Tetrahedron Letters 54 (2013) 4467–4470

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Construction of functionalized tricyclic dihydropyrazino-quinazolinedione chemotypes via an Ugi/*N*-acyliminium ion cyclization cascade

Steven Gunawan [a,b], Christopher Hulme [b,*]

[a] Department of Chemistry and Biochemistry, The University of Arizona, Tucson, AZ 85721, United States
[b] Department of Pharmacology and Toxicology, College of Pharmacy, The University of Arizona, BIO5 Oro Valley, Tucson, AZ 85737, United States

ARTICLE INFO

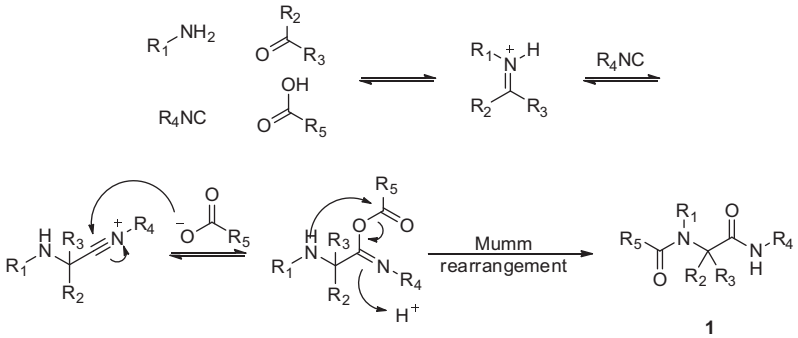
Article history:
Received 23 April 2013
Revised 5 June 2013
Accepted 11 June 2013
Available online 19 June 2013

Keywords:
Peptidomimetics
Ugi reaction
Multi-component reaction
N-acyliminium ion
Heterocycles

ABSTRACT

Dihydropyrazino-quinazolinedione chemotypes are complex and structurally challenging structures of biological interest, being found in the marine alkaloids such as brevianamide M–N and fumiquinazolines A–C. Herein we report the synthesis of this tricyclic system in three synthetic operations by means of an Ugi multi-component reaction (MCR) followed by a tandem *N*-acyliminium ion cyclization-intramolecular nucleophilic addition reaction sequence. Additional structural diversification for further library enrichment was also accomplished via sequential N-alkylation and N-acylation/sulfonation.

The compelling quest to discover novel small molecules that modulate protein function has enabled access to ever-growing regions of chemical space.[1] Over the past 20 years, isocyanide-based MCRs (IMCRs) have proven to be a convenient and versatile approach toward expeditious molecular diversity generation, allowing the generation of numerous unique, drug-like small molecules for biological evaluation.[2] In particular, the Ugi IMCR (Scheme 1), which proceeds through reaction of an aldehyde or ketone, amines, isocyanides, and carboxylic acids to produce the dipeptide-like adduct **1**, has undergone many post-condensation modifications, accessing numerous new scaffolds. To cite a few examples, these post-MCR transformations comprise Ugi/deprotection/cyclization (UDC),[3] Ugi/Heck,[4] Ugi/Pictet-Spengler,[5] Ugi/RCM,[6] Ugi/Knoevenagel,[7] Ugi/cycloaddition,[8] Ugi/Diels–Alder,[9] Ugi/Pd-catalyzed arylation,[10] Ugi/Mitsunobu[11] and, most recently, elegant Ugi/Aldol methodologies.[12] In this Letter, Ugi/*N*-acylimini-



Scheme 1. The Ugi MCR.

* Corresponding author.
E-mail address: hulme@pharmacy.arizona.edu (C. Hulme).

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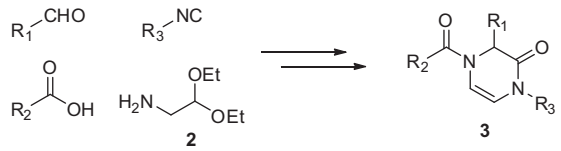
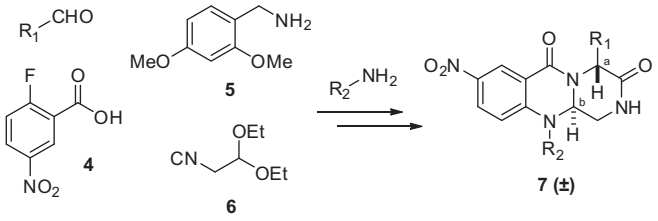
http://dx.doi.org/10.1016/j.tetlet.2013.06.042



Scheme 2. Synthesis of Δ^5-2-oxopiperazines **3**.



Scheme 3. General Ugi/*N*-acyliminium ion cyclization sequences.

um ion sequences used to expand our toolbox of heterocyclic chemotypes are relatively underexploited, and only one article has been published that describes the synthesis of Δ^5-2-oxopiperazines **3** (Scheme 2) using aminoacetaldehyde diethylacetal **2** as the carbonyl surrogate.[13] However, reports do exist on *N*-acyliminium ion strategies being employed with other MCRs.[14] Herein, post-condensation modifications of the Ugi adduct driven by *N*-acyliminium ion cascade reactions are reported to prepare ketopiperazine containing tricyclic chemotypes **7** (Scheme 3) whose unusual core structure is found in the marine alkaloids brevianamide M–N[15] **8** and **9** and fumiquinazolines A–C[16] **10**, **11**, and **12** possessing insecticidal and antineoplastic activity, respectively (Fig. 1).

Thus, studies began with evaluation of reagent compatibility for the Ugi MCR (Scheme 4). Specifically, mixing an aldehyde, 2-fluoro-5-nitro-benzoic acid **4**, the ammonia surrogate 2,4-dimethoxybenzylamine **5**[17] and 1,1-diethoxy-2-isocyanoethane **6**[18] rendered Ugi products **13** upon overnight stirring at ambient temperature in moderate to good yields (43–82%, Table 1). It is worth noting that isocyanide **6** can be readily synthesized in two steps and has also been reported to be an extremely valuable building block for the preparation of several families of heterocycles that include imidazoles[19] and thiazoles.[20] Subsequent displacement of the fluorine group in **13** by a primary amine was achieved under mild conditions in DCE and afforded **14**, which was subjected without purification to an acid-mediated double cyclization generating tricyclic system **7** (Table 1). Mechanistically, this pathway is presumably initiated by the generation of an oxonium ion and concomitant removal of the acid labile 2,4-dimethoxybenzyl moiety **15** (Scheme 4). Closure of the amidic nitrogen onto the oxonium ion thus leads to the formation of hemiaminal **16**, which under the acidic reaction conditions affords *N*-acyliminium ion **18** with the associated loss of a molecule of ethanol. The sequence concludes through nucleophilic attack of the anilinic amine onto the newly formed *N*-acyliminium ion **18** to give the desired dihydropyrazino-quinazolinedione **7**.

Scaffold **7** is likely to exist as an *anti*-diastereomer in which the two hydrogens of the two chiral centers, 'a' and 'b', are predicted to be in a pseudo-*trans* relationship (Fig. 2). Molecular dynamics studies reveal that both enantiomers of **7a** exist in a lower energy state than the corresponding pair of enantiomers (**20** and **22**) of the

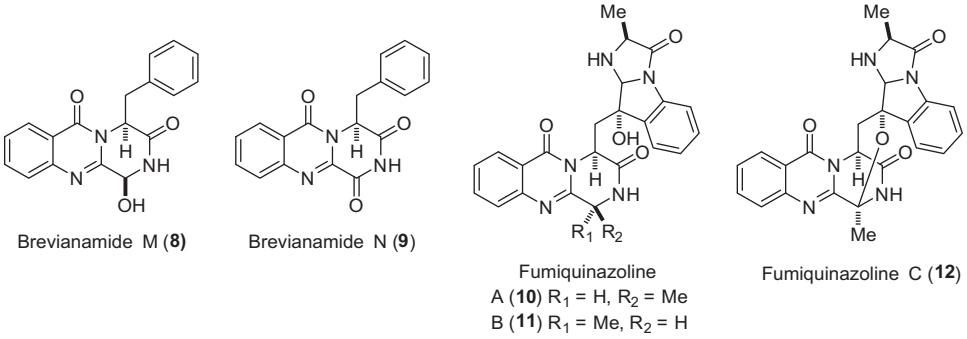
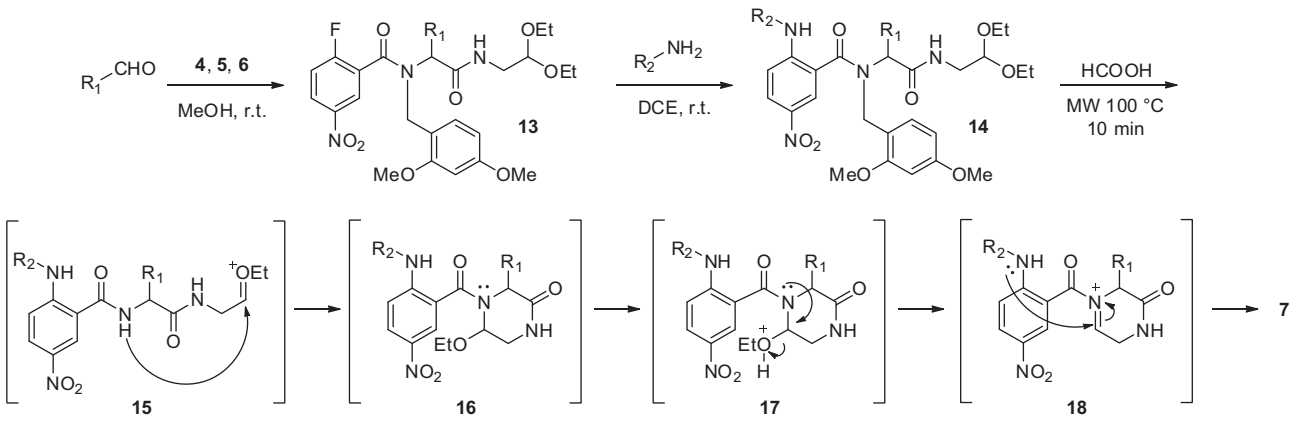


Figure 1. Brevianamide M–N (**8** and **9**) and fumiquinazolines A–C (**10**–**12**).



Scheme 4. Synthesis of dihydropyrazino-quinazolinedione **7**.

Table 1
Tricyclic analogs **7a–f**

Entry	Ugi product	R_1	Yield (%)	**7**	R_2	Yield[a] (%)
1	**13a**	Propyl	67	**7a**	Isobutyl	67
2	**13b**	Phenyl	78	**7b**	Isobutyl	79
3	**13c**	3-(Methylthio)ethyl	43	**7c**	Isobutyl	41
4	**13d**	Cyclopropyl	82	**7d**	2-Methoxyethyl	41

[a] Two-step yield for fluoride displacement and acid treatment.

alternate diastereomer, thus suggesting preferential formation of **7a**.[21] Observed stereoselectivity may be explained by the steric hindrance between the propyl group and the approaching anilinic nitrogen of intermediate **19** (*R*-enantiomer) at the *si*-face that negates formation of **20** (*R*,*R*), affording **7a** (*R*,*S*) as the strongly preferred product (Fig. 2). In analogous fashion, *si*-attack on the intermediate **21** (*S*-enantiomer) affording **7a** (*S*,*R*) (Fig. 2) is suggested to be favored [Note that comparison of the relative energies of two diastereomers is only justified when assuming reversibility of reactions going through either 19 or 21, with product 7 preferred over 20 under thermodynamic control]. This configuration is in accordance with a report by Patek et al. describing the assembly of 1-acyl-3-oxopiperazines via a multi-step solid-phase synthesis.[21] Unequivocal structural confirmation of **7a** was also provided by X-ray crystallography (Fig. 3).

With **7a** in hand as the 'model study' molecule, a small collection of compounds was prepared to demonstrate the generality of the reaction sequence utilizing different aldehydes and primary amines (Table 1). Concurrently, further functionalization of **7** was also enabled via N-alkylation on the amidic nitrogen and by N-

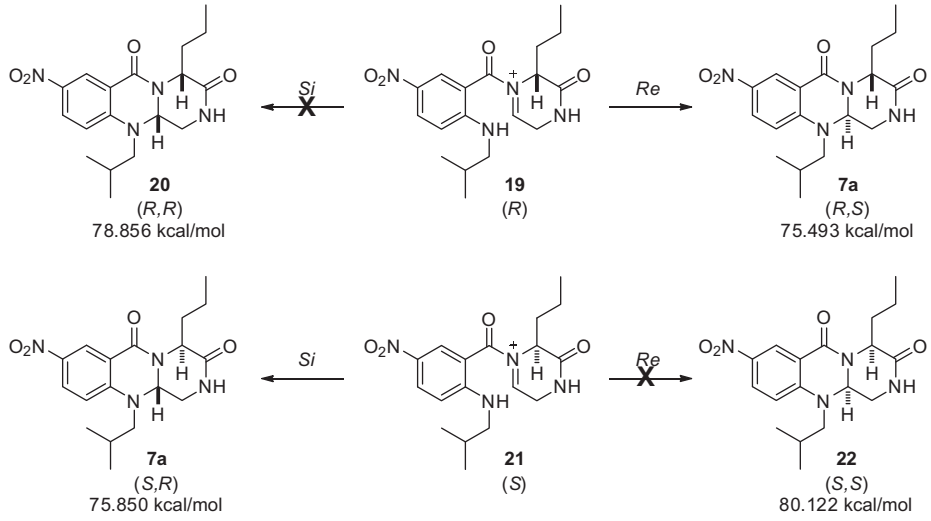


Figure 2. Stereoselectivity and calculated energy for each diastereomer.

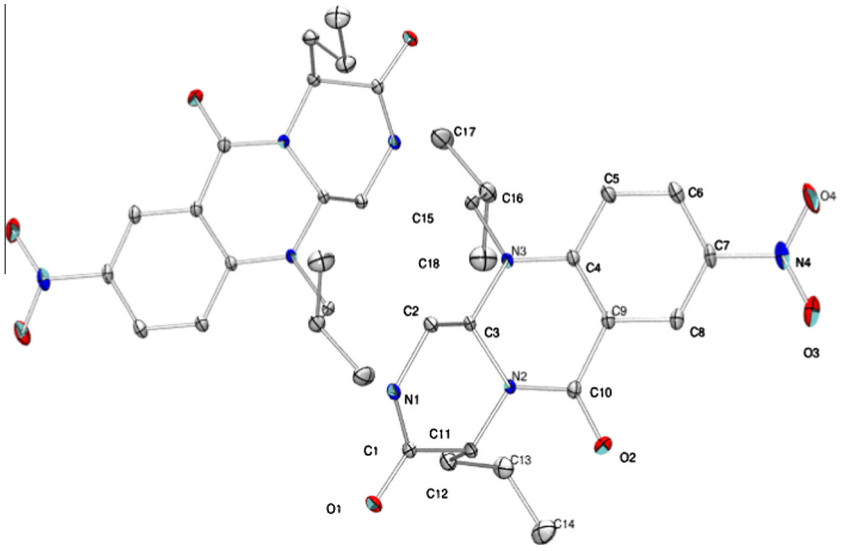
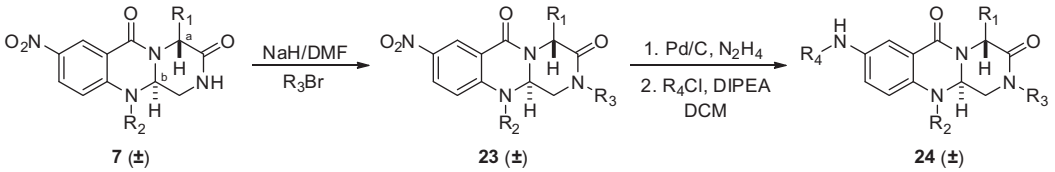


Figure 3. Definitive structural confirmation by X-ray crystallography of **11a**.



Scheme 5. Synthesis of dihydropyrazino-quinazolinedione **7**.

Table 2
Functionalized tricyclic chemotype **23**

Entry	7	R_3	23	Yield (%)
1	**7a**	3-Methoxybenzyl	**23a**	94
2	**7a**	4-Fluorophenethyl	**23b**	87
3	**7a**	Cyclobutylmethyl	**23c**	87
4	**7b**	3-Methoxybenzyl	**23d**	71
5	**7b**	4-Fluorophenethyl	**23e**	46

Table 3
Functionalized tricyclic chemotype **24**

Entry	23	R_4	24	Yield[a] (%)
1	**23a**	CO-Ph	**24a**	85
2	**23b**	SO_2Me	**24b**	83
3	**23b**	CO-Ph	**24c**	75
4	**23c**	SO_2Me	**24d**	80
5	**23c**	CO-Ph	**24e**	89

[a] Two-step yield for hydrogenation and N-acylation.

acylation and/or sulfonation upon reduction of the nitro group, leading to the addition of two further diversity points (Scheme 5). Tables 2 and 3 summarize selected alkyl bromides and acyl/sulfonyl chlorides employed to attain **23** and **24**, respectively, in high overall yields.

In summary, a concise three-step synthesis of a collection of tricyclic dihydropyrazino-quinazolinediones **7** has been successfully established with only one diastereomer formed utilizing an Ugi/*N*-acyliminium ion cyclization-intramolecular nucleophilic addition reaction cascade. Moreover, this scaffold can be readily diversified via sequential N-alkylation and N-acylation and/or sulfonation, adding two further variety points by means of commercially available alkyl bromides and acyl and/or sulfonyl chlorides. Due to the uniqueness of the chemotypes produced, their favorable drug-like properties, and the potential for structural diversification, this procedure represents a practical and enticing approach for the enrichment of small molecule libraries in a high-throughput and operationally friendly manner.

Acknowledgments

The authors thank Dr. Sue Roberts for X-ray crystallography work, Drs. Fabio De Moliner and David M. Bishop for proofreading, and the National Institutes of Health (P41GM086190) for financial support.

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