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Synthesis of Quinazolines from *N*-(2-Nitrophenylsulfonyl)iminodiacetate and α-(2-Nitrophenylsulfonyl)amino Ketones via 2*H*-Indazole 1-Oxides

Soňa Křupková,[†,§] Greg A. Slough,[‡] and Viktor Krchňák*,[†]

[†]*Department of Chemistry and Biochemistry, 251 Nieuwland Science Center, University of Notre Dame, Notre Dame, Indiana 46556, and* [‡]*Chemistry Department, Kalamazoo College, 1200 Academy St., Kalamazoo, Michigan 49006.* [§]*Present address: Department of Organic Chemistry, Faculty of Science, University of Palacký, 771 46 Olomouc, Czech Republic.*

vkrchnak@nd.edu

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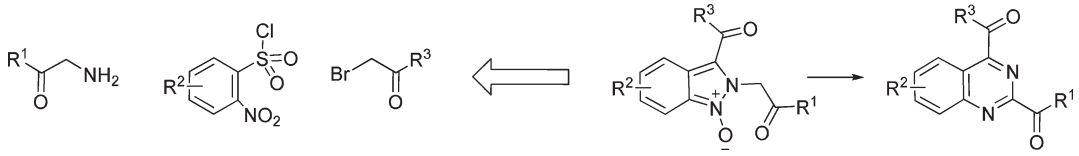

Base-catalyzed rearrangement of 2*H*-indazoles 1-oxides, prepared by tandem carbon−carbon followed by nitrogen−nitrogen bond formations from easily accessible *N*-alkyl-2-nitro-*N*-(2-oxo-2-aryl-ethyl)-benzenesulfonamides using glycine, 2-nitrobenzenesulfonyl chlorides, and bromo ketones/acetates, yielded high purity quinazolines.

Introduction

Quinazolines represent a group of pharmacologically important compounds exhibiting a wide range of biological activities including antitumoral,[1] antibacterial,[2] antimalarial,[3] and anticonvulsant[4]activities. The FDI-approved drug Tarceva, a tyrosine kinase inhibitor, is a quinazoline derivative.[5] Significant biological effects were also found in naturally occurring alkaloids with quinazoline moiety.[4] Therefore this class of heterocycles became the center of attention in many research studies, and a substantial effort was dedicated to devising synthetic approaches to these molecules.[6] Since combinatorial chemistry has become an integral part in research and development of new pharmaceuticals, particularly in connection with solid-phase synthesis, invention of efficient synthetic methods provided access to this class of heterocycles on polymer support. Wang and Hauske developed a method utilizing 2-nitrocinnamic acid to form a polymer-supported iminophosphorane intermediate that was cyclized to 3,4-dihydroquinazolines.[7] Lou described the synthesis starting from 4-bromomethyl-3-nitrobenzoate or the corresponding amide bound to solid phase. After substitution of bromide with amine nuclophiles, acylation with carboxylic acid, and subsequent reduction of nitro group, the resulting precursors underwent cyclocondensation to quinazolinone derivatives.[8] Vögtle and Marzinzik[9] and Kamal and co-workers[1] have summarized these and other approaches to solid-phase synthesis in review articles.

We recently discovered an efficient synthetic route to indazoles.[10] N-Alkylation of polymer-supported 2-nitrobenzenesulfonyl (2-Nos)-activated/protected amines by bromoketones (a variant of the Fukuyama method[11]) provided α-(2-nitrobenzenesulfonyl)amino ketones. Treatment of these 2-Nos derivatives with DBU led to tandem carbon−carbon followed by nitrogen−nitrogen bond formation to produce indazole oxides of excellent purity. Encouraged by this unexpected and very clean transformation leading to pharmacologically relevant heterocycles, we expanded the original scope of the tandem reaction to more complex structures. The target indazoles contained a carbonyl functional group

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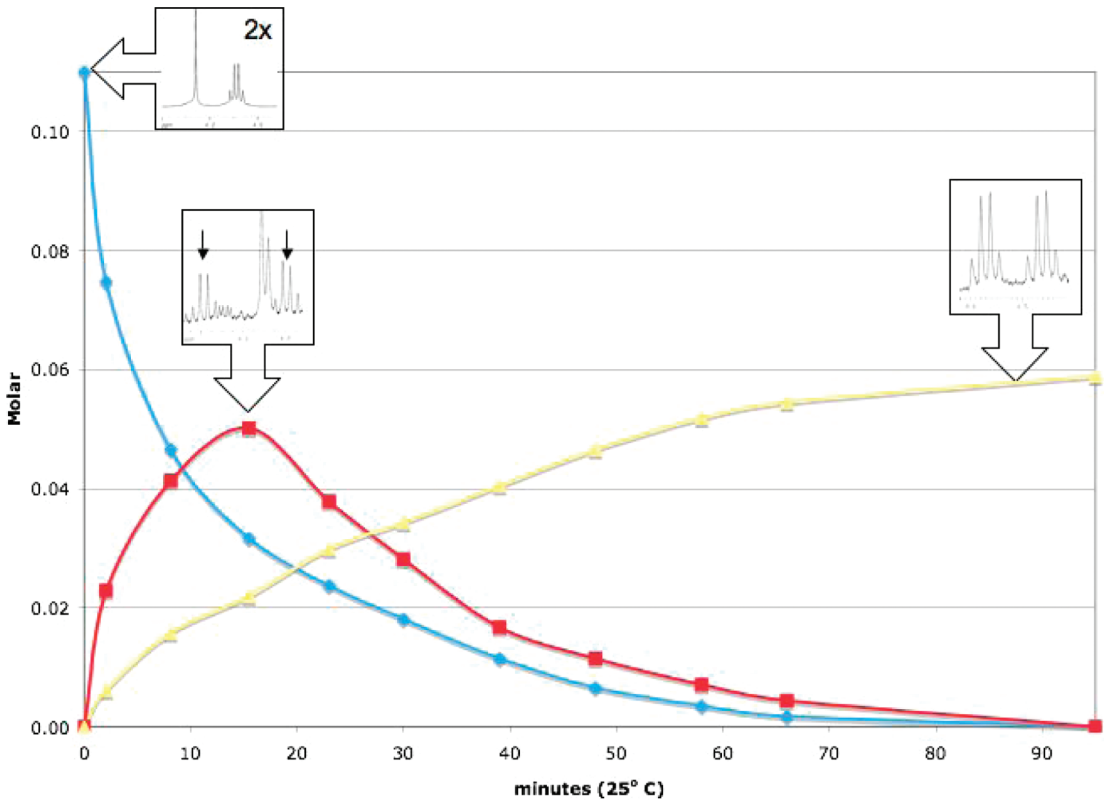


FIGURE 1. Time study of the sequential cyclization sulfonamide **1** to quinazoline **3** in the presence of DBU.

attached to the side chain of the substituent in position 2 of the indazole ring. The carbonyl group enabled subsequent transformations of indazoles and formation of a fused pyrazine ring via an intramolecular nucleophile located on the R^1 side chain, providing a route for pyrazino[1,2-*b*]indazole synthesis.[12] We also used our indazole chemistry to prepare 2-(2-amino/hydroxyethyl)-1-aryl-3, 4-dihydropyrazino[1,2-*b*] indazol-2-iums that cyclized in neutral pH to fused polycyclic heterocycles[13] that unexpectedly rearranged to as yet unexplored 2,3-dihydro-1*H*-imidazo[1,2-*b*]indazoles.[14]

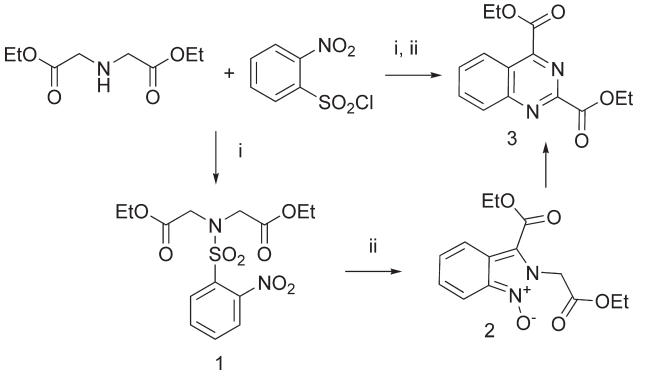
While attempting to further expand the scope of this rearrangement, we discovered a new ring-expansion reaction. Here, we describe its use for the synthesis of quinazolines and development of methodology for combinatorial synthesis of target quinazolines with three diversity positions.

Results

Diethyl iminodiacetate reacted with 2-nitrobenzenesulfonylchloride in the presence of a mild base, lutidine, and yielded the expected sulfonamide **1**. Exposure of the crude reaction mixture to a strong base, DBU, in DMF triggered the subsequent transformation to quinazoline **3** (Scheme 1).

Qualitative details associated with the sequential cyclization of **1** to **3** came from a time-study ^{1}H NMR experiment. When a 0.11 M solution of **1** in DMSO-d_6 was treated with 3 equiv of DBU, an immediate color change ensued and proton signals (δ 4.16 (s), 4.09 (q)) for sulfonamide **1** rapidly

SCHEME 1. Quinazolines from Iminodiacetate and 2-Nitrobenzenesulfonylchloride[a]



[a]Reagents and conditions: (i) lutidine, DCM, rt, overnight; (ii) DBU, DMF, rt, overnight.

decreased. An intermediate set of signals (δ 4.39 (q), 4.19 (q)) increased in intensity, and then these signals declined with production of quinazoline **3** (δ 4.56 (q), 4.45 (q)) (see Figure 1). Attempts to extract quantitative information for this reaction were complicated by ester hydrolysis and the presence of water in the initial reaction mixture. Ester hydrolysis occurred in all three materials involved in this reaction and accounted for the low overall yield of **3** (54%). The data plotted in Figure 1 resulted only after thorough drying of solvent and DBU.[15,16]

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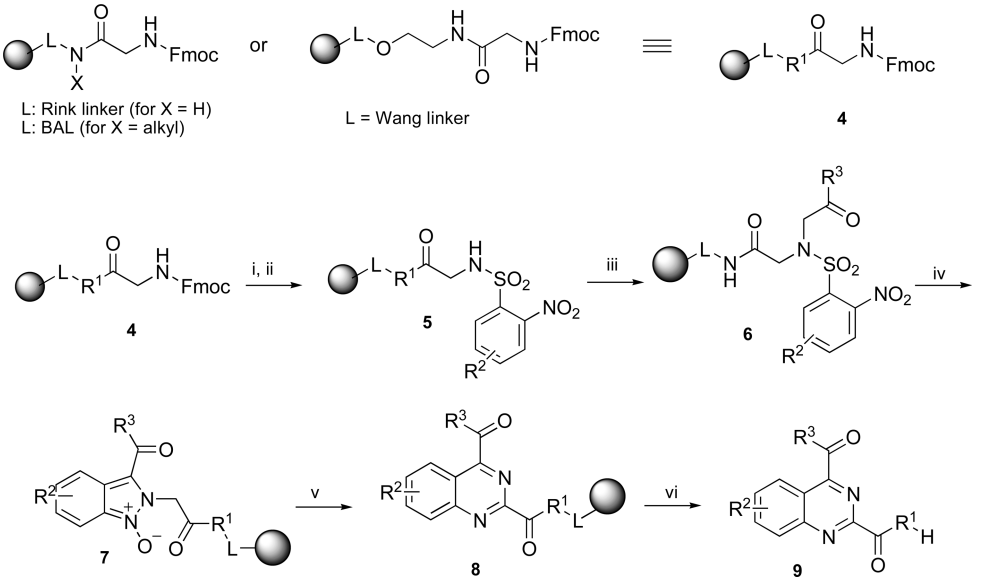
SCHEME 2. Synthesis of Quinazolines on Solid Phase[a]



[a]Reagents and conditions: (i) piperidine, DMF, rt, 15 min; (ii) 2-nitrobenzenesulfonyl chloride, lutidine, DCM, rt, overnight; (iii) bromoketone, DMF, rt, 0.5−7 h (see Experimental Section); (iv) DBU, DMF, rt, 30 min; (v) DBU, DMF, rt, 10 min to overnight (see Experimental Section); (vi) TFA, DCM, rt, 1 h.

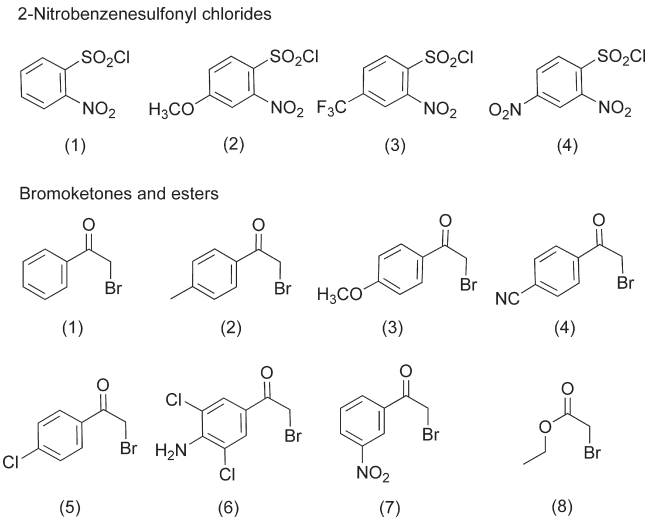


FIGURE 2. Diversity reagents.

In the presence of water, the consumption of **1** occurred at a rate similar to that shown in Figure 1, whereas cyclization to **3** can take up to 18 h to achieve 50% conversion.

To increase the diversity of compounds accessible by this ring-expansion transformation, we synthesized combinatorial ensembles of linear precursors with three diversity positions on solid-phase support. *N*-Alkyl-2-nitro-*N*-(2-oxo-2-aryl-ethyl)-benzenesulfonamides **6** were prepared by using glycine, 2-nitrobenzenesulfonyl chlorides and bromoketones following a route developed for the synthesis of indazole oxides.[10] When the indazole-oxides **7** were exposed to basic condition, we observed rearrangement to a six-membered ring **8** (Scheme 2). Thus, our previously described route for accessing indazole derivatives was used to acquire quinazolines. First, we evaluated the scope and limitation of this transformation. Model compounds were synthesized on Rink amide resin acylated with Fmoc-Gly-OH. Later we also used alkylated BAL resin and ethanolamine-derivatized Wang resin.

To optimize reaction conditions and to evaluate the effect of a diverse substitution pattern on 2-nitrobenzenesulfonyl chlorides and bromoketones on the yield and purity of products, we prepared a set of model compounds on Rink amide resin acylated with Fmoc-Gly-OH (Figure 2). Both 2-Nos chlorides and bromoketones were selected to bear electron-donating as well as electron-withdrawing groups. Synthesis of acyclic precursors followed from a published protocol.

The rate of *N*-alkylation was dependent upon the substitution pattern of both building blocks (bromoketone and benzenesulfonyl chloride). The presence of a nitro group on either bromoketone or 2-Nos chloride markedly accelerated the reaction; the alkylation was complete in 30 min. By contrast, when electron-donating substituents were present on either the ketone or benzenesulfonyl groups, the nitrogen alkylation reaction required several hours for completion. LCMS analysis of linear precursors prepared by alkylation of electron-deficient model compounds already revealed the presence of indazole-oxides, an indication that these activated systems cyclized even in the presence of DIEA used in the alkylation step.

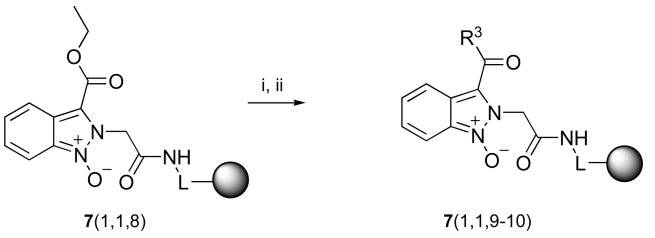
Extended exposure to DBU caused further transformation of indazole-oxides **7** to quinazolines **8**. The outcome of cyclization was highly dependent upon the substitution pattern. The effect was evaluated on a set of model compounds with particular attention given to the Nos substitution pattern, **6**(1,R^1,1). The electron-withdrawing nitro group accelerated the rearrangement to quinazolines. In comparison, nonsubstituted derivative **6**(1,1,1) (R^2, R^3 = H) required 0.2 M DBU overnight to achieve maximum yield of **8**(1,1,1), wheras quinazoline **8**(1,4,1) (R^2 = NO_2, R^3 = H) formed in 0.1 M DBU in 10 min. Prolonged reaction time for reactions involving **6**(1,4,1) led to product decomposition. The electron-

TABLE 1. Summary of the Prepared Derivatives

compound	R^1-H	R^2	R^3	method	purity (%)[a]	yield (%)[b]
9(1,1,1)	NH_2	H	Ph	A	88	23
9(1,1,2)	NH_2	H	4-Me-Ph	A	95	12
9(1,1,3)	NH_2	H	4-OMe-Ph	A	90	10
9(1,1,4)	NH_2	H	4-CN-Ph	B	25	15
9(1,1,5)	NH_2	H	4-Cl-Ph	A	98	11
9(1,1,6)	NH_2	H	4-NH_2-3,5-diCl-Ph	A	90	20
9(1,1,9)	NH_2	H	piperidin-1-yl	A	76	30
9(1,1,10)	NH_2	H	4-Ph-piperazin-1-yl	A	90	41
9(1,2,1)	NH_2	CF_3	Ph	A	91	31
9(1,2,6)	NH_2	CF_3	4-NH_2-3,5-diCl-Ph	A	98	23
9(1,4,1)	NH_2	NO_2	Ph	C	85	33
9(1,4,6)	NH_2	NO_2	4-NH_2-3,5-diCl-Ph	C	92	14
9(2,1,8)	NH-CH_2-Ph-4-Me	H	O-Et	A	45	18
9(3,1,1)	NH-$(CH_2)_2$)-OH	H	Ph	A	88	48
9(3,1,2)	NH-$(CH_2)_2$)-OH	H	4-Me-Ph	A	79	33
9(3,1,5)	NH-$(CH_2)_2$)-OH	H	4-Cl-Ph	A	84	36

[a]Purity of crude product before purification. [b]Yield after purification. Method A: 0.2 M DBU in DMF, rt, overnight; method B: 0.2 M DBU in DMF, rt, 1 day; method C: 0.1 M DBU in DMF, rt, 1.5 h.

SCHEME 3. Diversification of the R^3 Substituent[a]



[a]Reagents and conditions: (i) NaOH in THF/MeOH (1:1), 1 h; (ii) HOBt, DIC in DMF, 1 h, then piperidine or 1-phenylpiperazine, DMF, 1 h.

donating methoxy group in model compound **6**(1,2,1) cyclized to indazole-oxides only. Attempts to facilitate the conversion of the indazole-oxide ring to quinazoline by increasing the temperature led to decomposition, as demonstrated by NMR analysis of the cleaved resin product.

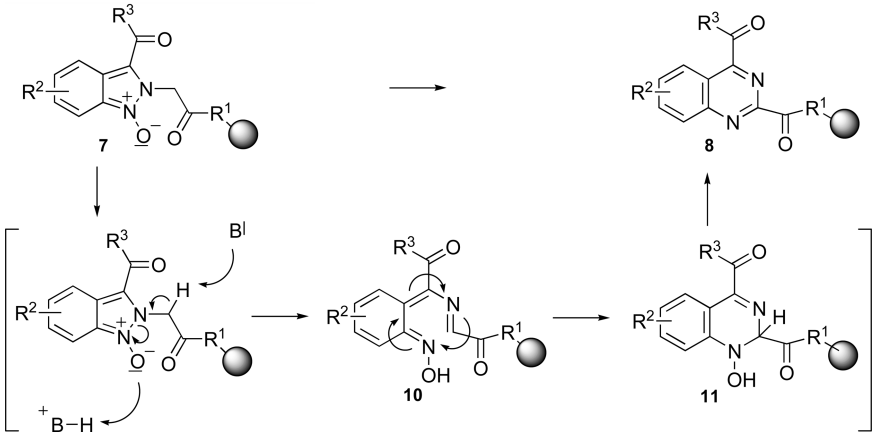
The structure of bromoketones influenced the conversion to quinazolines as well. The presence of a nitro group considerably accelerated the formation of indazole; however, 6-nitroquinazoline **8**(1,1,7) was obtained only in low yield in a complex mixture of unidentified compounds. Because we observed partial cyclization during alkylation in the presence of DIEA, we attempted to replace the DBU by DIEA. Indazole oxide was stable in the presence of DIEA at room temperature. Increased temperature facilitated the rearrangement to quinazoline, but the purity of crude product was low as a result of contamination by unidentified components.

The diversity of quinazolines was further expanded by alkylation of the resin **5** with ethyl bromoacetate. The intermediate **6**(R^3 = OEt) cyclized to indazole oxide **7**(1,1,8). At this stage, the ester **7**(1,1,8) was hydrolyzed and the carboxylate resin was converted to amides **7**(1,1,9−10) (Scheme 3). Subsequent overnight exposure to DBU converted the indazole oxides **7**(1,1,9−10) to quinazolines **8**(1,1,9−10). A summary of quinazoline formation is presented in Table 1.

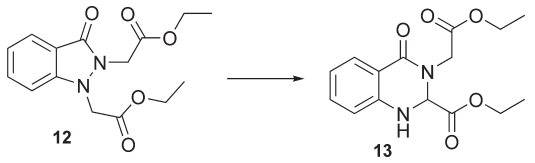
Discussion

Mechanism of Rearrangement. This base-catalyzed rearrangement started with scission of the nitrogen−nitrogen bond caused by the presence of the *N*-oxide, which was responsible for electronic activation of the electron-deficient nitrogen and assisted by the DBU-mediated proton subtraction (Scheme 4). Formation of the *N*-hydroxy derivative was important for subsequent water elimination facilitated by carbon−nitrogen bond formation. We confirmed the essential role of the *N*-oxide by preparing the deoxygenated analog of **7** according

SCHEME 4. Proposed Mechanism of Quinazoline Formation



SCHEME 5. Rearrangement of 2,2′-(3-Oxo-1*H*-indazole-1,2(3*H*)-diyl)diacetate



to a recently published protocol.[17] After 2 days of exposure to DBU containing DMF, no change of the indazole was observed.

No precedent for the transformation of indazole oxides to quinazolines was found. A distant analogy to the ring expansion of indazoles can be found in the rearrangement of diethyl 2,2′-(3-oxo-1*H*-indazole-1,2(3*H*)-diyl)diacetate **12** to ethyl 3-(2-ethoxy-2-oxoethyl)-4-oxo-1,2,3,4-tetrahydroquinazoline-2-carboxylate **13** (Scheme 5).[18,19]

Conclusion

We have described a convenient preparation of quinazolines via base-catalyzed rearrangement of 2*H*-indazoles 1-oxides, obtained by tandem carbon−carbon followed by nitrogen−nitrogen bond formations from easily accessible *N*-alkyl-2-nitro-*N*-(2-oxo-2-aryl-ethyl)-benzenesulfonamides using glycine, 2-nitrobenzenesulfonyl chlorides, and bromo ketones/acetates. The transformation tolerated a range of substituents; however, it was sensitive to their electronic properties. This synthesis does not require preparation of dedicated building blocks, rather it was carried out using commercially available compounds.

Experimental Section

Solid-phase syntheses were conducted on a manually operated Domino Block synthesizer[20] (www.torviq.com) in disposable polypropylene reaction vessels. Commercially available solvents, resins, and reagents were used. Wang resin (100−200 mesh, 1% DVB, 1.0 mmol/g) was obtained from Advanced ChemTech (Louisville, KY, www.peptide.com). Swelling of resins in DCM was measured before syntheses, and resins with swollen volume greater than 7 mL/g of dry resin were used.[21] All reactions occurred at ambient temperature (21 °C) unless stated otherwise.

Quinazoline-2,4-dicarboxylic Acid Diethyl Ester (3). A solution of diethyl iminodiacetate (1 mmol) in 2 mL of DCM and a solution of 2-nitrobenzenesulfonyl chloride (1 mmol) in 1 mL of DCM were combined. Lutidine (1 mmol) was added, and the reaction mixture was kept at ambient temperature overnight. The DCM was evaporated by a stream of nitrogen. The residual material was dissolved in anhydrous DMF, and DBU (4 mmol) was added. The reaction mixture remained at ambient temperature overnight. The product was isolated after purification by semipreparative HPLC. Yield 75.0 mg (25%). ESI-MS m/z = 275, $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.49 (d, J = 8.6 Hz, 1 H), 8.29 (d, J = 8.3 Hz, 1 H), 8.22 (t, J = 6.9 Hz, 1 H), 7.99 (t, J = 7.2 Hz, 1 H), 4.56 (q, J = 7.0 Hz, 2 H), 4.45 (q, J = 7.1 Hz, 2 H), 1.40 (q, J = 7.2 Hz, 6 H). ^{13}C NMR (300 MHz, DMSO): δ 164.7, 163.7, 159.1, 152.5, 151.5, 136.8, 132.1, 130.0, 126.6, 121.7, 63.5, 62.8, 14.8, 14.7 HRMS (FAB) m/z calcd for $C_{14}H_{15}N_2O_4$ 275.1026 $[M + H]^+$, found 275.1034.

Solid-Phase Synthesis Methods. Synthesis of the resins **5** was carried out according to published protocol.[10]

Alkylation with Bromoketones (Resins 6). The polypropylene fritted syringe was charged with the resin **5** (∼250 mg) and washed 3 times with DCM and 3 times with DMF. A solution of bromoketone (1.5 mmol) and DIEA (3 mmol) in 3 mL of DMF was added and shaken at room temperature for 7 h. Alkylation of resins **5** prepared from 4-CF_3-2-Nos-Cl and 4-NO_2-2-Nos-Cl or 4-CN and 3-NO_2 bromoketones was complete in 30 min. The resin was washed 3 times with DMF and 3 times with DCM.

Synthesis of Amides (Resins 7(1,1,9−10)). Resin **7**(1,1,8) (∼250 mg) was washed with THF and treated with a solution of 0.5 mL of 10 M NaOH in 10 mL of THF/MeOH (1:1) for 1 h. The resin was washed with THF, 3% AcOH in THF, THF, and DCM. A solution of HOBt (2 mmol, 306 mg) and DIC (2 mmol, 312 uL) in 4 mL of DMF was added to the resin and left at ambient temperature for 1 h. The resin was washed with DMF, and then a 1 M solution of amine (piperidine and 1-phenylpiperazine) in DMF (4 mL) was added and reacted for 1 h. The resin was washed with DMF and DCM.

Cyclization to Quinazolines (Resins 8). The polypropylene fritted syringe was charged with the resin **6** (∼250 mg) and washed 3 times with DCM and 3 times with anhydrous DMF. Cyclization was carried out at ambient temperature in 5 mL of DBU solution in DMF. Method A: 0.2 M DBU, overnight. Method B: 0.1 M DBU, 1.5 h. Method C: 0.1 M DBU, 10 min. The resin was washed 3 times with DMF, DCM, 5% AcOH in DCM, DCM, and MeOH.

Quinazolines 9. Resin **8** was treated with 50% TFA in DCM for 1 h. The cleavage cocktail was collected, and the resin was washed 2 times with 50% TFA in DCM. The washes were collected and evaporated by a stream of nitrogen. The oily residue was dissolved in MeOH and purified by semipreparative HPLC.

4-Benzoylquinazoline-2-carboxamide 9(1,1,1). Yield 10 mg (23%). ESI-MS m/z = 278, $[M + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.39−8.25 (m, 2 H), 8.19 (t, J = 7.5 Hz, 1 H), 8.03 (d, J = 8.0 Hz, 1 H), 8.00−7.91 (m, 3 H), 7.87 (t, J = 8.0 Hz, 1 H), 7.79 (t, J = 7.5 Hz, 1 H), 7.60 (t, J = 7.7 Hz, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 192.8, 165.0, 164.3, 153.7, 150.3, 135.9, 135.1, 134.6, 130.6, 130.5, 129.2, 129.2, 125.6, 121.0. HRMS m/z calcd for $C_{16}H_{11}N_3O_2$ $[M + H]^+$ 278.0924, found 278.0915

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Supporting Information Available: Spectroscopic data and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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