JOC The Journal of Organic Chemistry

pubs.acs.org/joc Note

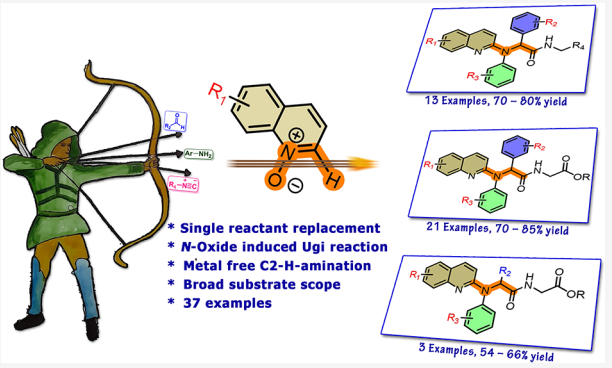
N-Oxide-Induced Ugi Reaction: A Rapid Access to Quinoline-C2-amino Amides via Deoxygenative C(sp^2)–H Functionalization

Naveenkumar Anugu, Sanjeeva Thunga, Soumya Poshala, and Hari Prasad Kokatla*

Cite This: *J. Org. Chem.* 2022, 87, 10435–10440 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A logic-based replacement of the carboxylic acid component of the Ugi reaction by quinoline *N*-oxides has been developed. In this approach, the carboxylic isostere, quinoline *N*-oxide, plays a vital role by shifting the equilibria toward the product side with irreversible addition onto the C2-position of the *N*-oxide. Thus, aldehydes react with amines, isocyanides, and quinoline *N*-oxides to furnish quinoline four-component Ugi adducts. The unique reactivity of *N*-oxides with Ugi components opens an efficient synthetic route for the preparation of biologically active compounds.



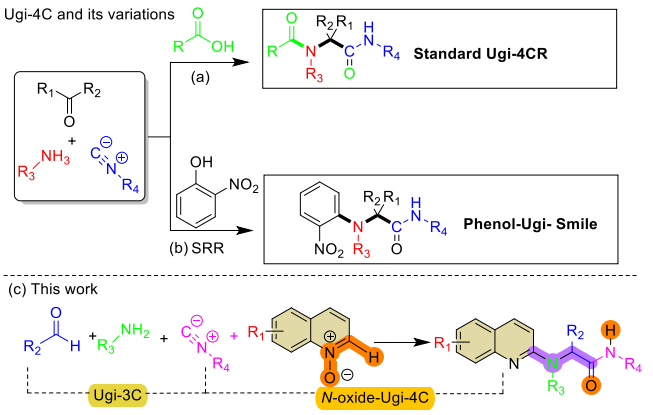
The Ugi four-component reaction (U-4CR) is one of the most extensively studied multicomponent reactions, which readily gives access to peptide-like structures known as bis-amides or peptomers with potent biological activity and structural diversity.[1,2] This revolutionary approach by Ugi in 1959 has opened a new platform in isocyanide-based multicomponent reactions (IMCRs), and it has also been in the limelight recently for adhering to green chemistry principles such as atom-economy, reduced number of steps, and use of green solvents.[3]

Due to the emergence of combinatorial chemistry and high-throughput screening for efficient preparation of bioactive molecules, medicinal chemists have focused more on the Ugi reaction in polymer-supported solid-phase synthesis, in combination with postcondensation and modified Ugi conditions.[4] Modifications to the Ugi reaction have mainly relied on the single reactant replacement (SRR) approach.[5] The single reactant replacement approach involves the logic-based alteration of one component by another component with a similar mode of reactivity which is required for the known MCR to improve its efficiency and to provide new synthetic routes. For instance, the Ugi reaction is the first SRR approach of the Passerini reaction and has led to new MCRs in which imines were introduced in place of carbonyls to synthesize a library of α-acylamino amides. This novel SSR approach triggered the development of new MCRs in the field of drug discovery (Scheme 1a).

In this approach, replacement of multifaceted carboxylic acids in U-4CR poses challenges because of the key role they play in many equilibrium steps, including formation of the imine, nucleophilic addition of moderately reactive isocyanides, and the final Mumm rearrangement to provide the target compound.[6] In fact, exchange of the carboxylic acid with other acidic components in the Ugi reaction has shown inferior results.[7−13]

Later in 2005, El Kaïm et al. reported the first use of Smiles rearrangements in the Ugi reaction to synthesize *N*-arylated

Scheme 1. Single Reactant Replacements in the Ugi Reaction



Received: April 17, 2022
Published: July 18, 2022

https://doi.org/10.1021/acs.joc.2c00904
J. Org. Chem. 2022, 87, 10435−10440

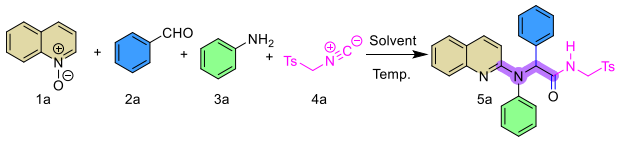
peptides (Scheme 1b).[14] In this phenol Ugi–Smiles multicomponent reaction, electron-deficient phenols are used as acidic surrogates to give *O*-aryl- and *N*-arylamides.[15] This sequence opened rapid access to *O*-aryl- and *N*-arylamides but has its own limitations such as the requirement of strong activation energy, moderate yields, and pK_a dependency. Thus, replacement of the carboxylic acid in U-4CR with (i) weak inorganic acids (H_2O, HN_3, HOCN, HSCN, H_2S, H_2Se) or (ii) electron-deficient nitrophenols, pyridines, and pyrimidines has found limited access since the discovery of the reactions.

Recently, aromatic amine *N*-oxides have attracted considerable attention due to the ability of the *N*-oxide moiety to act as an ortho-directing group to control the regioselectivity of the C–H activation.[16] In particular, *N*-oxide-directed C2-selective C–N bond formation has become a focus due to the importance of 2-aminoquinolines in medicinal chemistry and pharmaceuticals.[17] In all the approaches, *N*-oxides either react with promotors or coordinate with metals to activate the C2-position of aromatic *N*-oxides. Thus, the activated C2-position and nucleophilicity of oxygen of the *N*-oxide could be a promising route for single reactant replacement in the Ugi reaction to achieve a *N*-oxide-mediated Ugi four-component reaction (Scheme 1c).

In the continuation of our work on C2–H functionalization of aromatic amine *N*-oxides using isocyanides,[18] herein we report a *N*-oxide-induced Ugi reaction to access a library of 2-phenyl-2-(phenyl(quinolin-2-yl)amino)acetamide derivatives in one-pot reactions via C(sp^2)–H functionalization.

To test our hypothesis, initial screening experiments were conducted on quinoline *N*-oxide **1a** with benzaldehyde **2a**, aniline **3a**, and *p*-toluenesulfonylmethyl isocyanide (TosMIC) **4a** in suitable solvents and at temperatures to optimize the reaction conditions, and only the key results are reported in Table 1. The reaction of quinoline *N*-oxide **1a** (0.5 mmol) with benzaldehyde **2a** (0.5 mmol), aniline **3a** (0.5 mmol), and TosMIC **4a** (0.5 mmol) in CH_2Cl_2 at room temperature failed to give **5a** but at elevated temperature afforded the desired product **5a** in 10% yield (Table 1, entries 1 and 2). Standard spectroscopic analysis identified **5a** as *N*-(4-methylbenzyl)-2-phenyl-2-(phenyl(quinolin-2-yl)amino)acetamide, in line with the original design. This result revealed that the quinoline *N*-oxide **1a** indeed acted as a carboxylic acid isostere in the traditional Ugi reaction.

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	temp (°C)	time (h)	yield[b]
1	CH_2Cl_2	rt	24	0
2	CH_2Cl_2	40	12	10
3	$CHCl_3$	60	12	40
4	DCE	60	12	60
5	toluene	60	12	10
6	CH_3CN	60	9	80
7	CH_3NO_2	60	12	40
8	THF	60	12	70
9	CH_3OH	60	8	50
10	EtOH	60	8	45
11	DMF	60	12	trace
12	DMSO	60	2	20
13	CH_3CN	80	24	79

[a]Reaction conditions: quinoline *N*-oxide **1a** (0.5 mmol), benzaldehyde **2a** (0.5 mmol), aniline **3a** (0.5 mmol), isocyanide **4a** (0.5 mmol), and solvent (2.0 mL). [b]Isolated yield.

To our delight, the yield of *N*-(4-methylbenzyl)-2-phenyl-2-(phenyl(quinolin-2-yl)amino)acetamide **5a** was increased to 60% at elevated temperatures (Table 1, entries 3 and 4). These results suggested that heating is required to get a better yield of product. Next, we carried out the reaction in various solvents to assess their effect on the reaction efficiency. Among other solvents tested, such as toluene, CH_3NO_2, THF, alcohols, DMF, and DMSO, CH_3CN turned out to be superior for this transformation (Table 1, entries 5–12). Further change in the temperature and time has no effect on the yields of the reaction (Table 1, entry 13).

To explore the scope of this new four-component reaction, we examined diversely substituted quinoline *N*-oxides with aromatic aldehydes, anilines, and TosMIC (Table 2a). Quinoline *N*-oxides unsubstituted and substituted at various positions reacted smoothly to give the respective products in excellent yields (Table 2a). Substitutions on the nitrogenous quinoline ring were also well tolerated to deliver corresponding *N*-(4-methylbenzyl)-2-phenyl-2-(phenyl(quinolin-2-yl)-amino)acetamides **5e,f** in 74–77% yields (Table 2a). Presence of a donor group on the fourth and sixth position of quinoline gave the target products **5g,h** in 80% yield.

Likewise, 4,7-dichloro- and 4-chloro-6-bromo substitutions on the quinoline *N*-oxides gave target products **5i,j** in 70–75% yields, respectively. Electron-donating and electron-withdrawing groups on the aldehyde allowed smooth reaction under the optimized reaction conditions.

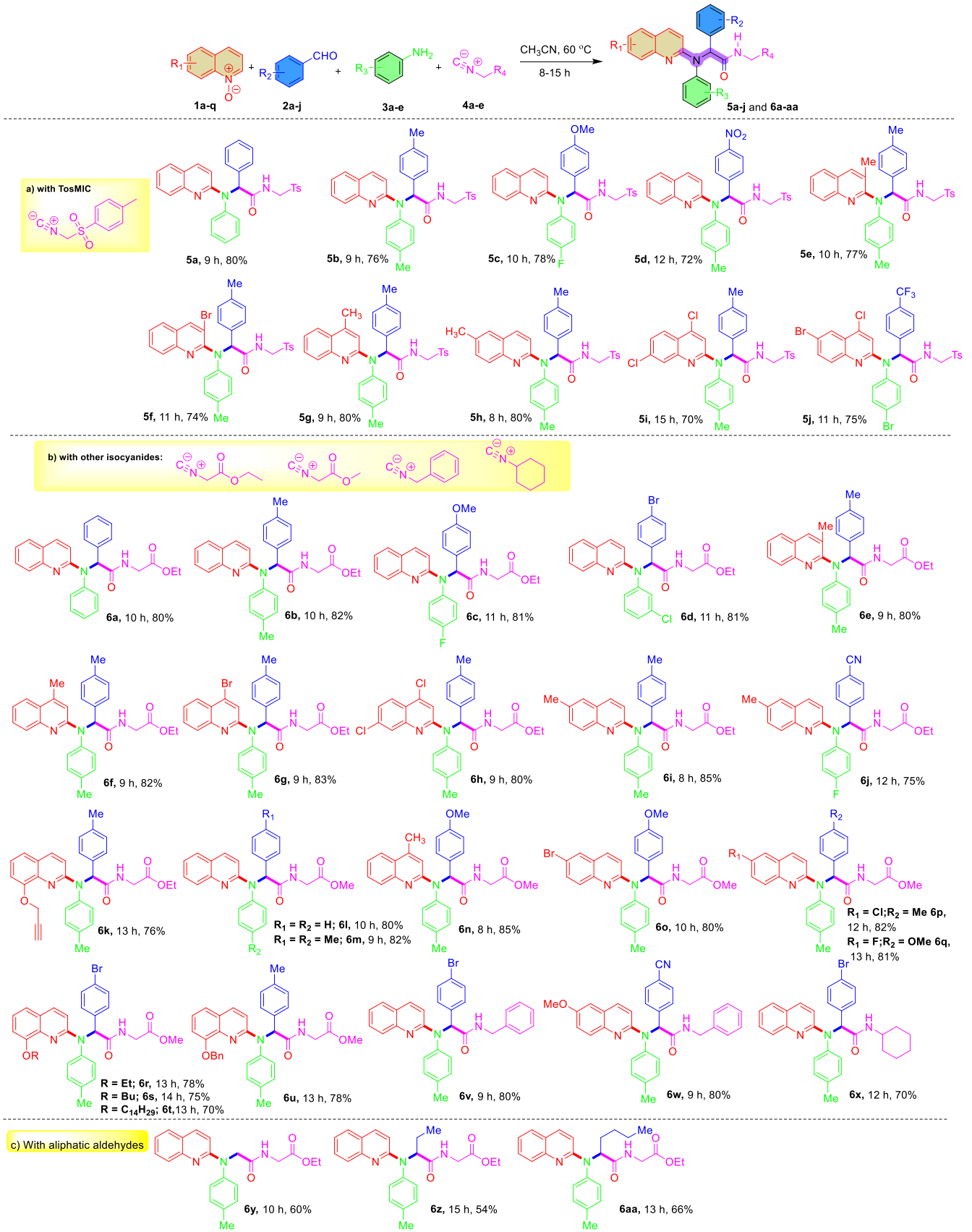
Next, we turned our attention to test the scope of various isocyanides with different quinoline *N*-oxides. Methyl 2-isocyanoacetate, ethyl 2-isocyanoacetate, benzyl isocyanide, and cyclohexyl isocyanide reacted smoothly with various quinoline *N*-oxides to obtain the Ugi products **6a–x** in 70–85% yield (Table 2b). The substitution on quinoline *N*-oxides with methyl, F, Cl, Br, and alkyl ethers did not alter the product yields (Table 2b).

Surprisingly, aliphatic aldehydes such as paraformaldehyde, propionaldehyde, and valeraldehyde gave the corresponding adducts **6y**, **6z**, and **6aa** in 60%, 54%, and 66% yields, respectively, which are less in comparison with aromatic aldehydes (Table 2c). Simple pyridine *N*-oxides are not reactive under these optimized conditions, which could be on account of their lower reactivity. Finally, we have evaluated the gram-scale synthesis of the developed protocol and obtained **6a** (2.17g) in 74% yield (see SI).

Next, we carried out several control experiments to determine the reaction mechanism (Scheme 2). Initially, quinoline **7** was treated with benzaldehyde **2a**, aniline **3a**, and isocyanide **4a** under the standard conditions, but no reaction was observed, which indicated the important role of *N*-oxide in this transformation (Scheme 2a). Later, 2-substituted quinoline *N*-oxide **8** was used to test the reactive position of quinoline *N*-oxide and found to be nonreactive under the optimized conditions (Scheme 2b). Then we conducted three-component reactions by varying the isocyanide and quinoline *N*-oxide and recorded the HRMS of reaction aliquots during the course of the reaction to determine the formation of intermediates (Scheme 2c,d).

https://doi.org/10.1021/acs.joc.2c00904
J. Org. Chem. 2022, 87, 10435–10440

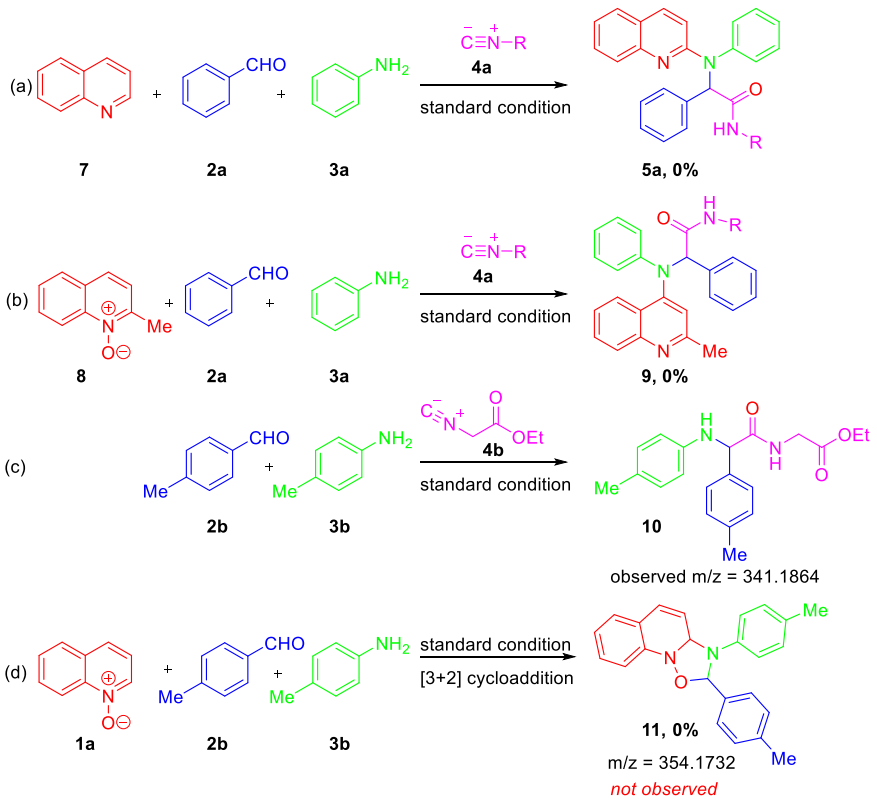
Table 2. Substrate Scope[a,b]



[a]Reaction conditions: quinoline *N*-oxides **1a−q** (0.5 mmol), aldehydes **2a−j** (0.5 mmol), anilines **3a−e** (0.5 mmol), isocyanides **4a−e** (0.5 mmol), CH_3CN (2 mL), 60 °C. [b]Isolated yields.

https://doi.org/10.1021/acs.joc.2c00904
J. Org. Chem. 2022, 87, 10435−10440

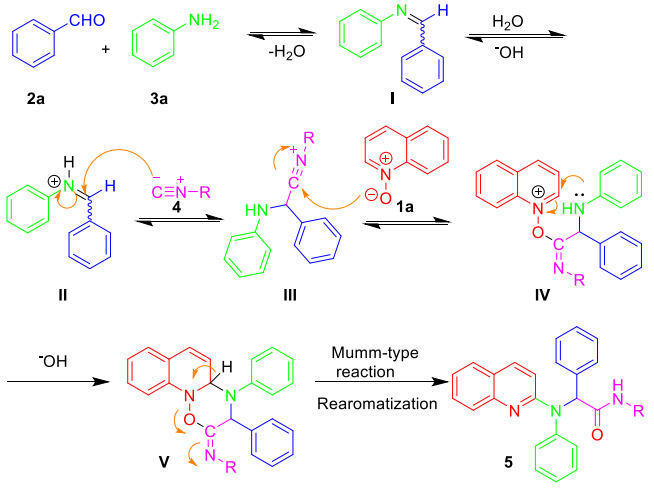
Scheme 2. Control Experiments



The HRMS data reveal the following points: (i) 4-methylbenzaldehyde **2b** initially reacts with *p*-toluidine **3b** to form an imine intermediate (observed m/z = 210.1280) which further undergoes addition by the ethyl 2-isocyanoacetate **4b** followed by hydrolysis to obtain product **10** (observed m/z = 341.1864) in the absence of quinoline *N*-oxide (Scheme 2c); (ii) quinoline *N*-oxides do not undergo [3 + 2] cycloaddition with the imine intermediate under standard conditions (Scheme 2d). On the basis of our control experiments and previous literature,[19,20] a plausible mechanism is illustrated in Scheme 3.

Initially, reaction between benzaldehyde **2a** and aniline **3a** forms imine intermediate **I**. Next, intermediate **I** undergoes protonation followed by nucleophilic addition of isocyanide **4** to form intermediate **III**. Later, the nucleophilic oxygen of *N*-oxide subsequently adds the carbon of the nitrilium ion to generate intermediate **IV**. Further, an irreversible nucleophilic addition of nitrogen (aniline) onto the activated C2-carbon of quinoline furnishes bicyclic intermediate **V**. Finally, intermediate **V** undergoes a Mumm-type reaction and rearomatization to obtain the desired product **5**.

Scheme 3. Proposed Mechanism



In summary, an aromatic *N*-oxide-based single reactant replacement approach of the Ugi reaction has been successfully developed. This approach opens a new era for quinoline *N*-oxides to be potent acid surrogates in multicomponent reactions. This method provides a one-pot synthesis of α-quinolinamino amides while ensuring a wide substrate scope with functional group tolerance. Further, exploring the use of Lewis acids and expanding the substrate scope of other aromatic *N*-oxides are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c00904.

Experimental details and procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 2159541 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

https://doi.org/10.1021/acs.joc.2c00904
J. Org. Chem. 2022, 87, 10435−10440

AUTHOR INFORMATION

Corresponding Author

Hari Prasad Kokatla − *Department of Chemistry, National Institute of Technology Warangal, Warangal, Telangana 506004, India;* orcid.org/0000-0001-7517-3377; Email: harikokatla@nitw.ac.in

Authors

Naveenkumar Anugu − *Department of Chemistry, National Institute of Technology Warangal, Warangal, Telangana 506004, India*

Sanjeeva Thunga − *Department of Chemistry, National Institute of Technology Warangal, Warangal, Telangana 506004, India*

Soumya Poshala − *Department of Chemistry, National Institute of Technology Warangal, Warangal, Telangana 506004, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.2c00904

Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by DST-INSPIRE (DST/INSPIRE/04/2014/002550) funded to H.P.K, N.A is thankful to DST-INSPIRE, and S.T. and S.P. are thankful to NIT Warangal for a fellowship. We are grateful to Mr. Peram Shyam Prasad and Dr. Satheesh Vanaparthi for valuable discussions. CRIF NITW for NMR and HRMS analysis is acknowledged.

DEDICATION

Dedicated to Professor Mahesh K. Lakshman on the occasion of his 60th birthday.

REFERENCES

(1) (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. Versammlungsberichte. *Angew. Chem.* **1959**, *71*, 386. (b) Ugi, I.; Steinbrückner, C. Über ein neues Kondensations-Prinzip. *Angew. Chem.* **1960**, *72*, 267−268. (c) Pirrung, M. C.; Sarma, K. D. Multicomponent Reactions Are Accelerated in Water. *J. Am. Chem. Soc.* **2004**, *126*, 444−445. (d) Bonnaterre, F.; BoisChoussy, M.; Zhu, J. Rapid Access to Oxindoles by the Combined Use of an Ugi Four-Component Reaction and a Microwave-Assisted Intramolecular Buchwald-Hartwig Amidation Reaction. *Org. Lett.* **2006**, *8*, 4351−4354. (e) Ilyin, A.; Kysil, V.; Krasavin, M.; Krashvili, I.; Ivachtchenko, A. V. Complexity-Enhancing Acid-Promoted Rearrangement of Tricyclic Products of Tandem Ugi 4CC/Intramolecular Diels−Alder Reaction. *J. Org. Chem.* **2006**, *71*, 9544−9547. (f) Sanudo, M.; Marcaccini, S.; Basurto, S.; Torroba, T. Synthesis of 3-Hydroxy-6-oxo[1,2,4]triazin-1-yl Alaninamides, a New Class of Cyclic Dipeptidyl Ureas. *J. Org. Chem.* **2006**, *71*, 4578−4584. (g) Marcaccini, S.; Torroba, T. The use of the Ugi four-component condensation. *Nature Protoc.* **2007**, *2*, 632−639.

(2) (a) For recent reviews, see: Fouad, M. A.; Abdel-Hamid, H.; Ayoup, M. S. Two decades of recent advances of Ugi reactions: synthetic and pharmaceutical applications. *RSC Adv.* **2020**, *10*, 42644−42681. (b) Dömling, A. Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry†. *Chem. Rev.* **2006**, *106*, 17−89. (c) Banfi, L.; Riva, R. The Passerini Reaction. *Org. React.* **2005**, *65*, 1−140. (d) Zhu, J. Recent Developments in the Isonitrile-Based Multicomponent Synthesis of Heterocycles. *Eur. J. Org. Chem.* **2003**, *2003*, 1133−1144. (e) Ugi, I.; Werner, B.; Dömling, A. The Chemistry of Isocyanides, their MultiComponent Reactions and their Libraries. *Molecules* **2003**, *8*, 53−66. (f) Hulme, C.; Gore, V. Multi-component reactions: emerging chemistry in drug discovery" 'from xylocain to crixivan. *Curr. Med. Chem.* **2003**, *10*, 51−80.

(3) Barreto, A. d. F. S.; Santos, V. A. d.; Andrade, C. K. Z. Synthesis of acylhydrazino-peptomers, a new class of peptidomimetics, by consecutive Ugi and hydrazino-Ugi reactions. *Beilstein J. Org. Chem.* **2016**, *12*, 2865−2872.

(4) (a) Ma, Z.; Xiang, Z.; Luo, T.; Lu, K.; Xu, Z.; Chen, J.; Yang, Z. J. Synthesis of Functionalized Quinolines via Ugi and Pd-Catalyzed Intramolecular Arylation Reactions. *Comb. Chem.* **2006**, *8*, 696−704. (b) Xua, Z.-G.; Ding, Y.; Meng, J.-P.; Tang, D.-Y.; Li, Y.; Lei, J.; Xu, C.; Chen, Z.-Z. Facile Construction of Hydantoin Scaffolds via a Post-Ugi Cascade Reaction. *Synlett* **2018**, *29*, 2199−2202. (c) Vàradi, A.; Palmer, T. C.; Notis Dardashti, R.; Majumdar, S. Isocyanide-Based Multicomponent Reactions for the Synthesis of Heterocycles. *Molecules* **2016**, *21*, 1−22. (d) Zech, G.; Kunz, H. Synthesis of a Polymer-Bound Galactosylamine and Its Application as an Immobilized Chiral Auxiliary in Stereoselective Syntheses of Piperidine and Amino Acid Derivatives. *Chem.-Eur. J.* **2004**, *10*, 4136−4149. (e) Cankařová, N.; Krchňák, V. Isocyanide Multicomponent Reactions on Solid Phase: State of the Art and Future Application. *Int. J. Mol. Sci.* **2020**, *21*, 9160.

(5) (a) For reviews, see: Ganem, B. Strategies for Innovation in Multicomponent Reaction Design. *Acc. Chem. Res.* **2009**, *42*, 463−472. (b) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. Multicomponent Reaction Design in the Quest for Molecular Complexity and Diversity. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234 For selected examples, see:. (c) Xia, Q.; Ganem, B. Metal-promoted variants of the Passerini reaction leading to functionalized heterocycles. *Org. Lett.* **2002**, *4*, 1631−1634.

(6) (a) Mumm, O. Umsetzung von Säureimidchloriden mit Salzen organischer Säuren und mit Cyankalium. *Ber. Dstch. Chem. Ges.* **1910**, *43*, 886−893. (b) Schwarz, S. P. Preparation of acyclic isoimides and their rearrangement rates to imides. *J. Org. Chem.* **1972**, *37* (18), 2906−2908.

(7) Ugi, I. The α-Addition of Immonium Ions and Anions to Isonitriles Accompanied by Secondary Reactions. *Angew. Chem., Int. Ed.* **1962**, *1*, 8−21.

(8) (a) Keating, T. A.; Armstrong, R. W. The Ugi Five-Component Condensation Using CO_2, CS_2, and COS as Oxidized Carbon Sources. *J. Org. Chem.* **1998**, *63*, 867−871. (b) Heck, S.; Dömling, A. A Versatile Multi-Component One-Pot Thiazole Synthesis. *Synlett* **2000**, 424−426 and references cited therein.

(9) (a) McFarland, J. W. Reactions of Cyclohexylisonitrile and Isobutyraldehyde with Various Nucleophiles and Catalysts. *J. Org. Chem.* **1963**, *28*, 2179−2181. (b) Opitz, G.; Merz, W. Enamine, X. Einwirkung von Carbonsäuren auf Dien-amine. *Justus Liebigs Ann. Chem.* **1962**, *652*, 163−175.

(10) (a) Ugi, I.; Rosendahl, F. K.; Bodesheim, F. Isonitriles, XIII. Condensation of primary amines and ketones with isonitriles and rhodanic acid. *Liebigs Ann. Chem.* **1963**, *666*, 54−61. (b) Bienayme, H.; Bouzid, K. Synthesis of rigid hydrophobic tetrazoles using an Ugi multi-component heterocyclic condensation. *Tetrahedron Lett.* **1998**, *39*, 2735−2738 and references cited therein.

(11) (a) Hagedorn, I.; Eholzer, U.; Winkelmann, H. D. Beitrag zur Isonitril Chemie. *Angew. Chem.* **1964**, *76*, 583−584. (b) Hagedorn, I.; Eholzer, U. Isonitrile, VII. Einstufige Synthese von α-Hydroxysäure-amiden durch Abwandlung der Passerini-Reaktion. *Chem. Ber.* **1965**, *98*, 936−940.

(12) (a) Ugi, I.; Meyr, R. Isonitrile, V. Erweiterter Anwendungsbereich der Passerini-Reaktion. *Chem. Ber.* **1961**, *94*, 2229−2233. (b) Nixey, T.; Hulme, C. Rapid generation of cis-constrained norstatine analogs using a $TMSN_3$-modified Passerini MCC/N-capping strategy. *Tetrahedron Lett.* **2002**, *43*, 6833−6835.

(13) Henkel, B.; Beck, B.; Westner, B.; Mejat, B.; Dömling, A. Convergent multicomponent assembly of 2-acyloxymethyl thiazoles. *Tetrahedron Lett.* **2003**, *44*, 8947−8950.
(14) (a) El Kaïm, L.; Grimaud, L.; Oble, J. Phenol Ugi-Smiles Systems: Strategies for the Multicomponent *N*-Arylation of Primary Amines with Isocyanides, Aldehydes, and Phenols. *Angew. Chem., Int. Ed.* **2005**, *44*, 7961−7964. (b) El Kaïm, L.; Gizolme, M.; Grimaud, L. O-Arylative Passerini Reactions. *Org. Lett.* **2006**, *8*, 5021−5023. (c) El Kaïm, L.; Grimaud, L.; Pravin, P. Ugi-Smiles Couplings of 4-Substituted Pyridine Derivatives: A Fast Access to Chloroquine Analogues. *Org. Lett.* **2012**, *14*, 476−478 and references cited therein.
(15) (a) For reviews of Ugi-Smiles couplings, see: El Kaïm, L.; Grimaud, L. Ugi-Smiles and Passerini-Smiles Couplings: A Story About Phenols in Isocyanide-Based Multicomponent Reactions. *Eur. J. Org. Chem.* **2014**, *35*, 7749−7762. (b) El Kaïm, L.; Grimaud, L. Ugi-Smiles couplings: new entries to N-aryl carboxamide derivatives. *Mol. Divers.* **2010**, *14*, 855−867.
(16) (a) For reviews, see: Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. Synthesis of Pyridine and Dihydropyridine Derivatives by Regio- and Stereoselective Addition to *N*-Activated Pyridines. *Chem. Rev.* **2012**, *112*, 2642−2713. (b) Wang, D.; Désaubry, L.; Li, G.; Huang, M.; Zheng, S. Recent Advances in the Synthesis of C2-Functionalized Pyridines and Quinolines Using N-Oxide Chemistry. *Adv. Synth. Catal.* **2021**, *363*, 2−39. (c) Corio, A.; Gravier-Pelletier, C.; Busca, P. Regioselective Functionalization of Quinolines through C-H Activation: A Comprehensive Review. *Molecules* **2021**, *26*, 5467.
(17) (a) For selective examples, see: Behera, A.; Sau, P.; Sahoo, A. K.; Patel, B. K. Cyano-Sacrificial (Arylthio)arylamination of Quinoline and Isoquinoline *N*-Oxides Using *N*-(2-(Arylthio)aryl)cyanamides. *J. Org. Chem.* **2018**, *83*, 11218−11231. (b) Kim, D.; Ghosh, P.; Kwon, N.-Y.; Han, S. H.; Han, S.; Mishra, N. K.; Kim, S.; Kim, I.-S. Deoxygenative Amination of Azine-*N*-oxides with Acyl Azides via [3 + 2] Cycloaddition. *J. Org. Chem.* **2020**, *85*, 2476−2485. (c) Nanaji, Y.; Kirar, S.; Pawar, S. V.; Yadav, A. K. A mild and metal-free synthesis of 2- and 1-alkyl/aryl/dialkyl-aminoquinolines and isoquinolines. *RSC Adv.* **2020**, *10*, 7628−7634. (d) Londregan, A. T.; Jennings, S.; Wei, L. General and Mild Preparation of 2-Aminopyridines. *Org. Lett.* **2010**, *12*, 5254−5257.
(18) Anugu, N.; Thunga, S.; Golla, S.; Kokatla, H. P. Iodine Catalyzed C2-H Formamidation of Quinoline *N*-Oxides using Isocyanides: A Metal-Free Approach. *Adv. Synth. Catal.* **2022**, *364*, 149−157.
(19) Flores-Reyes, J.; Islas-Jácome, A.; González-Zamora, E. The Ugi three-component reaction and its variants. *Org. Chem. Front.* **2021**, *8*, 5460−5515.
(20) (a) Bhat, S. I. One-Pot Construction of Bis-Heterocycles through Isocyanide Based Multicomponent Reactions. *ChemistrySelect* **2020**, *5*, 8040−8061. (b) Neochoritis, C. G.; Zhao, T.; Dömling, A. Tetrazoles via Multicomponent Reactions. *Chem. Rev.* **2019**, *119*, 1970−2042.

https://doi.org/10.1021/acs.joc.2c00904
J. Org. Chem. 2022, 87, 10435−10440