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Synthesis of substituted 3,4-dihydroquinolin-2(1*H*)-one derivatives by sequential Ugi/acrylanilide [6π]-photocyclizations

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Abstract—We report the synthesis of highly functionalized 3,4-dihydroquinolin-2(1*H*)-ones via sequential Ugi/acrylanilide photocyclization reactions. The [6π]-photocyclization proceeds in excellent yields and with preferential trans-selectivity for the newly formed ring system.
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Isocyanide-based multicomponent reactions (IMCRs) followed by a variety of other transformations have provided access to numerous complex molecules in only few synthetic steps.[1] In particular, the Ugi reaction has been extensively used in these types of sequences due to its ability to accommodate a wide range of functional groups.

Moreover, the use of photochemistry is an attractive alternative to conventional methods of synthesis to obtain novel structures in an atom economical manner. We have recently reported our efforts in combining the Ugi reaction with [2+2] photocycloaddition reactions to access uniquely shaped three-dimensional molecules.[2] The framework of the Ugi adducts also provided an ideal scaffold to explore acrylanilides in the [6π]-photocyclization reaction. The [6π]-photocyclization reaction was reported in the late 1960s[3] and has since been extensively investigated,[4] including enantioselective variations.[5]

Mechanistic studies[6] revealed an initial conrotary [6π]-photocyclization of acrylanilides 1 to provide intermediates 2, which undergo tautomerization and rearomatization via two proposed pathways to afford the final fused lactam products 4 and 5 (Scheme 1). In aprotic solvents tautomerization occurred primarily via a suprafacial
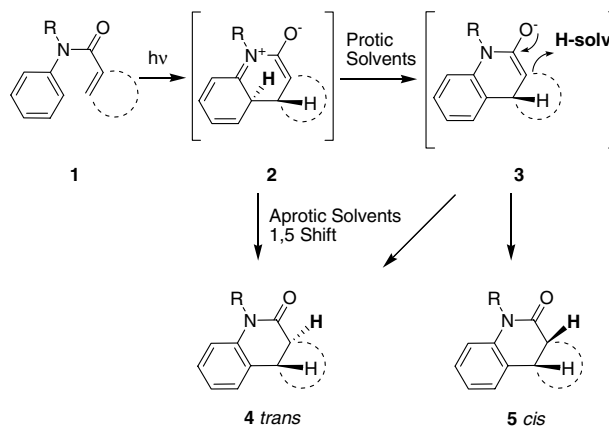

Scheme 1. Acrylanilide [6π]-photocyclizations.

1,5-proton shift to provide trans-adduct 4. However, in protic solvents the proton was delivered to tautomer 3 from the solvent giving rise preferentially to cis-adducts 5. Essentially, the selection of solvent can provide enriched samples of trans- or cis-products.

The basic dihydroquinolinone cores are parts of numerous alkaloid natural products[7] and the Ugi reaction provided a convenient 2-step procedure to access highly functionalized analogs of these structures. Herein, we report our efforts in combining the Ugi reaction with the acrylanilide photocyclization to produce substituted 3,4-dihydroquinolin-2(1*H*)-ones as shown in Scheme 2.

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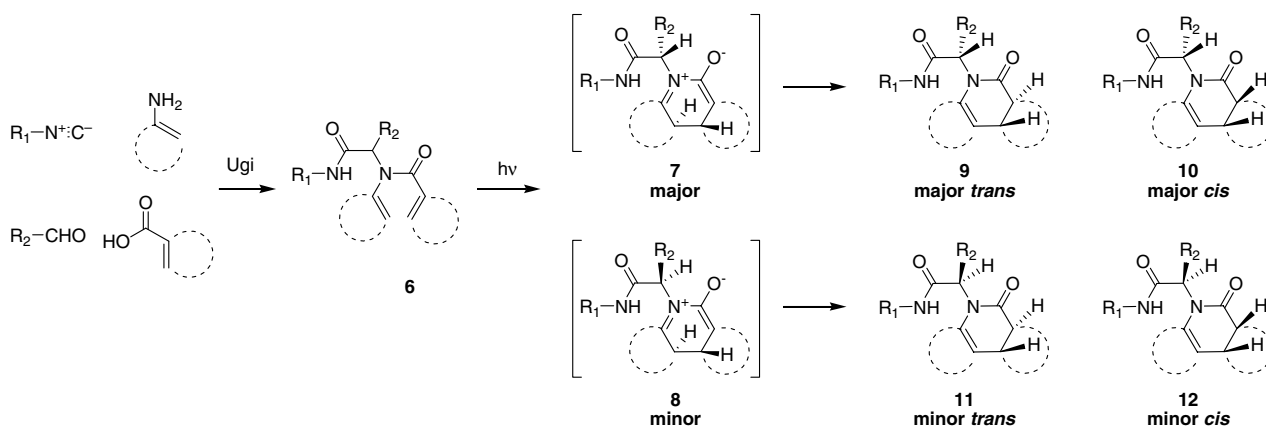
Scheme 2. General method of Ugi/[6π]-photocyclizations.

The Ugi reaction proceeded smoothly in MeOH to provide adducts **6**, which were subjected to irradiation in protic and aprotic solvents using an immersion well reactor equipped with a quartz Pen-Ray 5.5 W, low pressure, cold cathode, mercury lamp.[8,9] The existence of a racemic chiral center in the initial Ugi products could potentially lead to the formation of four diastereomers as racemic mixtures. However, it appeared that the substituent at the Ugi chiral center, derived from the aldehyde component (R$_2$), dictated to some degree the outcome of the photocyclization, resulting in products deriving from intermediate **7**. In most cases the major trans-diastereomer **9** was isolated in moderate yields. (Table 1).

The photocyclization reaction proceeded efficiently with a variety of carboxylic acid inputs. Mono- (Table 1, entries 1 and 2) and di-substituted (Table 1, entry 3) acyclic as well as cyclic (Table 1, entries 4 and 5) carboxylic acids all participate in the Ugi reaction to provide Ugi products in moderate to high yields. Subsequent photocyclization afforded the fused lactams as a mixture of diastereomers in high overall yields (Table 2, entries 1–5). Typically, diastereomer **9** was the major component of these mixtures and could be isolated as a single or highly enriched diastereomer. Assignment of the relative stereochemistry of the four products was achieved using diagnostic NMR analysis of crude and enriched mixtures of cis- and trans-isomers.

Table 1. Sequential Ugi/[6π]-photocyclizations

	Aldehyde	Amine	Isocyanide	Acid	Ugi product	Ugi yield (%)	Isolated photocyclization product	Product yield[a] (%)
1						83		30
2						67		32
3						59		30
4						70		35

Table 1 (*continued*)

Aldehyde	Amine	Isocyanide	Acid	Ugi product	Ugi yield (%)	Isolated photocyclization product	Product yield[a] (%)
5					51		48
6					51		18
7					64		37[b]
8					75		38

[a] Reactions carried in MeCN.
[b] Reaction performed in MeOH.

Table 2. Diastereomeric distribution of [6π]-photocyclization products after 5 h irradiation in acetonitrile

Entry	Cyclization products yield[a] (%)	Major cis 10 yield[b] (%)	Minor trans 11 yield[b] (%)	Major trans 9 yield[b] (%)	Minor cis 12 yield[b] (%)
1	80	NA	28	52	NA
2	89	NA	38	51	NA
3	93	23	14	39	17
4	87	29	11	47	ND
5[c]	94	8	32	54	ND
6	59	ND	ND	ND	ND
7a	96	33	15	28	19
7b[d]	88	51	4	18	16
8a	91	10	14	62	5
8b[d]	93	33	14	28	19

NA not applicable. ND not determined.
[a] Isolated yield of mixture of diastereomers.
[b] Calculated based on NMR integration.
[c] Reaction mixture was irradiated for 2 h.
[d] Reactions were performed in MeOH.

The relative stereochemistry of the major trans-diastereomer was unambiguously determined in the case of entry 5 (Table 1) by X-ray crystallography (Fig. 1). Furthermore, we observed in ^{1}H NMR a large coupling constant between the trans-bridgehead protons ($J_{HH} = 14.0$ Hz) in contrast to the coupling constant of the cis-configuration ($J_{HH} = 3.87$ Hz). The chemical shifts and coupling patterns were used in the analysis of subsequent samples in order to confirm the bridgehead stereochemistry.

Consistent with literature precedence, when the Ugi product of entry 8, Table 1 was subjected to irradiation in an aprotic solvent such as MeCN the major diastereomer isolated was **9** (Table 2, entry 8a). Alternatively, when the reaction was carried out in MeOH (Table 2,
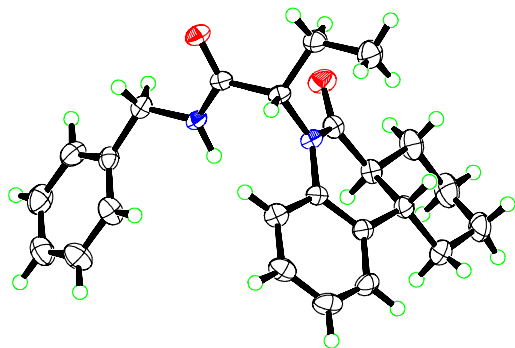
Figure 1. X-ray structure of photocyclization product entry 5 (Table 1).

entry 8b) a significant amount of cis-diastereomer **10** was also observed.

In the case of the *meta*-chloroaniline (Table 1, entry 7) the photocyclization occurred with complete regioselectivity providing the product from participation of the proton between the amino and chloro groups as confirmed by ^1H–^{13}C HMQC and ^1H–^1H ROESY experiments. The cis-diastereomer was the predominant product even in aprotic solvents (Table 2, entry 7a), although a significant amount of the trans-isomer was also observed. In protic solvents (Table 2, entry 7b) cis-diastereomer **10** is predominant and could be cleanly isolated (Table 1, entry 7). Interestingly, although the *ortho*-chloro aniline provided the corresponding Ugi product, the subsequent photocyclization provided a complex mixture of unidentifiable products.

In conclusion, we have developed a multicomponent/photochemical cyclization sequence to access highly functionalized 3,4-dihydroquinolin-2(1H)-ones. The photocyclization proceeds in high yields and with preferential trans-selectivity. Moderate levels of diastereoinduction were observed for the initial [6π]-photocyclization, and in most cases an enriched all trans-diastereomer could be cleanly isolated, albeit in moderate yields.

References and notes

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8. An immersion well reactor was employed following: Penn, J. H.; Orr, R. D. *J. Chem. Educ.* **1989**, *66*, 86–88, When the reaction was performed in a capped vial placed next to a regular photochemical reactor, equipped with a quartz immersion well and a medium pressure, 450 W, mercury lamp, photocyclization was very sluggish and proceeded in poor yields.
9. A typical procedure exemplified for entry 5 (Table 1) was as follows: 1-Propionaldehyde (0.12 mL, 1.64 mmol), allyl-amine (0.12 mL, 1.64 mmol), 1-cyclohexene-1-carboxylic acid (207 mg, 1.64 mmol) and benzyl isocyanide (0. 2 mL, 0.64 mmol) were stirred in MeOH (10 mL) for 24 h. The solvent was evaporated and the crude mixture was purified by column chromatography (15% ethyl acetate/hexanes, then 30% EtOAc/hexanes) to provide the Ugi product as a colorless viscous liquid (317 mg, 51% yield). The Ugi product (65 mg, 0.17 mmol) was then dissolved in MeCN (10 mL) and loaded into the immersion well unit. A flow of N_2 was passed through the solution during the entire experiment. The solution was allowed to degass for 10 min and the mercury lamp was then turned on. The solution was irradiated for 2 h, concentrated and passed through a small plug of silica gel to yield a mixture of all diastereomers. The product mixture was further purified by column chromatography (15% EtOAc/hexanes) to give the pure major trans-diastereomer (31 mg, 48% yield).