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Diverse Isoquinoline Scaffolds by Ugi/Pomeranz−Fritsch and Ugi/Schlittler−Müller Reactions

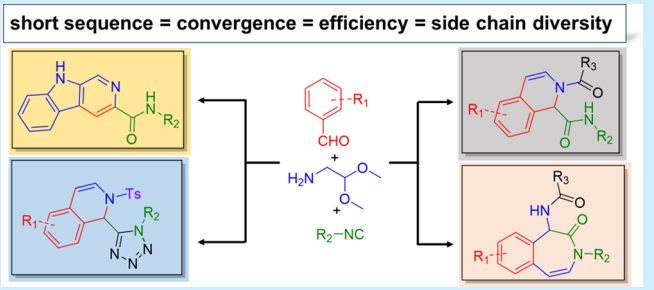
Yuanze Wang,[†] Pravin Patil,[†] Katarzyna Kurpiewska,[‡] Justyna Kalinowska-Tluscik,[‡] and Alexander Dömling*[,†]

[†]Drug Design, University of Groningen, Deusinglaan 1, 7313 AV Groningen, The Netherlands

[‡]Faculty of Chemistry, Jagiellonian University, 3 Ingardena Street, 30-060 Krakow, Poland

Supporting Information

ABSTRACT: The Pomeranz−Fritsch reaction and its Schlittler−Müller modification were successfully applied in the Ugi postcyclization strategy by using orthogonally protected aminoacetaldehyde diethyl acetal and complementary electron rich building blocks. Several scaffolds, including isoquinolines, carboline, alkaloid-like tetrazole-fused tetracyclic compounds, and benzo[*d*]azepinone scaffolds, were synthesized in generally moderate to good yield. All our syntheses provide a short MCR-based sequence to novel or otherwise difficult to access scaffolds. Hence, we foresee multiple applications of these synthesis technologies.

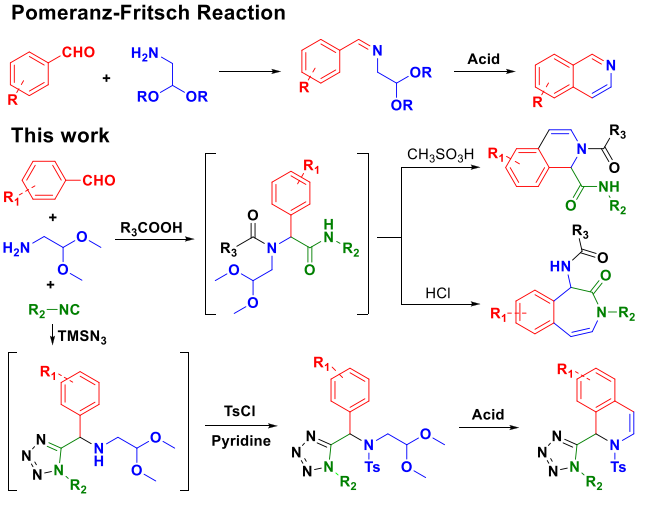


Isoquinoline represent as an important heterocyclic template and privileged moiety in medicinal chemistry and exhibit a wide variety of biological and pharmacological properties.[1−7] The known traditional methods to construct the isoquinoline core include the Bischler−Napieralski reaction,[8] the Pictet−Spengler reaction,[9] and the Pomeranz−Fritsch reaction.[10] The Bischler−Napieralski reaction is by far the most frequently explored isoquinoline alkaloids synthesis approach in the past decades. The Pictet−Spengler reaction has not only been explored as a convenient method for the asymmetric synthesis of isoquinoline alkaloids, but also was widely used for the synthesis of alkaloid-like polycyclic compounds by combining with MCR chemistry in recent years.[11] The Pomeranz−Fritsch reaction is the synthesis of isoquinolines via an acid-mediated electrophilic cyclization of benzalaminoacetals. Since the first and concurrent report by Pomeranz and Fritsch in 1893, this reaction has been extensively modified.[12] To improve the reaction yield, the Fischer modification involved the treatment of benzalaminoacetal with fuming sulfuric acid. In 1948, E. Schlittler and J. Müller modified the reaction by using benzyl amines and glyoxal semiacetal as the starting material. Later on, Bobbitt reported synthesizing the 1,2,3,4-tetrahydroisoquinolines by hydrogenation of the imine intermediate in situ to the aminoacetal, which allows for the preparation of 1-, 4-, and *N*-substituted isoquinolines. At the same time, Jackson described the dehydrogenation of 1,2-dihydroisoquinoline via a *N*-tosyl derivative to a fully aromatic system.

Although a variety of modifications have been introduced to improve the Pomeranz−Fritsch strategy, it has not been explored as often as the Bischler−Napieralski reaction and Pictet−Spengler reaction. Only a few isolated reports on the synthesis of isoquinoline derivatives based on Pomeranz−Fritsch reaction have been published.[13] Inspired by the fact that the Pictet−Spengler reaction has been successfully used in the Ugi postcondensation strategy in our lab,[11j] we surmised that the combination of Ugi reaction with Pomeranz−Fritsch reaction and Schlittler−Müller reaction could also be attractive way to form diversified isoquinolines (Scheme 1).

We first explored the Pomeranz−Fritsch reaction as the post-Ugi strategy. By using 3,4,5-trimethoxybenzaldehyde, aminoacetaldehyde diethyl acetal, 4-chlorophenylacetic acid,

Scheme 1. Ugi/Pomeranz−Fritsch Reaction



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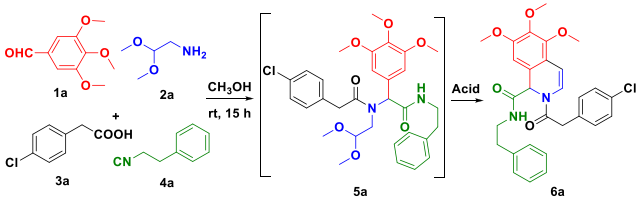
and phenylethyl isocyanide as test substrate, the Ugi reaction was conducted in methanol at room temperature for 15 h. As the Ugi reaction works excellently with aliphatic aldehydes and amines, the crude Ugi adduct **5a** was directly treated with various acid conditions (Scheme 2). It is worthy to note that

Scheme 2. Optimization of Reaction Conditions

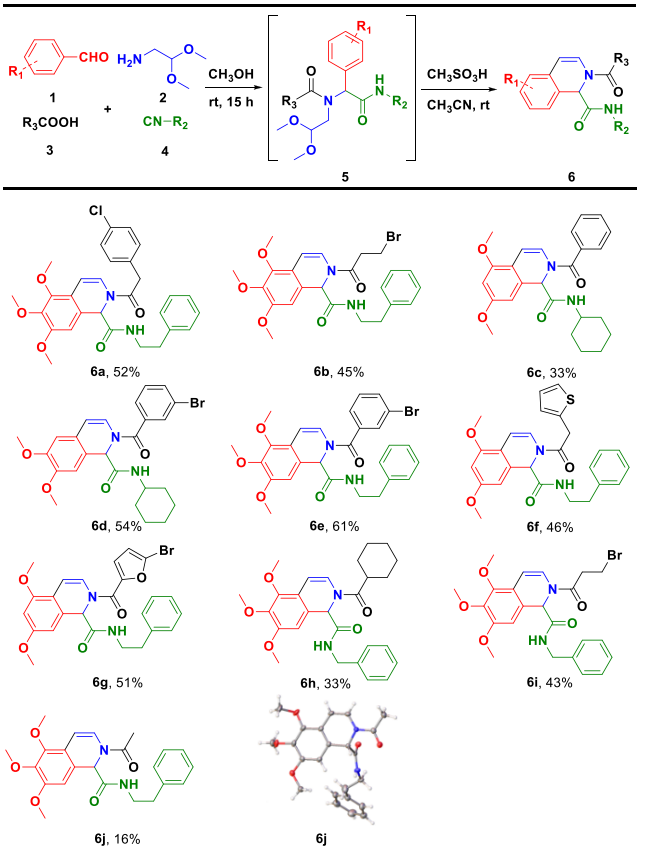


Entry	Acid	Yield of **6a**[a](%)
1	HCOOH	-
2	CH_3COOH	-
3	CH_3COOH/conc. H_2SO_4(v/v) = 3:1	33
4	CH_3COOH/conc. H_2SO_4(v/v) = 2:1	36
5	CH_3COOH/conc. H_2SO_4(v/v) = 1:1	30
6	CF_3COOH	46
7	37% aq. HCl/ dioxane(v/v) = 1:2	-
8	37% aq. HCl/ dioxane(v/v) = 1:1	-
9	CH_3SO_3H (2 eq)/ CH_3CN	Traces
10	CH_3SO_3H (10 eq)/ CH_3CN	35
11	CH_3SO_3H (20 eq)/ CH_3CN	52
12	CH_3SO_3H (20 eq)/ DCM	43
13	CH_3SO_3H	15

Nadzan and co-workers has reported the formation of 2-oxopiperazines by Ugi-*N*-acyliminium ion cyclization with good yield using TFA as acid condition.[14] Thus, potentially there is a competition between Ugi-*N*-acyliminium ion cyclization and Ugi-Pomeranz–Fritsch reaction to be expected. To our delight, no 2-oxopiperazines product was observed in all the acid conditions we screened, and 46% of isoquinoline product **6a** was formed when TFA was used as the acid. However, HCOOH, CH_3COOH, and 37% $HCl_{(aq)}$ solution in dioxane failed to give any isoquinoline product. CH_3COOH and coc. H_2SO_4 were found to be a good combination for this reaction, which afforded **6a** in 30–36% yield. Methanesulfonic acid, which has been proved to be a good acid condition for Ugi/Pictet-sprengler reaction, also works well in our Ugi/Pomeranz–Fritsch sequence.[15] Although only trace amount of product was formed when two equivalents of methanesulfonic acid were used, the reaction yield increased to 35% when methanesulfonic acid was increased to 10 equiv. Finally, 20 equiv of methanesulfonic acid in acetonitrile turned out to be the best condition for this reaction, which afforded **6a** in 52% yield in two steps. Solventless methanesulfonic acid was inferior.

With optimized reaction conditions in hand, nine isoquinoline products **6** were synthesized by using three aldehyde, three isocyanide, and eight acid building blocks (Scheme 3). Both aromatic and aliphatic isocyanides work well for this reaction. Regardless of the acid moiety, all Ugi adducts obtained from aromatic acid afforded isoquinolines in good to moderate yield.

Scheme 3. Examples of N,2-Disubstituted Isoquinolines Derivatives



Albeit in lower yields, most of the aliphatic acids also work except pivalic acid, which failed to give any cyclized product from isolated Ugi adduct. The structure of **6j** was confirmed by X-ray crystallography.

To figure out the unexpected failure of pivalic acid in the Ugi/Pomeranz–Fritsch reaction, we rescreened all the acid conditions in Scheme 2. Surprisingly, we observed the formation of the benzo[*d*]azepinone scaffold in good yield when 37% $HCl_{(aq)}$ solution in dioxane was used as the cyclizing acid. As a class of seven-membered *N*-heterocycles, benzo[*d*]-azepinone scaffolds are also interesting in medicinal chemistry, where they represent as an important class of so-called "privileged scaffolds".[16] To show some scope, we synthesized five compounds in 39–52% yield by changing the aldehyde and isocyanide moiety as shown in Scheme 4. A single crystal X-ray analysis further confirmed the structure of **8a**.

Recently, we reported the isoquinoline synthesis of **10** by Ugi/Schlittler–Müller modification using an unprecedented fast nanoscale technology.[17] This efficient method was explored to synthesize hundreds of derivatives of **10** with the help of acoustic droplet ejection (ADE). 3,4,5-Trimethoxylbenzylamine, 3,4-(methylenedioxy)benzylamine, four dimethoxy substituted benzylamine, and thiophen-3-yl-methylamine were used previously by us as amine component in the Ugi reaction. To further extend the reaction scope, we further explored some other electron rich aromatic amines (Scheme 5). To our delight, 3-methoxylbenzylamine, 4-(aminomethyl)-2-methoxyphenol, and heterocyclic 1*H*-indol-2-ylmethylamine were successfully applied by increasing the concentration of the acid and extension of the reaction time in the

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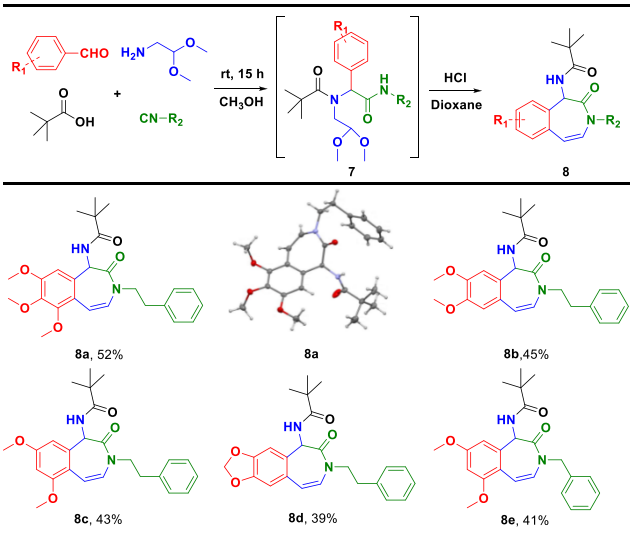
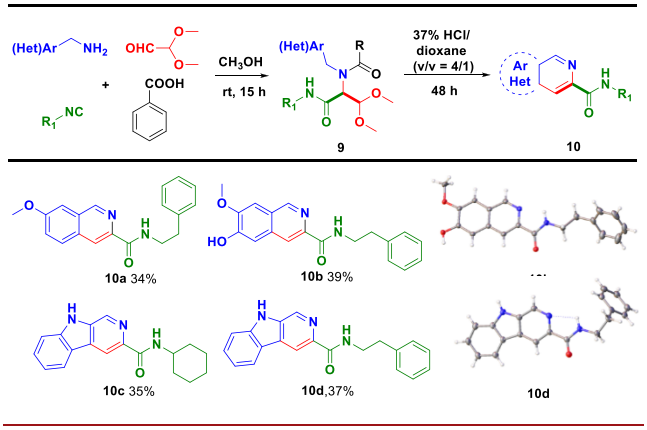
Scheme 4. Synthesis of Benzo[*d*]azepinone Scaffold



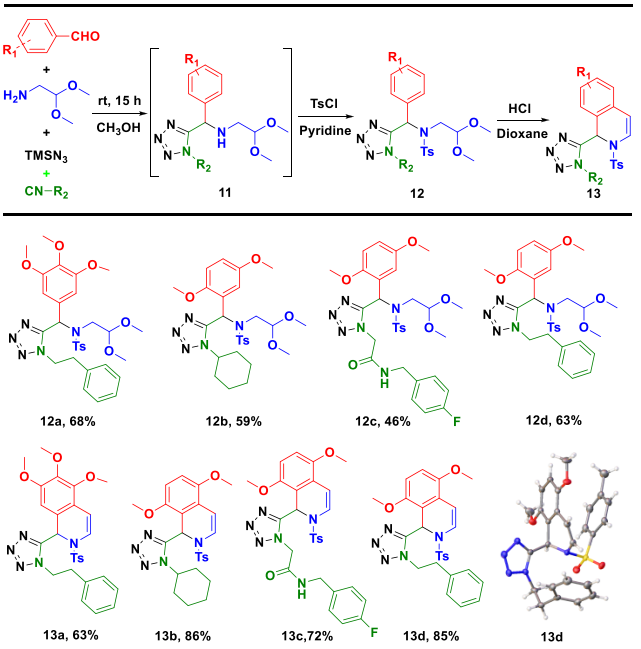
Scheme 5. Synthesis of Isoquinoline and Carboline Scaffold



postcyclization step. The structures of **10b** and **10d** were confirmed by X-ray crystallography.

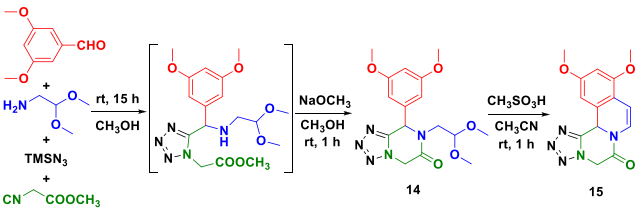
As valuable bioisosteres of carboxylic acid and cis-amide, tetrazole is an important drug-like scaffold, which often exhibits improved pharmacokinetics in drug discovery.[18] Exploration of the Ugi-Azide MCR and postcyclization by Hulme et al. and others has created several unique scaffolds as exemplified by ketopiperazine-tetrazoles,[19] quinoxaline-tetrazoles,[20] azepine-tetrazoles,[21] benzodiazepine-tetrazoles,[22] and lactam-tetrazoles.[23] Inspired by these methodologies, we successfully constructed the isoquinoline-tetrazoles by combining the Ugi-azide with the Pomeranz–Fritsch reaction (Scheme 6). Initially, we subjected the Ugi-azide product **11** directly to acidic condition for cyclization. To our surprise, however, the subsequent Pomeranz–Fritsch reaction was very sluggish and only trace amount of product was formed. In addition, variation of the acid condition and solvent did not greatly improve to the reaction performance. We reasoned that the exposed secondary amine could interfere with the reaction and cause side reactions. Thus, we first protected the secondary amine by a tosyl group in situ to obtain product **12**, which then undergoes clean cyclization to form the isoquinoline-tetrazoles **13**. This stepwise reaction proved to be highly superior and the desired product was isolated in good to excellent yields. Eight diverse intermediates and products were characterized, and the X-ray structure of **13d** was obtained.

Scheme 6. Synthesis of Isoquinoline-Tetrazoles



Finally, as a further application of our isoquinoline-directed Ugi postcondensation strategy, we synthesized an alkaloid-like tetrazole-fused tetracyclic compound by using isocyanide prepared from amino acid ester as starting material (Scheme 7). Instead of tosyl group protection, the methyl ester from

Scheme 7. Synthesis of Tetracyclic Isoquinolines



isocyanide moiety will react with the exposed secondary amine in basic condition to form the tetrazolopyrazinone **14**, followed by the Pomeranz–Fritsch cyclization to afford tetracyclic product **15**. To support the diversity of our isoquinoline-based scaffolds, we generated virtual libraries of each 100 randomly generated molecules and for comparison ChEMBL using JChem software.[24] The chemical properties MW and log P were calculated and plotted in Figure SI-1 (see Supporting Information p S75). Moreover, an SCI-FINDER sub- and Markush structure query revealed 8 and 9, 0 and 1, 2353 and 848, 847 and 61, 1 and 0, 0 and 0 results for the herein described scaffolds **6**, **8**, **10**-isoquinoline, **10**-carboline, **13**, and **15**, respectively. Also, ChEMBL substructure searches found one hit for scaffold **6**, zero hits for scaffold **8**, 422 hits for scaffold **10**-isoquinoline, 182 hits for scaffold **10**-carboline, and zero hits for scaffold **13** and scaffold **15**, respectively. In conclusion, we have developed several straightforward methods to assemble isoquinoline derivatives, benzo[*d*]-azepinone and carboline scaffold. The Ugi postcyclization strategy is probably the most powerful tool to create structural diversity and large compound numbers while keeping the number of synthetic steps low. It already has gained lots of

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interest in the field of medicinal chemistry.[25] Our new strategy of Ugi/Pomeranz–Fritsch reaction is an expedited and convergent access to skeletal diverse compounds. Significantly, isoquinoline-tetrazoles and tetrazole-fused tetracyclic compound can now be constructed in just two steps with this method. One of the herein described reactions in a variation already has found an application in nanoscale accelerated and automated synthesis; however, we foresee many more applications in the discovery of novel biologically active compounds.[17]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00778.

Experiment procedures, compounds data, NMR spectra, HRMS and crystal structure determinations (PDF)

Accession Codes

CCDC 1573261, 1827865, 1827938, 1828772, and 1856636 contain 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: a.s.s.domling@rug.nl.

ORCID

Pravin Patil: 0000-0002-0903-8174
Justyna Kalinowska-Tluscik: 0000-0001-7714-1651
Alexander Dömling: 0000-0002-9923-8873

Notes

The authors declare no competing financial interest.

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