Synlett M. A. Dahab et al. Letter

Thieme Chemistry Journals Awardees – Where Are They Now? A Cascade Synthesis of 1,2,4-Triazin-3(2*H*)-ones Using Nitrogen-Substituted Isocyanates

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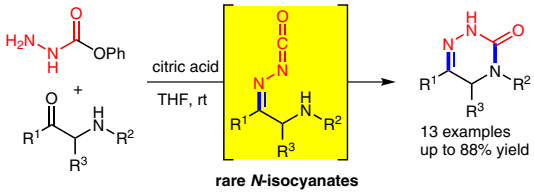

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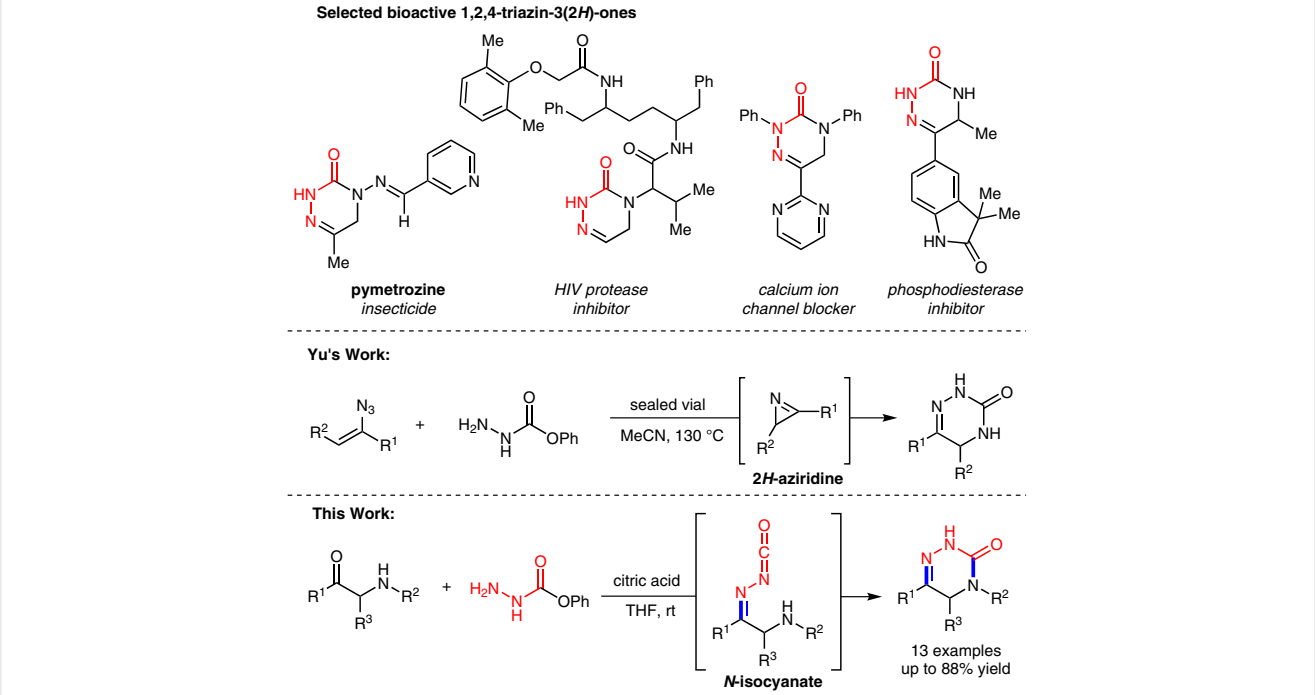
Abstract A cascade synthesis of 1,2,4-triazin-3(2*H*)-ones is reported from readily accessible α-amino ketones and phenyl carbazate as a masked *N*-isocyanate precursor. The mild protocol provides a simple route to products with substitution patterns which are difficult to form directly. This also presents the first *N*-isocyanate cascade requiring the use of acidic conditions, which accelerates formation of the hydrazone intermediate and the cyclization step. This cascade further highlights that high control can be achieved in reactions forming highly reactive *N*-isocyanate intermediates.

Key words *N*-isocyanates, cascade reaction, 1,2,4-triazin-3(2*H*)-one, α-amine ketone

André Beauchemin was born in Quebec city on August 6, 1974. He obtained his BSc chemistry from the Université Laval, graduating in 1996 (working with Prof. J. Boukouvalas). He then studied at the Université de Montréal under the guidance of Prof. André B. Charette, obtaining his Ph.D. in 2001. His post-doctoral appointment was at Harvard University, under the guidance of Prof. David A. Evans, working toward the total synthesis of the marine natural product azaspiracid A. In August 2004, André started as an assistant professor at the University of Ottawa and was promoted to associate professor in 2010 and full professor in 2015. From August to December 2013, André was a visiting professor at ETH Zürich. His research interests include novel approaches to bioactive nitrogen-containing molecules, ideally using inexpensive reagents and catalysts. André has received the Thieme Chemistry Journals Award in 2006.

The development of new, efficient syntheses of nitrogen-containing heterocycles is important given their widespread application within the pharmaceutical and agrochemical industry.[1] 1,2,4-Triazinones are important heterocycles displaying a broad range of biological activities as a result of their analogous structure to pyrimidine bases.[2] 1,2,4-Triazin-3(2*H*)-one derivatives have also attracted significant interest, especially within the field of medicinal chemistry.[3] This interest can also be illustrated by the development of pymetrozine, an antifeedant insecticide currently being employed in the United States and Europe.[4] Despite the potential value of 1,2,4-triazin-3(2*H*)-ones, synthetic approaches to this heterocycle have remained largely rudimentary, typically requiring multistep syntheses or forcing conditions.[3e,5] Recently, Yu and coworkers reported a novel cascade synthesis of this motif using phenyl carbazate and vinyl azides (Scheme 1).[6] This method provided a variety of 1,2,4-triazin-3(2*H*)-ones in good yield, but required the synthesis and thermolysis of vinyl azides. Interestingly in this approach vinyl azides serve as precursors for 2*H*-azirines, which then react as primary α-aminoketone equivalents. As a result of this, the reaction does not allow access to products substituted at the 4-position. In contrast, we were interested in a complementary approach involving phenyl carbazate and suitable secondary α-amino ketones. Given our previous work in heterocyclic synthesis using *N*-isocyanates as reactive intermediates,[7] we hypothesized that a condensation (hydrazone formation)–cyclization ap-



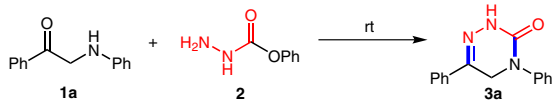
Scheme 1 1,2,4-Triazin-3(2*H*)-ones and their syntheses using *N*-isocyanate cascade reactions

proach could occur preferentially to the intermolecular reaction of the secondary amine with the carbazate,[7d] and provide the first example of a cascade in which the hydrazone *N*-isocyanate precursor is formed in situ. Herein, we report such a *N*-isocyanate cascade, using secondary α-amino ketones to form 1,2,4-triazin-3(2*H*)-ones using citric acid as promoter.

As hinted above, all previous examples using hydrazones as *N*-isocyanate precursors for heterocyclic synthesis involved the preparation of the substrate in a prior step using condensation chemistry. However, such condensations can be difficult to achieve, especially with hindered ketones as substrates.[8] Additional difficulties present with this system are that both *N*-isocyanates and α-amino ketones could form homodimers.[9,10] Conceptually, we hypothesized that catalysis could allow for controlled reactivity, for example, by base-catalyzed intermolecular addition of the secondary amine on phenyl carbazate (followed by intramolecular condensation), or by acid-catalyzed condensation, followed by intramolecular cyclization on the *N*-isocyanate intermediate. With this in mind we initiated our investigation probing conditions to form the desired 1,2,4-triazin-3(2*H*)-one using phenyl carbazate and 2-anilinoacetophenone as model system (Table 1). This particular α-amino ketone was chosen due to its ease of access as well as its reduced tendency to dimerize.

Initially, basic conditions were tested using 1,8-diazabicycloundec-7-ene (DBU). Previously, we reported that DBU

Table 1 Optimization of Reaction Conditions[a]

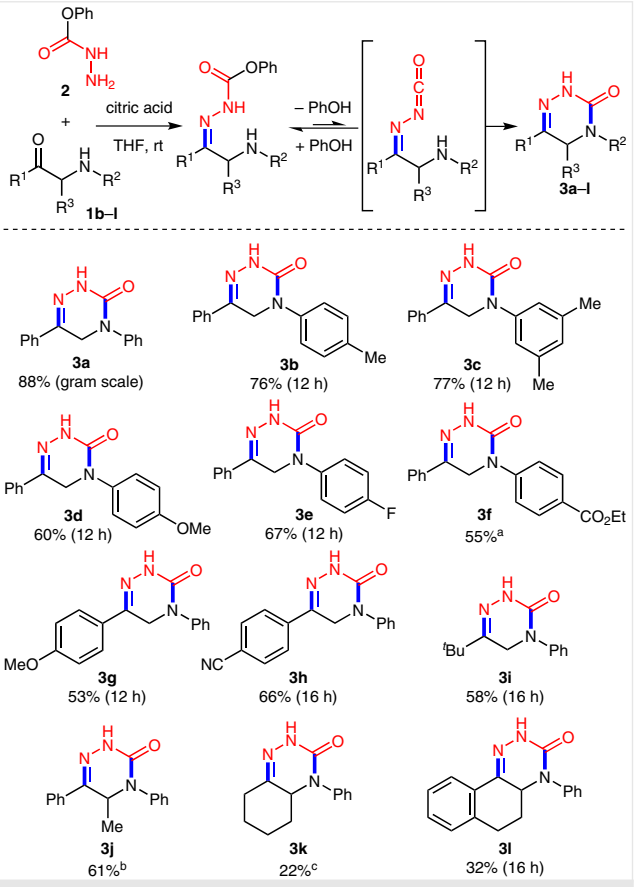


Entry	Additive (equiv)	Solvent (M)	Time (h)	Yield (%)[b]
1	DBU (0.2)	THF (0.3)	16	degradation
2[c]	none	THF (0.3)	16	no reaction
3[c]	Et_3N (0.2)	THF (0.3)	16	degradation
4	citric acid (1.0)	THF (0.5)	12	73
5	citric acid (1.0)	MeCN (0.5)	12	60
6	citric acid (1.0)	$PhCF_3$ (0. 5)	12	11
7	citric acid (1.0)	MeOH (0.5)	12	62
8	citric acid (1.0)	THF (0.1)	12	27
9	citric acid (1.0)	THF (1.0)	12	**73** (74)[d]
10	none	THF (1.0)	12	no reaction

[a] Reaction conditions: phenyl carbazate (**2**, 1.0 equiv), **1a** (1.05 equiv), and citric acid (1 equiv) in THF (0.5 M) stirred at r.t.
[b] ^1H NMR yield based on 1,3,5 trimethoxybenzene as internal standard.
[c] Reflux.
[d] Isolated yield.

was a competent catalyst for simple substitution reactions of phenyl carbazate.[7i] Unfortunately, these conditions did not provide the desired semicarbazide or product but instead resulted in the degradation of the α-amino ketone and dimerization of the carbazate (Table 1, entry 1). Ther-

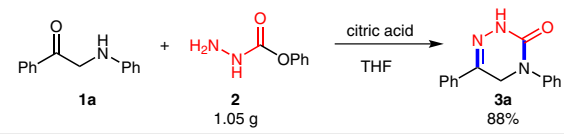
mal conditions were also tested yielding no reaction (entry 2), and in the presence of a mild base produced the same results observed with DBU (entry 3). These results suggested that the nucleophilicity of the aniline is not sufficient to outcompete phenyl carbazate dimerization and led to a survey of conditions which would promote the condensation reaction. This proved fruitful with stoichiometric amounts of citric acid[11] providing the desired product in 73% NMR yield after stirring for 12 hours at room temperature (entry 4). A solvent scan was performed showing that THF was the optimal solvent for this cascade reaction (entries 5–7). The concentration of the reaction was observed to have significant effect on the overall reaction with a 0.1 M reaction resulting in a 27% yield (entry 8) while increasing the reaction concentration from 0.5 to 1 M resulted in no change in yield (entry 9). A control reaction performed in the absence of citric acid stressed its importance in this cascade reaction with neither the condensation product (hydrazone) or desired 1,2,4-triazin-3(2*H*)-one detected by NMR spectroscopy (entry 10). With optimized conditions in hand, we proceeded to probe the applicability of this reaction (Scheme 2).



Scheme 2 Scope of cascade reaction forming 1,2,4-triazin-3(2*H*)-ones. *Reagents and conditions*: phenyl carbazate (**2**, 1.0 equiv), **1b–l** (1.05 equiv), and citric acid (1.0 equiv) in THF (1.0 M) stirred at r.t. [a] Stirred at r.t. for 7 h, followed by reflux for 20 h. [b] Stirred at r.t. for 12 h, followed by reflux for 24 h. [c] Stirred at r.t. for 12 h, followed by reflux for 20 h.

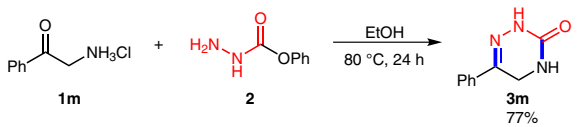
The substituent effect on the aniline moiety was evaluated first. Electron-donating substituents on the aniline ring were well tolerated under the reaction conditions with *p*-methyl (**3b**), 3,5-dimethyl (**3c**), and *p*-methoxy (**3d**) all providing the 1,2,4-triazin-3(2*H*)-one in good yields. Electron-withdrawing groups also afforded the desired product, as illustrated with *p*-fluoro-substituted product **3e**, and even the strongly electron-withdrawing ester yielded product although heating was necessary to achieve cyclization (**3f**). We then surveyed the reactivity of a variety of different ketone substituents on the α-amino ketone. Both electron-rich (**3g**) and electron-poor (**3h**) aromatics provided the product in moderate to good yield. An alkyl substituent was also a competent reaction partner under the reaction conditions, despite the increased steric bulk (**3i**). Finally, the impact of substitution at the α position was probed. As expected the presence of a methyl group at this position had a substantial effect on the reaction: heating was required to achieve efficient cyclization to form product **3j** in good yield. Cyclic derivatives also proved amenable to the cascade although these were found to be low-yielding (**3k** and **3l**). Overall, this methodology provides mild access to an array of 1,2,4-triazin-3(2*H*)-ones.

We next sought to probe applicability of this procedure to the large scale synthesis of 1,2,4-triazin-3(2*H*)-one **3a**. The reaction was performed on a 1.05 g scale using substrate **1a** under standard reaction conditions (Scheme 3). This led to an 88% isolated yield of the desired product, a crystalline product that could also be obtained in an unoptimized 60% yield by crystallization.[12]



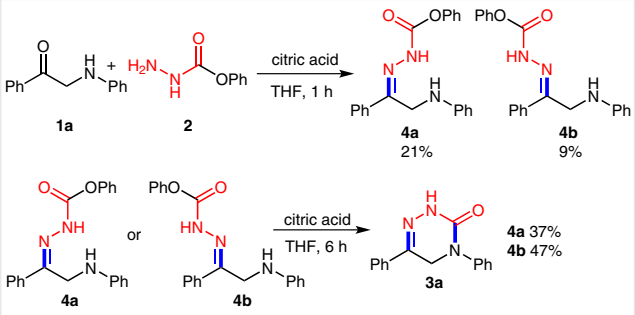
Scheme 3 Gram-scale synthesis

The applicability of this protocol was then explored with a primary α-aminoketone (Scheme 4), using commercially available 2-aminoacetophenone hydrochloride as the test substrate. This substrate was not amenable to room-temperature reactivity, in fact, reflux in ethanol in the presence of excess of carbazate **2** was required to obtain a high yield of **3m**. This preliminary data suggests the scope of this protocol could be expanded to include other α-aminoketones.



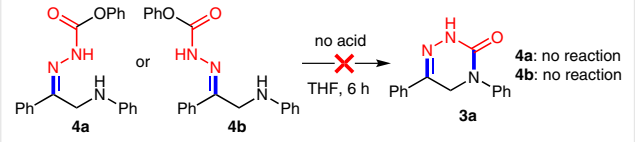
Scheme 4 Reaction of a primary α-aminoketone

Finally, we turned our attention to the mechanism of this cascade reaction. In order to support our proposed mechanism, that is, intermolecular condensation followed *N*-isocyanate formation and intramolecular cyclization, we sought to isolate the α-aminocarbazone intermediate. Substrate **1a** was submitted to the standard reaction conditions, and the reaction was interrupted after one hour. This resulted in the formation and isolation of both the *Z* (**4a**) and the *E* (**4b**) isomer of the desired α-aminocarbazone (Scheme 5, top). Both of these intermediates were submitted to standard reaction conditions to probe their capacity to form product. Gratifyingly, both isomers were observed to form the desired 1,2,4-triazin-3(2*H*)-one, albeit in modest yield, supporting their role as intermediates in the reaction cascade (Scheme 5, bottom). Moreover, this demonstrates the ease with which *E*/*Z* isomerization occurs under the reaction conditions, as reaction monitoring indicated that both reactions looked identical by TLC shortly after the addition of citric acid.



Scheme 5 Isolation of intermediates and control experiments

The effect of citric acid on the cyclization was also investigated (Scheme 6). It was initially assumed that acid only benefited the initial condensation given the lack of formation of **4a** and **4b** in the absence of acid. Moreover, given our previous work using base catalysis to achieve *N*-isocyanate formation, it would be possible that acid impedes *N*-isocyanate formation. Unexpectedly, submitting both **4a** and **4b** to the standard reaction conditions without citric acid yielded starting material with no detectable product formed. To our knowledge, this represents the first evidence of acid-promoted cyclization of a blocked (masked) *N*-isocyanate.



Scheme 6 Control experiments without acid

In conclusion, we have developed a new 1,2,4-triazin-3(2*H*)-one synthesis through a controlled cascade reaction between a masked *N*-isocyanate precursor and α-amino ketones. This strategy provides access to various 1,2,4-triazin-3(2*H*)-ones under mild reaction conditions. Moreover, this work contains the first evidence of an acid-promoted *N*-isocyanate formation. This provides a novel strategy in *N*-isocyanate cascade reactions which should be applicable in the context of other heterocyclic syntheses. This also presents the first cascade reaction where the masked *N*-isocyanate precursor is formed in situ. The development of other cascade reactions involving rare heteroatom-substituted isocyanates is ongoing and will be reported in due course.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588099.

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(12) Recrystallization resulted in a 60% yield of the desired compound while the remaining 28% was obtained through column purification. See Supporting Information for details.
(13) **General Procedure for the Cascade Reaction**
In a dry microwave vial equipped with a stir bar, the α-amino ketone (1.05 equiv) was added to phenyl carbazate (1.0 equiv) and citric acid (1.0 equiv). The vial was then sealed and purged with argon followed by the addition of purified THF (1.0 M). The resulting solution was left stirring at r.t. for 12–16 h. The reaction mixture was concentrated under reduced pressure, diluted with a sat. $NaHCO_3$ solution (20 mL), and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The crude products were purified by column chromatography or through recrystallization in MeOH.
(14) **4,6-Diphenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (3a)**
Synthesized according to the general procedure using α-amino ketone **1a** (0.133 g, 0.630 mmol), phenyl carbazate (0.0912 g, 0.600 mmol), and citric acid (0.115 g, 0.600 mmol), then purified THF (0.6 mL, 1.0 M) was added under argon. The resulting solution was left stirring at r.t. for 12 h. The title compound was purified by column chromatography (5% EtOAc–CH_2Cl_2) to yield a white solid (0.186 g, 74%). TLC: R_f = 0.23 in 5% EtOAc–CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1 H), 7.68 (ddd, *J* = 4.4, 2.5, 1.4 Hz, 2 H), 7.44 (t, *J* = 2.7 Hz, 2 H), 7.42 (dd, *J* = 2.7, 1.6 Hz, 4 H), 7.40 (d, *J* = 3.1 Hz, 1 H), 7.31–7.26 (m, 1 H), 4.74 (s, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.5, 143.3, 140.4, 133.4, 130.0, 129.2, 128.8, 126.6, 125.3, 124.5, 47.7. IR (ATR diamond): 3216, 3097, 1662, 1625, 1593, 1195, 772 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{15}H_{13}N_3O$ [M]$^+$: 251.1053; found: 251.1056.
(15) **Procedure for the Primary α-Amino Ketone: 6-Phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (3m)**
In a dry microwave vial equipped with a stir bar, 2-aminoacetophenone hydrochloride (0.103 g, 0.600 mmol) was added to a solution of phenyl carbazate (0.273 g, 1.80 mmol) in EtOH (1.20 mL, 0.50 M) and refluxed under argon for 24 h. The reaction mixture was concentrated under reduced pressure, and dry loaded onto silica gel. The title compound was purified by column chromatography (100% EtOAc to 5% MeOH–CH_2Cl_2) to yield a white solid (0.0813 g, 77%). TLC: R_f = 0.27 in 5% EtOAc–CH_2Cl_2. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.90 (d, *J* = 1.8 Hz, 1 H), 7.63–7.61 (m, 2 H), 7.40–7.34 (m, 3 H), 7.22 (s, 1 H), 4.60 (d, *J* = 1.8 Hz, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 152.4, 141.9, 134.6, 129.7, 129.0, 125.5, 40.5.