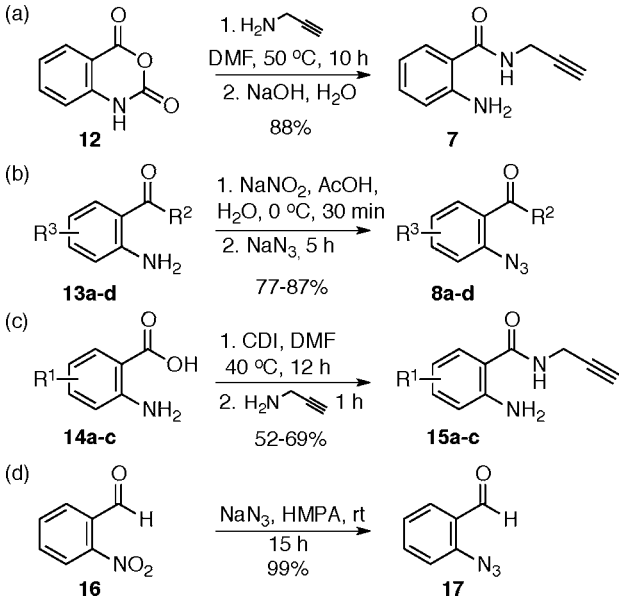
(6) Iodine may also play a role in the click reaction as the effective temperature (50 °C) is lower than that generally required (80−120 °C) for intramolecular azide−alkyne 1,3-dipolar cycloadditions. It is, however, difficult to probe this mechanistic aspect as intermediate azidoalkyne **11** is not isolable.

(7) Twin, H.; Batey, R. A. *Org. Lett.* **2004**, *6*, 4913–16.

(8) Stokes, B. J.; Vogel, C. V.; Urnezis, L. K.; Pan, M.; Driver, T. G. *Org. Lett.* **2010**, *12*, 2884–87.

are not generally available. Fortunately, substituted *o*-amino-*N*-(prop-2-yn-1-yl)benzamides (**15a**–**c**; **15a**: R^1 = *o*-OMe; **15b**: R^1 = *m*-OMe; **15c**: R^1 = *p*-Br) can also be prepared by 1,1′-carbonyldiimidazole (CDI)-mediated coupling of substituted anthranilic acids (**14a**–**c**) with propargylamine (Scheme 4c; note that aniline protection is unnecessary).[9] *o*-Azidobenzaldehyde (**17**) can also serve as the electrophilic carbonyl center in this methodology. Direct displacement of the nitro group of *o*-nitrobenzaldehyde (**16**) with sodium azide affords **17** (Scheme 4d).[8]

Scheme 4. Preparation of Starting Materials



The versatility/limitations of this method were evaluated by examining substrate scope (Figure 2, isolated yields listed) using the conditions outlined in Scheme 3. These results show that R-group substitution can have a significant effect on product yield. For instance, electron-donating substituents in both the R^1 (*o*-OMe and *m*-OMe with respect to the aniline: **19**, **20**, **22**, and **23**) and R^3 (dioxole: **21**–**23**) positions are well tolerated by this system. One explanation for this –OMe tolerance at R^1 is that the donating character of the methoxy group enhances aniline nucleophilicity and in turn facilitates imine formation. It is also interesting to note that when R^1 is substituted with a halogen (Br), the yield drops substantially (**18** = 30%; the inductively withdrawing character of the Br may have had the opposite effect of the -OMe group). Not surprisingly, when R^2 is a phenyl group, the lowest yields are obtained (**24** = 25%, **25** = 11%, and **26** = 11%) as a consequence of steric congestion. Furthermore, when an aldehyde (**17**; R^2 = R^3 = H) is employed in place of a ketone, the final quinazolino[1,2,3]triazolo[1,4]benzodiazepine is delivered

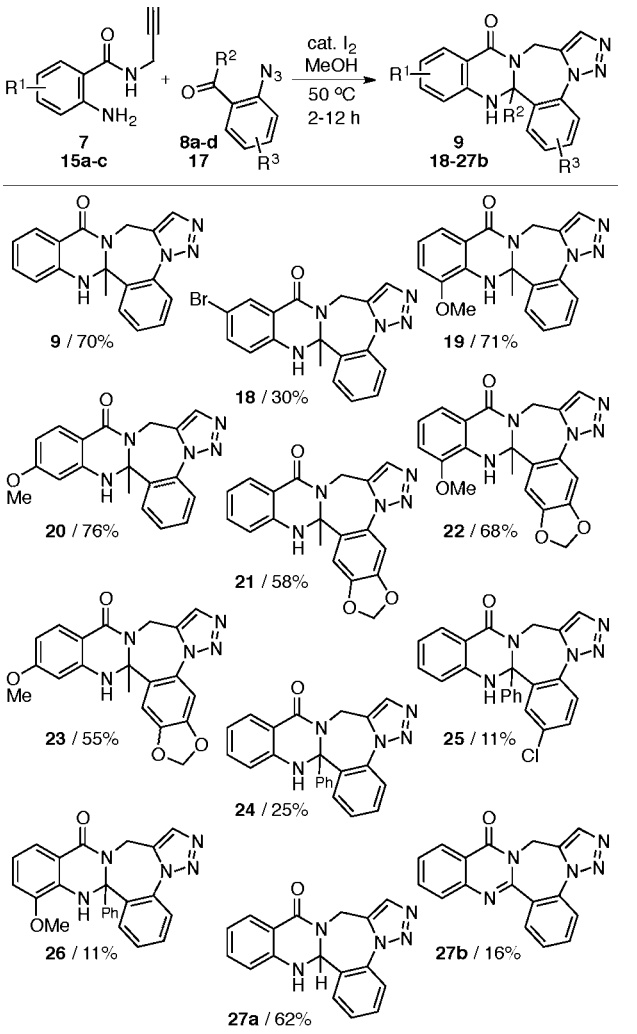
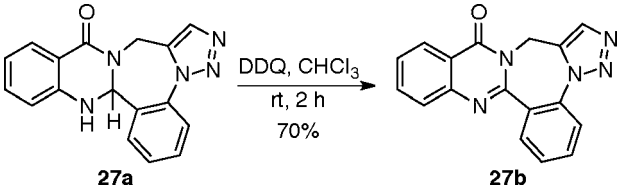


Figure 2. Substrate scope; isolated yields shown. Note: all products were characterized by ^{1}H and ^{13}C NMR, IR, and HRMS.

Scheme 5. Oxidation of **27a** to **27b**[a,b]



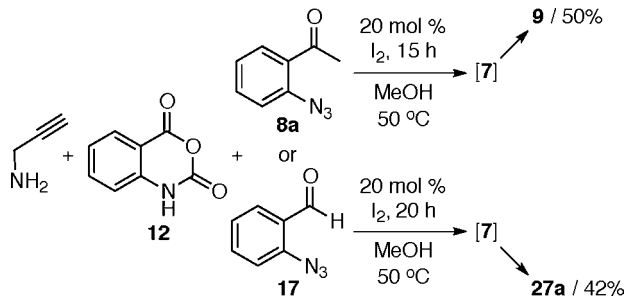
[a] Product characterized by ^{1}H and ^{13}C NMR, IR, and HRMS. [b] Isolated yield after silica gel column chromatography.

in good yield (**27a** = 62%) together with the air- or I_2-oxidized side product **27b** (16%).

Formation of quinazolinones **27a** and **27b** was intriguing and prompted us to explore the possibility of converting **27a** to **27b** under oxidative conditions. Indeed, the facile

(9) Mizutani, T.; Nagase, T.; Ito, S.; Miyamoto, Y.; Tanaka, T.; Takenaga, N.; Tokita, S.; Sato, N. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6041–45.

Scheme 6. Multicomponent Examples[a]



[a] Isolated yields after silica gel column chromatography.

conversion of **27a** to **27b** can be achieved with DDQ (Scheme 5) in good isolated yield (70%).

Multicomponent reactions are important because they deliver complex, diverse final products from relatively simple starting materials in one operational step.[10] We were interested in investigating the possibility of developing a multicomponent version of this method (Scheme 6); if successful, a starting material synthetic step would be circumvented. Indeed, multicomponent preparations of quinazolinones have been reported, which typically utilize isatoic anhydride (**12**), ammonium acetate, and an aldehyde.[1d,11] Two successful multicomponent experiments—delivering quinazolino[1,2,3]triazolo[1,4]benzodiazepines **9** and **27a**—are delineated in Scheme 6. In these two examples, propargylamine, isatoic anhydride (**12**), *o*-azidoacetophenone (**8a**), or *o*-azidobenzaldehyde (**17**), and 20 mol % I_2 (at 0.2 M MeOH) were simultaneously combined in one pot. The in situ formed *o*-amino-*N*-(prop-2-yn-1-yl)benzamide (**7**; Scheme 6) went on to deliver the targeted heterocycles, albeit in lower yields compared to the two-component versions.

In conclusion, an atom-economical, cascade, five-centered, one-pot, two-step method has been developed, exploiting the inexpensive, environmentally friendly catalyst I_2. The substrate scope has been examined showing that this method is tolerant of various functional groups and aryl substitutions. We have also shown that multicomponent examples of this method are possible. All final compounds have been sent to the Molecular Libraries Small Molecule Repository (MLSMR) with the goal of identifying biologically active molecules.

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Supporting Information Available. Full experimental details and characterization data (^{1}H NMR, ^{13}C NMR, IR, HRMS, and mp) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(11) (a) Chen, J.; Su, W.; Wu, H.; Liu, M.; Jin, C. *Green Chem.* **2007**, *9*, 972–75. (b) Zeng, L.-Y.; Cai, C. *J. Heterocycl. Chem.* **2010**, *47*, 1035–39. (c) Mohammadi, A. A.; Dabiri, M.; Qaraat, H. *Tetrahedron* **2009**, *65*, 3804–08.