

Synthesis of Novel and Uniquely Shaped 3-Azabicyclo[4.2.0]octan-4-one Derivatives by Sequential Ugi/[2+2] Ene–Enone Photocycloadditions

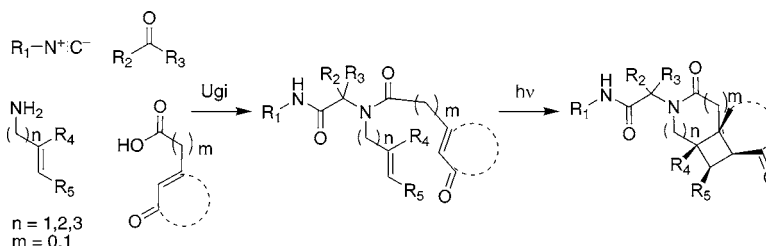
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ABSTRACT



We report a new methodology for the construction of novel and uniquely shaped 3-azabicyclo[4.2.0]octan-4-one derivatives by combining the Ugi multicomponent reaction with [2+2] enone–olefin photochemical transformations. The overall sequence is capable of creating up to five stereocenters; however, in most cases, only two diastereomers are observed.

Isocyanide-based multicomponent reactions (IMCRs) coupled with subsequent transformations provide highly diverse and complex structures in only a few synthetic steps.¹ One of the most frequently used IMCRs is the Ugi reaction, a very robust and versatile reaction that tolerates a wide variety of functional groups.²

We have recently reported on several post-Ugi transformations to afford unique scaffolds based on sequential Ugi/

Heck,³ Ugi/intramolecular nitrile oxide cycloaddition,⁴ and Ugi/intramolecular alkyne–azide cycloaddition⁵ sequences.

As part of our continuing efforts to develop synthetic routes to access novel molecules, we became interested in combining the Ugi reaction with photochemical transformations because intramolecular [2+2] cycloadditions were expected to provide novel molecular architectures and uniquely shaped three-dimensional structures in two synthetic steps.

[2+2] Enone–olefin photochemical reactions are well studied in both their inter- and intramolecular versions.⁶ Typically, the intramolecular photocycloadditions proceed with high regioselectivity when the double bonds are

(1) For reviews, see: (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (c) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80. (d) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144.

(2) For early examples of post-Ugi modifications, see: (a) Tempest, P.; Ma, V.; Kelly, M. G.; Jones, W.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4963–4968. (b) Paulvannan, K. *Tetrahedron Lett.* **1999**, *40*, 1851–1854. (c) Hulme, C.; Peng, J.; Morton, G.; Salvino, J. M.; Herpin, T.; Labaudiniere, R. *Tetrahedron Lett.* **1998**, *39*, 7227–7230. (d) Hulme, C.; Morrisette, M. M.; Volz, F. A.; Burns, C. J. *Tetrahedron Lett.* **1998**, *39*, 1113–1116. (e) Park, S. J.; Keum, G.; Kang, S. B.; Koh, H. Y.; Kim, Y. *Tetrahedron Lett.* **1998**, *39*, 7109–7112. (f) Strocker, A. M.; Keating, T. A.; Tempest, P. A.; Armstrong, R. W. *Tetrahedron Lett.* **1996**, *37*, 1149–1152. (g) Short, K. M.; Ching, B. W.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 7489–7492.

(3) Gracias, V.; Moore, J. D.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 417–420.

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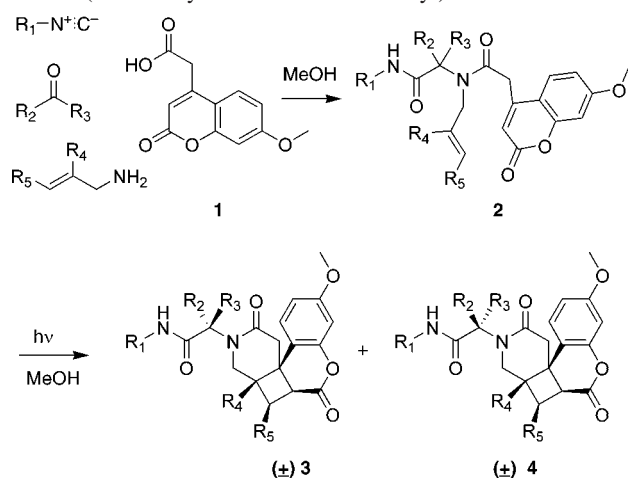
(5) Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 8439–8441.

(6) (a) Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453–1473. (b) Fleming, S. A.; Bradford, C. L.; Gao, J. J. *Mol. Supramol. Photochem.* **1997**, *1*, 187–243. Griesbeck, A. G.; Fiege, M. *Mol. Supramol. Photochem.* **2000**, *6*, 33–100.

connected with 2–4 atom tethers and with high diastereoselectivity providing in most cases a single diastereomer via a 1,4 biradical intermediate. The photocycloaddition products incorporate fused four-membered rings with at least three new stereocenters and geometries that extend substituents in numerous directions in three-dimensional space.

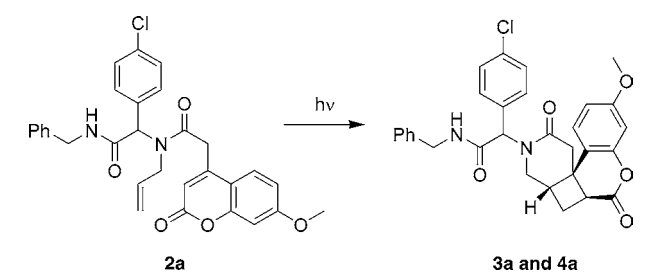
In this letter, we present, to our knowledge, the first combination of an MCR reaction with a photochemical transformation to access highly complex and novel azabicyclo-[4.2.0]octan-4-one derivatives. We initiated our studies with chromenone acetic acid **1** (Scheme 1). The Ugi reaction

Scheme 1. Sequential Ugi/[2+2] Ene–Enone Photocycloadditions with 2-(7-Methoxy-2-oxo-2H-chromen-4-yl)acetic Acid **1**



proceeded in moderate yields to provide adducts **2**, which were subjected to irradiation⁷ to yield a mixture of diastereomers **3** and **4** as racemic mixtures.

Table 1. [2+2] Photocyclizations in Various Solvents upon Irradiation for 5 h



entry	solvent	starting material yield % ^a	byproduct yield % ^a	products yield % ^a	products ratio ^b
1	MeOH	7	0	80	1.3:1
2	MeCN	32	5	37	1.2:1
3	CH ₂ Cl ₂	40	7	46	1.3:1
4	benzene	35	6	23	1.1:1
5	THF	68	11	14	1.1:1

^a Calculated based on isolated crude yield by ¹H NMR. ^b **3a** over **4a**.

Table 2. Ugi Reactions and Subsequent [2+2] Photocyclizations in MeOH upon Irradiation for 5 h

entry	R1	R2	R3	R4	Ugi yield %	[2+2] product	[2+2] yield %
1	iPr	p-Cl-Ph	H		60		92 ^a
2	iPr	p-Cl-Ph	H		42		93 ^a
3	iPr	Me	Me		35		64 ^b
4	iPr				36		58 ^c

^a Diastereomeric ratios of **3b/4b** and **3c/4c** were 3:1 based on ¹H NMR.

^b Photocycloaddition was performed in 6:1 MeCN/MeOH for 12 h. ^c Photocycloaddition was performed in 4:1 MeOH/MeCN.

Although intramolecular photocycloadditions of systems such as **2** are not known in the literature, we were pleased to observe in all cases a single regio- and diastereoisomer derived from the [2+2] photocycloaddition consistent with previous observations on related systems.^{8,9}

Using chromenone acetic acid **1** and *p*-chlorobenzaldehyde as the aldehyde input, we next optimized the photocycload-

(7) The reaction was performed in a capped vial, sparged with argon, and placed in 3-inch proximity to a medium pressure, 450 W, mercury lamp. When the reaction was performed in an immersion well reactor equipped with a quartz Pen-Ray 5.5 W, low-pressure, cold cathode, mercury lamp (Penn. J. H.; Orr, R. D. *J. Chem. Educ.* **1989**, *66*, 86–88.), the reaction was complete in 2 h. However, we preferred the former method due to the convenience of using vials as well as the ability to perform multiple reactions concurrently.

(8) Haywood, D. J.; Reid, S. T. *Tetrahedron Lett.* **1979**, *20*, 2637–2638.

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dition reaction by evaluating a variety of solvents (Table 1). The reaction was slow in most solvents, and an unidentifiable byproduct was also formed. MeOH proved to be superior to other solvents, provided a cleaner crude reaction and higher yields, and became the solvent of choice. In some instances, small amounts of acetonitrile were added to aid solubility.

Subsequent experiments with other allyl amines provided similar results. When the allyl amines were further substituted (entries 1 and 2, Table 2), we observed a stereoselectivity with respect to the Ugi stereocenter favoring diastereomer **3** over **4**. The structure of diastereomer **3b** was unambiguously assigned by X-ray crystallography (Figure 1). The stereo-

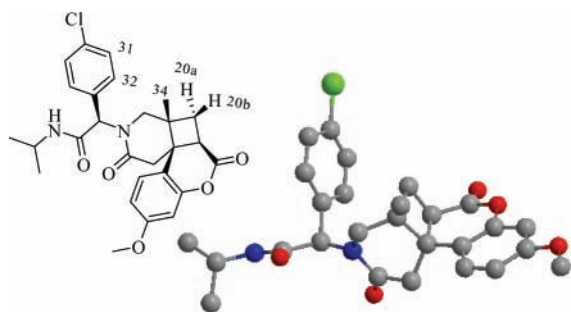


Figure 1. X-ray structure of racemic **3b**.

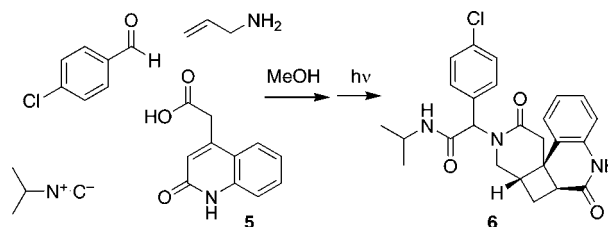
chemistry of the other diastereomer was assigned on the basis of NMR observations. We observed similar ^1H – ^{13}C and ^1H – ^1H correlations of the methyl protons of position 34 (Figure 1) to its environment in **3b** and **4b**, suggesting that the stereochemistry at these centers is preserved. Additionally, we have noted a substantial upfield shift of proton 20a of **3b** at 1.67 ppm vs **4b** at 3.06 ppm. This is consistent with the X-ray where the aromatic ring protons 31 and 32 are in close vicinity to proton 20a and provide a shielding effect. Furthermore, NOE correlations between protons 31 and 32 and 20a are observed in **3b** but not in **4b**.¹⁰ The stereochemistries of structures **3a/4a** and **3c/4c** were assigned on the basis of similar observations. On the basis of the above findings, we speculated that the observed facial selectivity is due to a favorable hydrophobic interaction between the *p*-chlorophenyl substituent and the substituted alkene, which is further intensified in polar solvents such as MeOH.

Remarkably, symmetric ketones such as acetone and cyclohexanone worked just as well as their aldehyde counterparts to provide only one diastereomer. In the case of entry 3, Table 2, upon irradiation in MeOH, we have observed predominantly transesterification of the lactone with MeOH to provide the open phenol–methyl ester product in 84% yield. Ring opening was easily avoided by performing the reaction in 6:1 MeCN/MeOH.

An inspection of the X-ray structure of **3b** gratifyingly confirmed our initial expectations of obtaining uniquely 3D

(10) For a detailed description of stereochemical assignments and justification, see Supporting Information.

Scheme 2. Sequential Ugi/[2+2] Ene–Enone Photocycloadditions with 2-(2-Oxo-1,2-dihydroquinolin-4-yl)acetic Acid^a

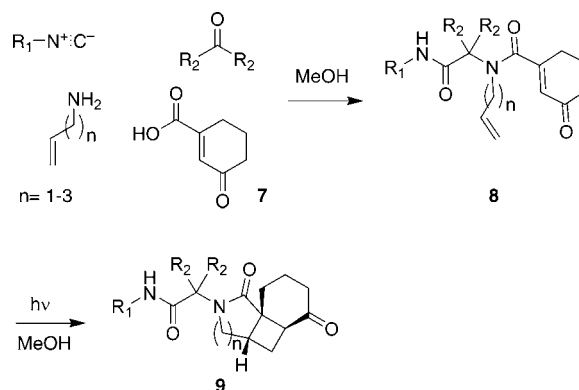


^a Photocyclization was performed in MeOH for 5 h.

shaped structures. Furthermore, the sequence provided a rapid, atom-economical way of providing such structures.

We also explored the utility of other carboxylic acid inputs such as dihydroquinolone acetic acid **5** (Scheme 2) and cyclohexenone carboxylic acid **7** (Scheme 3). Dihydroqui-

Scheme 3. Sequential Ugi/[2+2] Ene–Enone Photocycloadditions with 3-Oxocyclohex-1-enecarboxylic Acid^a



^a Photocyclization was performed in MeOH for 5 h.

nolone acetic acid **5** provided the Ugi adduct in 41% yield and the photocycloaddition product **6** in 87% yield as a 1.5:1 mixture of two diastereomers deriving from the Ugi stereocenter (Scheme 2).

Ugi reactions with oxo-cyclohexene acid **7**¹¹ (Scheme 3) provided products **8** in moderate to good yields, and subsequent photocycloadditions yielded compounds **9**. Variation of carbon chain lengths of amine inputs (Table 3) provided the opportunity to obtain different ring sizes upon cycloaddition.¹² Thus five-, six-, and seven-membered rings (entries 1–3, Table 3, respectively) fused with cyclobutane could easily be accessed in only two steps. In the case of

(11) Prepared by oxidation of cyclohexene carboxylic acid with CrO_3 in $\text{AcOH}/\text{Ac}_2\text{O}$ and deprotection with aq LiOH in THF according to: Fonteneau, L.; Rosa, S.; Buisson, D. *Tetrahedron: Asymmetry* **2002**, *13*, 579–585.

(12) (a) Le blanc, S.; Pete, J. P.; Piva, O. *Tetrahedron Lett.* **1993**, *34*, 635–638. (b) Faure, S.; Piva-Le Blanc, S.; Piva, O. *Tetrahedron Lett.* **1999**, *40*, 6001–6004.

Table 3. Ugi Reactions and Subsequent [2+2] Photocyclizations in MeOH upon Irradiation for 5 h

entry	R1	R2	R3	R4	Ugi yield %	[2+2] product
1	iPr	$\text{-(CH}_2\text{)}_5\text{-}$	$\text{-(CH}_2\text{)}_5\text{-}$	$\text{-(CH}_2\text{)}_5\text{-}$	51	88 ^a
2	iPr	Me	Me	$\text{-(CH}_2\text{)}_5\text{-}$	39	84
3	iPr	$\text{-(CH}_2\text{)}_5\text{-}$	$\text{-(CH}_2\text{)}_5\text{-}$	$\text{-(CH}_2\text{)}_5\text{-}$	37	81 ^b

^a Contains 20% of regioisomer **10a**.¹³ ^b Contains 30% of diastereomer **11c**.¹³

the five-membered ring, the other regioisomer was also present in small amounts, whereas in the case of the seven-membered ring, we also observed the formation of a different diastereomer.¹³

Scaffolds such as **9** can be further functionalized by reactions performed at the ketone group such as reductive aminations, α -brominations, and subsequent heterocyclic ring formations, Beckman rearrangements, etc.

In conclusion, we have developed a new methodology to access highly functionalized fused ring systems in only two synthetic steps. Despite the complexity of the products formed, [2+2] photocycloaddition occurred with high or complete diastereoselectivity with respect to the tri- and tetrasubstituted cyclobutane ring systems. When substituted allyl amines were employed, mild diastereoselectivity was observed relative to the Ugi-formed stereocenter in which two diastereomers were formed.

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Supporting Information Available: Experimental procedures, stereochemical assignments, and X-ray and spectral data for compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) See Supporting Information.