ACS Combinatorial Science

Research Article

pubs.acs.org/acscombsci

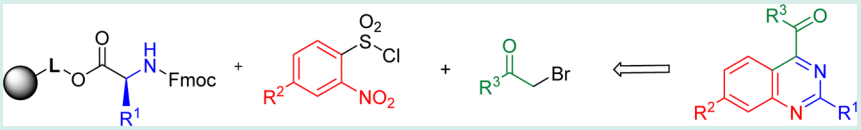
Traceless Solid-Phase Synthesis of Trisubstituted Quinazolines

Veronika Fülöpová,[†] Lauren Cziesla,[‡] Megan Fleming,[‡] Yiwei Lu,[‡] Adrienne Voelker,[‡] and Viktor Krchňák*[,†,‡]

[†]Department of Organic Chemistry, Institute of Molecular and Translational Medicine, Faculty of Science, Palacky University, 17. listopadu 12, 771 46 Olomouc, Czech Republic

[‡]Department of Chemistry and Biochemistry, University of Notre Dame, 251 Nieuwland Science Center, Notre Dame, Indiana 46556, United States

Supporting Information



ABSTRACT: A traceless polymer-supported synthesis of 4-benzoylquinazolines was developed using the following commercially available building blocks: Fmoc-α-amino acids, 2-nitrobenzensulfonyl chlorides and α-bromoacetophenones. The acyclic intermediates underwent base-catalyzed rearrangement involving C−C and N−N bond formation followed by ring expansion and yielded resin-bound dihydroquinazoline-2-carboxylic acids. After they were released from the resin by treatment with trifluoroacetic acid, base-mediated decarboxylation produced the target quinazolines in moderate-to-high yields and purities.

KEYWORDS: *amino acids, α-bromoacetophenones, bromoketone, indazole oxides, nitrobenzenesulfonyl chlorides, quinazolines, solid-phase synthesis, traceless synthesis*

INTRODUCTION

Natural and synthetic quinazolines are a particularly important class of biologically active nitrogenous heterocycles with known insecticidal,[1] antibacterial,[2] antiviral[3] and anticancer[4] effects. Quinazoline derivatives are used in the agrochemical, veterinary and pharmaceutical industries. Several commercial antitumor drugs, such as Iressa (Figure 1, structure **I**), Tarceva (**II**), and Caprelsa (**III**), are potent tyrosine kinase inhibitors.[5] Quinazolines condensed with different heterocycles have been shown to act as antitumor DNA ligands that target DNA topoisomerase.[6] In this context, the development of novel synthetic routes to access pharmacologically relevant quinazolines represents an attractive and practical task.

Although numerous reports have described the preparation and properties of structurally diverse quinazolines, only a few have addressed the synthesis and properties of 4-keto derivatives **IV**. Miyashita and co-workers[7] developed a method based on the reaction of 4-chloroquinazoline with *p*-substituted benzaldehydes in tetrahydrofuran. The presence of a catalytic amount of 1,3-dimethylimidazolium iodide facilitated the formation of the resulting quinazoline ketone **IV**. The second approach involves the introduction of aryl ketones to sp^3 C−H groups of 4-methylquinazolines through the use of a Pd(0) catalyst with atmospheric oxygen as the sole oxidant.[8] Toh and colleagues[9] reported a process involving the Cu(II)-catalyzed preparation of the target quinazolines via intramolecular aerobic oxidation of starting *N*-alkynylamidines. We have recently reported a polymer-supported synthesis of quinazoline ketones from α-ketosulfonamides via indazole oxide intermediates.[10] Exposure of α-ketosulfonamides to 1,8-diazabicycloundec-7-ene (DBU) led to *C*-arylation followed by spontaneous cyclization to the corresponding indazole oxide.[11] In the present report, we describe an efficient extension of the *C*-arylation methodology for the traceless solid-phase synthesis of derivatives of quinazoline **IV** with a substitution pattern not accessible by previous syntheses. Traceless solid-phase synthesis is a particularly attractive methodology because it enables the synthesis of target compounds without any "trace" of the linker that was used to immobilize the first building block while simultaneously taking advantage of the very time-efficient solid-phase synthesis method.[12]

RESULTS AND DISCUSSION

The traceless solid-phase synthesis of 4-benzoylquinazolines was carried out according to Scheme 1 using the following three commercially available building blocks: Fmoc-protected α-amino acids, 2-nitrobenzenesulfonyl (2-Nos) chlorides and α-bromoacetophenones (for the structures and numbering of the building blocks, refer to Figure 2). The first reaction step involved the immobilization of Fmoc-protected α-amino acids on Wang resin **1** via an ester bond. Removal of the Fmoc group provided the polymer-supported amines, which underwent sulfonylation with 2-Nos chlorides to yield resins **2**. In the next step, the activating/protecting 2-Nos group allowed Fukuyama alkylation[13] of the sulfonamide intermediates **2** with diversely substituted α-bromoacetophenones, thereby yielding resins **3**

Received: April 19, 2015
Revised: June 22, 2015
Published: July 6, 2015

DOI: 10.1021/acscombsci.5b00060
ACS Comb. Sci. 2015, 17, 470−473

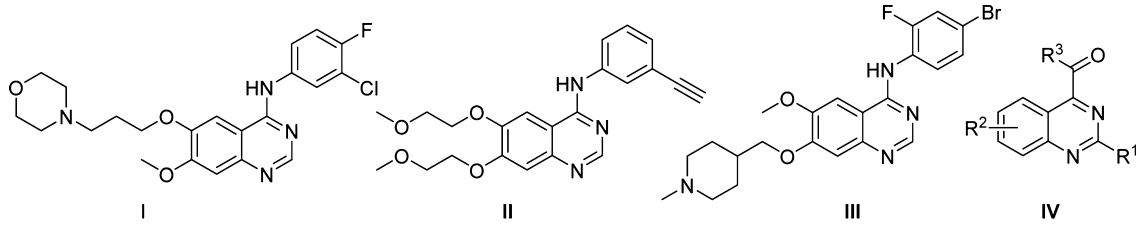
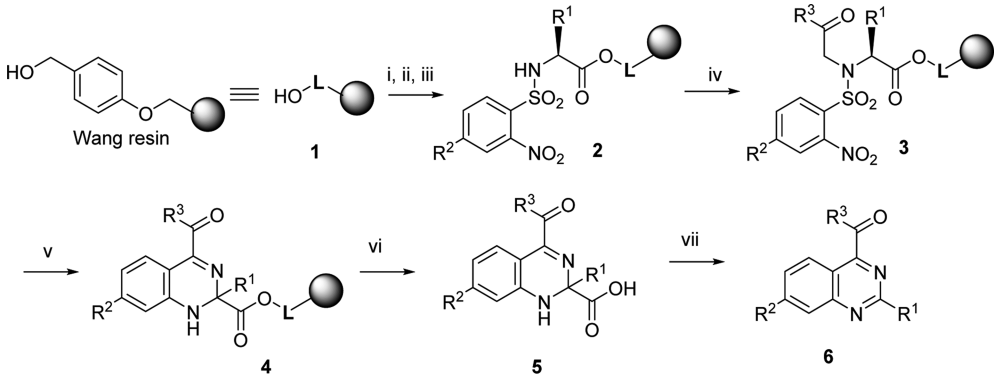


Figure 1. Structures of quinazolines.

Scheme 1. Synthetic Route for the Preparation of the Target 4-Benzoylquinazolines[a]



[a]Reagents: (i) Wang resin, Fmoc-protected α-amino acid, DMAP, DIC, dichloromethane (DCM)/DMF (1:1), rt, overnight; (ii) 50% piperidine in DMF, rt, 15 min; (iii) 2-Nos-Cl, 2,6-lutidine, DCM, rt, overnight; (iv) α-bromoacetophenone, DIEA, DMF, rt, overnight; (v) DBU, DMF, rt, 30 min to overnight (see Supporting Information); (vi) 50% TFA in DCM, rt, 1 h; (vii) neutralization with ammonium acetate, C18 cartridge, see Table 1 for decarboxylation time.

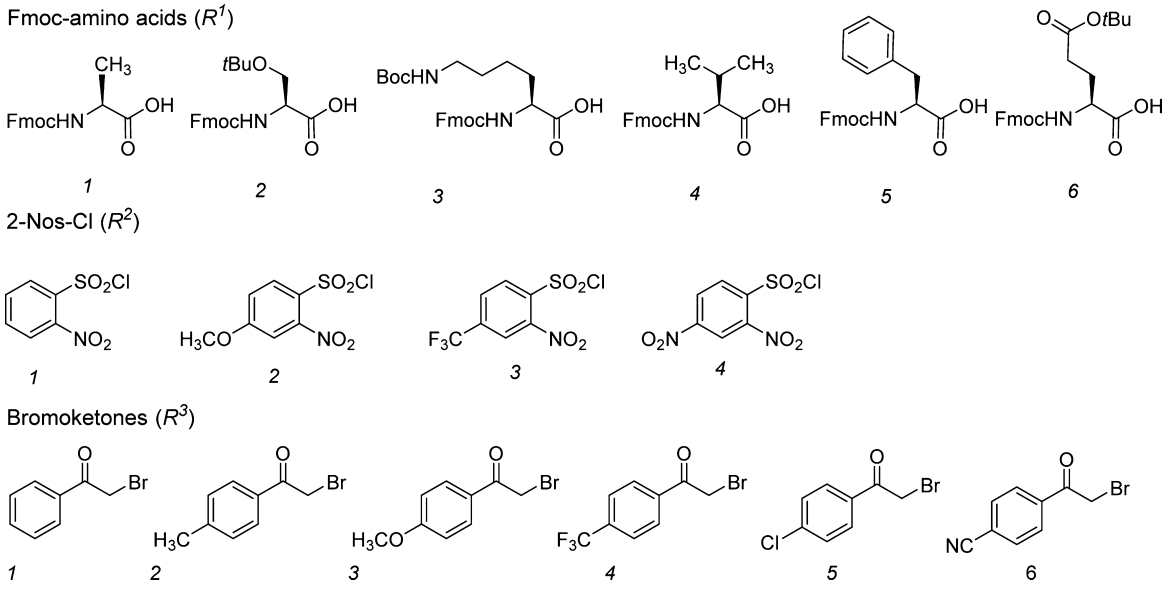


Figure 2. Fmoc-protected α-amino acids, 2-Nos-Cl, and α-bromoacetophenones used for the synthesis.

(overall purity >65%, as indicated by LC traces at 205−400 nm). Alkylation of some derivatives was repeated to achieve complete conversion (for details refer to Supporting Information).

Polymer-supported acyclic alkylated sulfonamides **3** were treated with DBU to trigger base-catalyzed tandem C−C bond formation followed by cyclization to indazole oxides via N−N bond formation[11] and conversion of the indazole oxides to quinazolines **4**.[10] Resin-bound quinazolines were cleaved from the polymer support by a cleavage cocktail of 50% TFA in DCM, yielding carboxylates **5** with acceptable purities (51−70%) for a 6-step synthesis (Table 1). LC/MS analysis of crude preparations did not reveal any presence of the decarboxylated compounds **6**. Only a trace amount of decarboxylated product **6** was detected by LC/MS analysis after HPLC purification in acetonitrile/aqueous 0.1% TFA and freeze-drying overnight.

To determine the decarboxylation reaction conditions, cleaved crude samples were purified by reversed-phase HPLC in an aqueous ammonium acetate buffer/acetonitrile. Compounds **5** spontaneously decarboxylated in aqueous ammonium acetate/acetonitrile solution at ambient temperature. The rate of decarboxylation, which was monitored by LC/MS, was

DOI: 10.1021/acscombsci.5b00060
ACS Comb. Sci. 2015, 17, 470−473

Table 1. Synthesized Derivatives of Quinazolines 6

entry	R^1	R^2	R^3	purity[a] [%]	decarb. time[b] (d)	yield[c] [%]
6{*1,1,1*}	CH_3	H	Ph	52	1	12
6{*1,1,2*}	CH_3	H	4-CH_3−C_6H_4	53	2	56
6{*1,1,3*}	CH_3	H	4-CH_3O−C_6H_4	70	1	16
6{*1,1,5*}	CH_3	H	4-Cl−C_6H_4	66	1	47
6{*1,1,6*}	CH_3	H	4-CN−C_6H_4	61	1	39
6{*1,3,1*}	CH_3	CF_3	Ph	55	4	41
6{*1,4,1*}	CH_3	NO_2	Ph	69	5	8
6{*2,1,1*}	CH_2OH	H	Ph	64	1	23
6{*3,1,2*}	$(CH_2)_4NH_2$	H	4-CH_3−C_6H_4	52	1	35
6{*4,1,1*}	$CH(CH_3)_2$	H	Ph	54	1	23
6{*4,1,4*}	$CH(CH_3)_2$	H	4-CF_3−C_6H_4	63	5	28
6{*5,1,1*}	CH_2Ph	H	Ph	51	1	24
6{*6,1,1*}	$(CH_2)_2CO_2H$	H	Ph	59	1	38

[a]Purity of the crude product **5** after a 6-step synthesis. [b]Decarboxylation time at ambient temperature. [c]Yield of HPLC-purified compound **6** after a 7-step synthesis.

dependent on the character of the substituents on the aromatic rings; it was typically done after overnight exposure, it slowed, as expected, in the case of electron-withdrawing substituents (Table 1).

Because the decarboxylation occurred under mild conditions (ambient temperature, ammonium acetate buffer that can be removed by freeze-drying) we did not search for alternative reaction conditions and used the following protocol for the synthesis on preparative scale (typically 250 mg of resin). Solution of crude sample was neutralized with ammonium acetate, adsorbed onto octadecyl-functionalized silica gel, eluted with 80% acetonitrile in aqueous ammonium acetate buffer and left at ambient temperature to decarboxylate (Table 1). The final products **6** were purified by semipreparative HPLC in aqueous ammonium acetate/acetonitrile and isolated after freeze-drying.

To address the scope and limitations of this route for quinazolines, we prepared resin-bound intermediates **3** using a set of α-amino acids, 2-Nos chlorides and α-bromoacetophenones containing electron-withdrawing and electron-donating groups (Figure 2). The synthesis was fully compatible with all of the tested building blocks, with the exception of 4-methoxy-2-nitrobenzenesulfonyl chloride, which contained the electron-donating OCH_3 group. The purities of the final crude compounds ranged from 52% to 70%, and the total yields were respectable given the 7-step synthesis (Table 1).

The LC/MS analysis of crude decarboxylated products revealed one common side-product, quinazoline 1-oxide, typically present in a relatively small amount (below 10%). To confirm the structure of the *N*-oxide, we isolated and characterized the *N*-oxides **7**{*1,1,1*} and **7**{*1,4,1*} (Figure 3). In those two cases the yields of compounds **6**{*1,1,1*} and **6**{*1,4,1*} were substantially lower compared to those of the other compounds and the *N*-oxides were major components of the crude preparation.

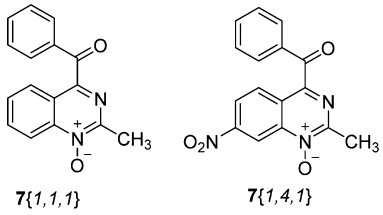


Figure 3. Formation of the *N*-oxide side-products **7**.

CONCLUSION

Traceless solid-phase synthesis of quinazolines using commercially available or easily accessible building blocks, including Fmoc-α-amino acids, 2-nitrobenzenesulfonyl chlorides, and α-bromoacetophenones, represents a convenient route to an important class of pharmacologically relevant nitrogenous heterocycles. The synthesis was compatible with a range of substituents on all of the building blocks, proceeded under mild reaction conditions, included three positions of diversity and provided the target compounds in good overall yields and crude purities.

EXPERIMENTAL PROCEDURES

General. The solid-phase syntheses were performed in plastic reaction vessels (syringes, each equipped with a porous disc) using a manually operated synthesizer.[14] Commercially available Wang resin (100−200 mesh, 1.0 mmol/g) was used. The volume of wash solvent was 10 mL per 1 g of resin. For washing, the resin slurry was shaken with fresh solvent for at least 1 min before the solvent was changed. The yields of the crude products were calculated with respect to the loading of the first building block. Individual reaction steps for the syntheses of resins **4** are described elsewhere.[10]

Cleavage, Decarboxylation, and Isolation of Quinazolines 6. Resin **4** (typically 100−250 mg) was treated with 50% TFA in DCM (1−3 mL) at rt for 90 min. The TFA solution was collected, the resin was washed 3× with 50% TFA in DCM (3 mL), and the combined extracts were evaporated by a stream of nitrogen. The oily residue **5** was dissolved in 2 mL of MeCN and diluted with 18 mL of 10 mM aqueous ammonium acetate. Depending on the type of compound, a solution or opalescent solution, occasionally with precipitation, was formed. The pH of the solution was adjusted to approximately 8 using solid ammonium acetate. A 10 mL SPE column was charged with 2 g of octadecyl-functionalized silica gel, and the plug was covered with a porous disc. The sorbent was wetted with 5 mL of MeCN and washed with 5 mL of 10 mM aqueous ammonium acetate. The solution of the target compound was passed through the column and washed with 5 mL of 10 mM aqueous ammonium acetate. The target compound was eluted with 10 mL of 80% MeCN in aqueous ammonium acetate. The

DOI: 10.1021/acscombsci.5b00060
ACS Comb. Sci. 2015, 17, 470−473

solution was analyzed by LC/MS to determine the decarboxylation progress. After decarboxylation was complete, typically overnight, the target compound was purified by semipreparative reversed-phase HPLC. All products **6** were isolated as amorphous solids by freeze-drying and were subsequently characterized by LC/MS, HRMS, and ^{1}H and ^{13}C NMR.

■ ASSOCIATED CONTENT

Supporting Information

Details of experimental procedures, spectroscopic data for synthesized compounds, and copies of NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00060.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: vkrchnak@nd.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Department of Chemistry and Biochemistry University of Notre Dame, by the project CZ.1.07/2.4.00/17.0015 from the European Social Fund.We gratefully appreciate the use of the NMR facility at the University of Notre Dame.

■ REFERENCES

(1) Latli, B.; Wood, E.; Casida, J. E. Insecticidal Quinazoline Derivatives with (Trifluoromethyl)diazirinyl and Azido Substituents as NADH:Ubiquinone Oxidoreductase Inhibitors and Candidate Photoaffinity Probes. *Chem. Res. Toxicol.* **1996**, *9* (2), 445−450.

(2) Bedi, P. M. S.; Kumar, V.; Mahajan, M. P. Synthesis and biological activity of novel antibacterial quinazolines. *Bioorg. Med. Chem. Lett.* **2004**, *14* (20), 5211−5213.

(3) Rojas-Aguirre, Y.; Hernández-Luis, F.; Mendoza-Martínez, C.; Sotomayor, C. P.; Aguilar, L. F.; Villena, F.; Castillo, I.; Hernández, D. J.; Suwalsky, M. Effects of an antimalarial quinazoline derivative on human erythrocytes and on cell membrane molecular models. *Biochim. Biophys. Acta, Biomembr.* **2012**, *1818* (3), 738−746.

(4) Gundla, R.; Kazemi, R.; Sanam, R.; Muttineni, R.; Sarma, J. A. R. P.; Dayam, R.; Neamati, N. Discovery of Novel Small-Molecule Inhibitors of Human Epidermal Growth Factor Receptor-2: Combined Ligand and Target-Based Approach. *J. Med. Chem.* **2008**, *51* (12), 3367−3377.

(5) Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. Microwave-Promoted Syntheses of Quinazolines and Dihydroquinazolines from 2-Aminoarylalkanone O-Phenyl Oximes. *J. Org. Chem.* **2009**, *74* (14), 4934−4942.

(6) Malecki, N.; Carato, P.; Rigo, B.; Goossens, J. F.; Houssin, R.; Bailly, C.; Hénichart, J. P. Synthesis of condensed quinolines and quinazolines as DNA ligands. *Bioorg. Med. Chem.* **2004**, *12* (3), 641−647.

(7) Miyashita, A.; Matsuda, H.; Suzuki, Y.; Iwamoto, K.; Higashino, T. Catalytic Action of Azolium Salts. IV. Preparations of 4-Aroylquinazolines and 4-Aroyl-1H-pyrazolo[3, 4-d]pyrimidines by Catalytic Action of 1, 3-Dimethylimidazolium Iodide. *Chem. Pharm. Bull.* **1994**, *42* (10), 2017−2022.

(8) Zhao, D.; Zhu, M. X.; Wang, Y.; Shen, Q.; Li, J. X. Pd(0)-catalyzed benzylic arylation-oxidation of 4-methylquinazolines via sp^3 C-H activation under air conditions. *Org. Biomol. Chem.* **2013**, *11* (37), 6246−6249.

(9) Toh, K. K.; Sanjaya, S.; Sahnoun, S.; Chong, S. Y.; Chiba, S. Copper-Catalyzed Aerobic Intramolecular Carbo- and Amino-Oxygenation of Alkynes for Synthesis of Azaheterocycles. *Org. Lett.* **2012**, *14* (9), 2290−2292.

(10) Křupková, S.; Slough, G. A.; Krchňák, V. Synthesis of Quinazolines from *N*-(2-Nitrophenylsulfonyl)iminodiacetate and a-(2-Nitrophenylsulfonyl)amino Ketones *via* 2*H*-Indazole 1-Oxides. *J. Org. Chem.* **2010**, *75* (13), 4562−4566.

(11) Bouillon, I.; Zajíček, J.; Pudelová, N.; Krchňák, V. Remarkably efficient synthesis of 2H-indazole 1-oxides and 2H-indazoles via tandem carbon-carbon followed by nitrogen-nitrogen bond formation. *J. Org. Chem.* **2008**, *73* (22), 9027−9032.

(12) Krchňák, V.; Holladay, M. W. Solid phase heterocyclic chemistry. *Chem. Rev.* **2002**, *102*, 61−91.

(13) Fukuyama, T.; Jow, C. K.; Cheung, M. 2- and 4-Nitrobenzenesulfonamides: Exceptionally versatile means for preparation of secondary amines and protection of amines. *Tetrahedron Lett.* **1995**, *36* (36), 6373−6374.

(14) Krchňák, V.; Paděra, V. The domino blocks: A simple solution for parallel solid-phase organic synthesis. *Bioorg. Med. Chem. Lett.* **1998**, *8* (22), 3261−3264.

DOI: 10.1021/acscombsci.5b00060
ACS Comb. Sci. 2015, 17, 470−473