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Divergent Reactivity of *N*-Isocyanates with Primary and Secondary Amines: Access to Pyridazinones and Triazinones

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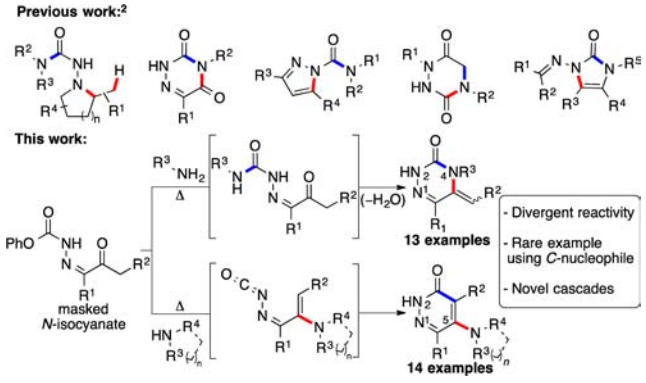
Supporting Information

ABSTRACT: Cascade reactions for the synthesis of 1,2,4-triazinones and 5-aminopyridazinones are reported using α-ketocarbazones as *N*-isocyanate precursors and exploiting the divergent reactivity observed with primary and secondary amines. Triazinones were formed with primary amines, likely through addition of the amine on the *N*-isocyanate, followed by cyclization (condensation) on the ketone. In contrast, such cyclization is impossible for secondary amines; this allows in situ formation of enamines, which, upon cyclization, generate 5-amino pyridazinones. This sequence further illustrates the versatility of *N*-isocyanates in heterocyclic synthesis and provides a rare example of carbon nucleophiles reacting with *N*-isocyanates.

Nitrogen-substituted isocyanates (*N*-isocyanates) are a rare class of isocyanates with a synthetic potential that remains largely untapped.[1] Their tendency to dimerize at temperatures as low as −40 °C[1h] typically prevented the use of these reactive intermediates as building blocks for the construction of N−N−C═O motifs, which are present in >50 pharmaceuticals and agrochemicals.[2i] Recently, our group has explored the reactivity of *N*-isocyanates in concerted cycloadditions and in heterocyclic synthesis[2] using an in situ generation approach from masked (blocked) isocyanate precursors.[3] The controlled reactivity provided by this approach enabled cascades and reaction sequences for the formation of several heterocyclic systems (Scheme 1, top). However, cascade reactions involving the use of ketones as either electrophiles or pronucleophiles have not been reported and would significantly expand the synthetic reach of *N*-isocyanates. Herein, we report such reactivity in the divergent syntheses of 1,2,4-triazinones and 5-aminopyridazinones from α-ketocarbazones. Indeed, the use of primary amines allows triazinone formation through condensation on the ketone, and the use of secondary amines enables pyridazinone formation via enamine cyclization[4] on the transient *N*-isocyanate intermediate (Scheme 1, bottom).

Scheme 1. *N*-Isocyanates in Heterocyclic Synthesis



1,2,4-Triazinones are an important class of nitrogen heterocycles epitomized by azauracils, which possess a broad range of biological activities and are present in pharmaceuticals and agrochemicals.[5] Dihydroazapyrimidinones have also attracted considerable interest exemplified by the success of pymetrozine as an insecticide. 1,2,4-Triazinones possessing an exocyclic unsaturation are interesting entities given their inherent reactivity yet have seldom been studied. Difficulties in accessing these compounds could explain their scarcity in the literature.[6] In contrast, 5-aminopyridazinones possess broad biological activities[7] and are present in agrochemicals (e.g., norflurazon) as well as pharmaceuticals (e.g., emorfazone). Novel pathways leading to these heterocycles would be useful given the limited synthetic methods that currently exist to access such motifs.[8]

α-Ketocarbazone-based *N*-isocyanates were envisioned as possible precursors for triazinones and pyridazinones. Indeed, the increased electrophilicity of the carbonyl and the ease of preparation of substrates proved attractive to explore this reactivity. However, potential challenges included (1) the possibility of side reactions of such densely functionalized precursors; (2) that the more stable *E* isomer of the carbazate is favored and cyclization requires the *Z* isomer; and (3) that the addition of the amine to the isocyanate intermediate occurs first,[2d,i] thus leading to a more difficult cyclization (triazinones) and requiring a reversible addition for secondary amines to access

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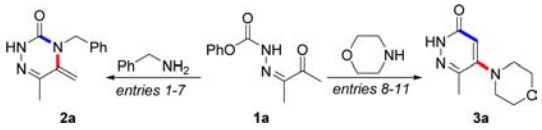
the isocyanate intermediate in the presence of the enamine (pyridazinones).

To assess the feasibility of both cascades, we began our investigation with the α-ketocarbazone **1a** derived from *O*-Ph carbazate and 2,3-butanedione. Encouraging results were observed for both reaction cascades. First, formation of triazinone **2a** was optimized using benzylamine as a model primary amine (Table 1, entries 1−7). An initial reaction at 150 °C for 2 h under microwave irradiation resulted in a 34% yield of **2a** with the remaining mass balance attributed to uncyclized addition product of benzylamine. A higher yield was observed upon heating at 175 °C (entry 2). However, severe degradation was observed at 200 °C with minimal uncyclized product remaining (entry 3); thus, 175 °C was selected as the optimal temperature. Both $MgSO_4$ (entry 4) and triethylamine (20 mol %, entry 5) proved to be beneficial additives, while the addition of acetic acid (20 mol %) led to near-quantitative product formation (entry 6). Alternatively, the use of $MgSO_4$ for a longer reaction time also provided the triazinone **2a** in high yield (entry 7).

Table 1. Cascades Forming Triazinones[a] or Pyridazinones:[b] Optimization Using α-Ketocarbazone 1a



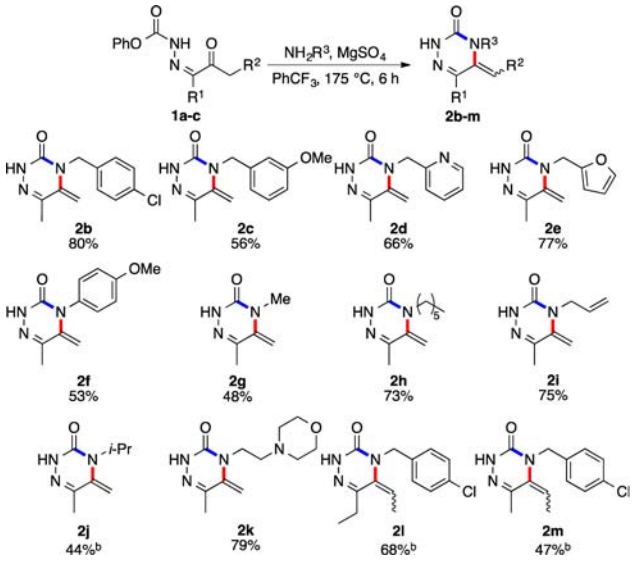
entry	amine	temp (°C), time (h)	additive	yield[c] (%)
1	$BnNH_2$[a]	150, 2	none	34
2	$BnNH_2$[a]	175, 2	none	44
3	$BnNH_2$[a]	200, 2	none	37
4	$BnNH_2$[a]	175, 2	$MgSO_4$[d]	56
5	$BnNH_2$[a]	175, 2	Et_3N[e]	64
6	$BnNH_2$[a]	175, 2	AcOH[e]	94
7	$BnNH_2$[a]	175, 6	$MgSO_4$[d]	87 (75)[f]
8	morpholine[b]	175, 2	none	64
9	morpholine[b]	175, 2	$MgSO_4$[d]	66
10	morpholine[b]	175, 2	PivOH[e]	73
11	morpholine[b]	175, 2	PivOH[e] + $MgSO_4$[d]	83 (71)[f]

[a]Conditions: carbazone (1.0 equiv), $BnNH_2$ (1.1 equiv) in $PhCF_3$ (0.3 M), heated in a microwave reactor. [b]Conditions: carbazone (1.0 equiv), morpholine (3.0 equiv) in $PhCF_3$ (0.3 M), heated in a microwave reactor. [c]NMR yield based on 1,3,5-trimethoxybenzene internal standard. [d]1 equiv. [e]0.2 equiv. [f]Isolated yield.

Second, formation of pyridazinone **3a** was optimized using morpholine as the model secondary amine (Table 1, entries 8−11). Morpholine was chosen based on a previous study reporting the ability of morpholine-derived semicarbazones to act as a masked *N*-isocyanate at 100 °C.[2d] The desired product **3a** was obtained in 64% yield upon microwave irradiation for 2 h at 175 °C (entry 8). Both $MgSO_4$ (entry 9) or pivalic acid (20 mol %, entry 10) could be used as additives; the use of both under the reaction conditions provided a high-yielding cascade for the formation of pyridazinone **3a** (entry 11).[9]

With optimized conditions to form both heterocycles in hand, the scope of these cascade reactions could then be investigated. However, it rapidly became apparent that for triazinones the conditions using acetic acid (Table 1, entry 6) led to functional group tolerance issues and reduced efficiency for this cascade. This is likely due to the sensitivity of the exocyclic alkene under acidic conditions. Thus, evaluation of the reaction scope relied on conditions using $MgSO_4$ (Table 1, entry 7); the results are presented in Table 2.

Table 2. Cascade Synthesis of Triazinones[a]



[a]Conditions: carbazone (1 equiv), amine (1.1 equiv), $MgSO_4$ (1 equiv), in $PhCF_3$ (0.3 M), heated in a microwave reactor for 6 h at 175 °C. Isolated yields are shown. [b]Performed at 200 °C.

A variety of primary amines were found to produce the desired triazinones, typically ranging from modest to good yields (Table 2). The benzylamine-derived triazinone was isolated in 75% yield (**2a**). Both electron-poor and electron-rich benzylic amines produced the desired product with moderate to good yield (**2b** and **2c**). The reaction conditions also allowed for heterocycle incorporation with both pyridinyl- (**2d**) and furanyl-containing triazinones (**2e**) isolated in good yields. Despite reduced nucleophilicity, an aniline could also be incorporated in the desired product although in modest yield (**2f**). Both short-chain (**2g**) and long-chain (**2h**) aliphatic amines afforded the desired products. In addition, allylamine was found to be a competent reaction partner (**2i**). Sterically demanding branched aliphatic amine (**2j**) also resulted in the desired triazinone product, although a higher temperature was necessary. Basic moieties were also well tolerated, leading to the desired triazinone product in good yield in the presence of a morpholine motif (**2k**). Reactions with α-ketocarbazones derived from different diones was also of interest. Fortunately, 3,4-hexanedione and 2,3-pentanedione-derived carbazones resulted in modest to good yields of the desired products **2l** and **2m**, albeit in an *E*/*Z* ratio of approximately 1:2.[10] Overall, this report provides an efficient methodology to access a diverse library of rare triazinones.

The scope of the cascade to form aminopyridazinones was then explored with secondary amines (Table 3). Cyclic amines, particularly 6-membered derivatives, proved optimal for this reaction. Morpholine (**3a**), piperidine (**3b**), and thiomorpholine (**3c**) proved to be good reaction partners. *N*-Methylpiperazine (**3d**) was also well tolerated under the reaction conditions but required a slight increase in reaction time. We were pleased to see that an ester functional group was compatible with the reaction conditions despite the presence of acid and excess amine (**3e**). The 7-membered heterocycle azepane was also a competent reaction partner, although a longer reaction time was again necessary (**3f**). In contrast, pyrrolidine-derived aminopyridazi-

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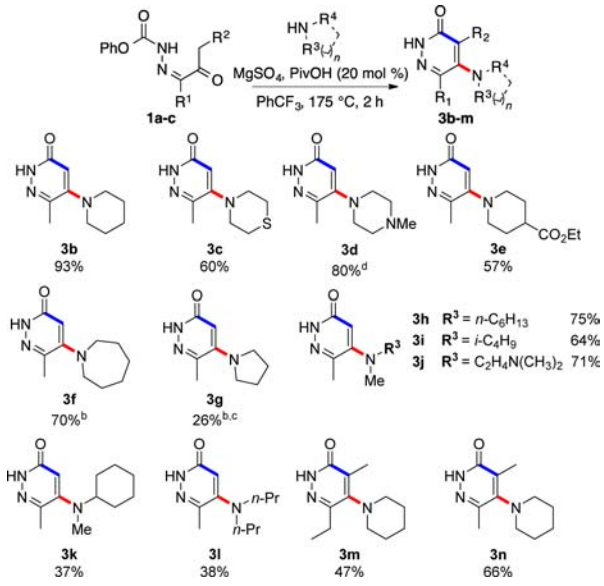
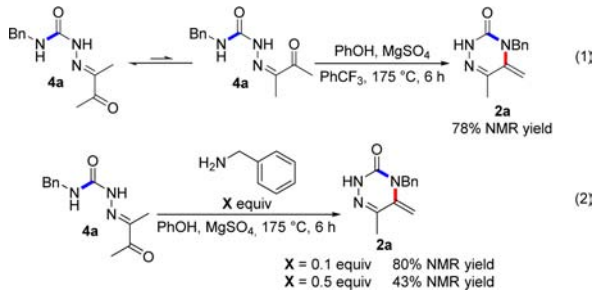
Table 3. Cascade Synthesis of Pyridazinones[a]



[a]Conditions: α-ketocarbazone (1 equiv), amine (3 equiv), $MgSO_4$ (1 equiv), pivalic acid (20 mol %), in $PhCF_3$ (0.3 M), heated in a microwave reactor for 2 h at 175 °C. Isolated yields are shown. [b]Performed at 200 °C for 6 h without acid. [c]NMR yield. [d]4 h, without $MgSO_4$.

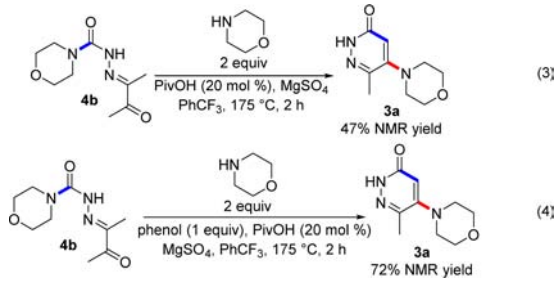
none was only formed in modest yield even at increased temperature and reaction time (**3g**). Acyclic amines were also competent reaction partners with *N*-methylhexylamine (**3h**), *N*-methylisobutylamine (**3i**), and *N,N,N′*-trimethylethylenediamine (**3j**), affording the desired products in good yields. A decrease in reaction efficiency was observed upon increasing the steric bulk of the acyclic amine with both dipropylamine (**3k**) and *N*-methylcyclohexylamine (**3l**). Finally, the effect of masked *N*-isocyanates derived from different diones was also examined. Surprisingly, the 3,4-hexanedione derivative (**3m**) resulted in a significantly lower yield than the 2,3-pentanedione derivative (**3n**). This was unexpected given the steric bulk at the nucleophilic carbon of the enamine remaining constant in both cases. Overall, this methodology was compatible with a broad scope of different amines and allows access to alkyl-substituted aminopyridazinones at the 4- and 6-positions. These are difficult to access with the currently reported literature methods, which require lengthy multistep reaction sequences.[8h,i] Overall, even if decomposition typically accounts for the lower yields obtained for the most challenging substrates of Tables 2 and 3, the multistep cascade reactions remain preparatively useful.

We next sought to probe the mechanism of these cascade reactions. Toward this end, a likely intermediate in the triazinone-forming cascade, semicarbazone **4a**, was formed as previously reported at room temperature in related systems.[2d,i] Semicarbazone **4a** was then subjected to the conditions of the cascade reaction, and as expected, triazinone formation proceeded smoothly to form triazinone **2a**, in a similar yield to that of the direct reaction from carbazone **1a** (eq 1). It is also noteworthy that semicarbazone **4a** exists exclusively as the *E* isomer in solution[11] and that efficient cyclization thus implies that isomerization to the *Z* isomer occurs under the reaction conditions.[2i] While this result supports that desired product **2a** could form through direct condensation of **4a** on the carbonyl, an alternative involving cyclization of an enamine onto the *N*-isocyanate is also possible. To probe this possibility, cyclization of



intermediate **4a** was attempted in the presence of excess amine, which would be required for enamine formation. Interestingly, the addition of benzylamine was observed to inhibit product formation (eq 2). Overall, these results support the feasibility of a pathway involving an intramolecular condensation of semicarbazone **4a**.

Morpholine-derived semicarbazone (**4b**) was then formed and submitted to standard reaction conditions for aminopyridazinone formation (eq 3). In this case, a lower yield was obtained in



contrast to the standard reaction conditions on carbazate **1a** (47% vs 83%). A possible explanation for the increased difficulty of **4b** to act as a *N*-isocyanate precursor relative to **1a**–**c** could be that formation of the enamine occurs before semicarbazone formation. However, this is highly unlikely since semicarbazones are formed from similar *N*-isocyanate precursors rapidly at room temperature (LG = OPh).[2d] Therefore, a control reaction with the addition of phenol was carried out to replicate the standard reaction conditions more closely, since phenol is generated upon reaction of the masked *N*-isocyanate precursor (eq 4). Interestingly, a significantly higher yield (72%) was observed, showing that efficient product formation can occur from intermediate **4b**. Moreover this provides the first evidence of a blocking/masking group of a *N*-isocyanate precursor as a useful "additive" in a subsequent cascade reaction. The beneficial effect that phenol displays could arise from its potential ability to facilitate isomerization of the C═N bond or to facilitate isocyanate formation from the semicarbazone **4b**: the mechanistic details are still under investigation. Control experiments regarding the involvement of a *N*-isocyanate intermediate were also performed, and the results are consistent with the formation of the reactive intermediate (see the Supporting Information for details).

In conclusion, new cascade reactions of *N*-isocyanates allowed syntheses of triazinones and pyridazinones from α-ketocarbazones and simple amines. Primary amines provided access to 1,2,4-triazinones possessing an exocyclic alkene, which are rare in the literature. In contrast, the use of secondary amines allowed formation of 5-aminopyridazinones. This latter cascade exploits the ability of enamines formed in situ to react with *N*-isocyanate intermediates and provides the first evidence of the blocking group released from the *N*-isocyanate precursor proving

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beneficial to the outcome of a cascade reaction. Studies to expand the reactivity of *N*-isocyanates and related amphoteric reactive intermediates in synthesis are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03590.

Additional optimization data, complete experimental procedures, characterization data, and NMR spectra (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(9) The use of microwave heating proved optimal from a reaction efficiency perspective. In contrast, the use of conventional heating yielded the triazinone (31%) and pyridazinone (23%) products using conditions similar to those of Table 1, entries 7 and 11, after heating for 14 h at reflux in 1,2-dichlorobenzene. While modest, these unoptomized results suggest that conventional heating could be envisioned.

(10) The major isomer observed in **2m** displayed a strong NOESY correlation between the hydrogen of the olefin and the aliphatic hydrogens at position 6, corresponding to the *Z* isomer. The minor isomer displayed a strong NOESY correlation between the methyl of the olefin and the methyl substituent at position 6, corresponding to the *E* isomer. See the Supporting Information for details.

(11) The presence of a sole isomer was observed in NMR experiments of **4a** and **4b** with strong NOESY correlation between the N−H of the carbazone and the methyl substituent directly attached to the carbon nitrogen double bond corresponding to the *E* isomer. See the Supporting Information for details.

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