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A Practical Approach to Semicarbazone and Hydrazone Derivatives via Imino-isocyanates

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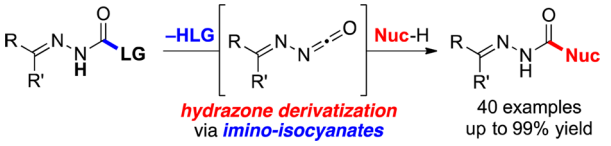
ABSTRACT



Complex hydrazone derivatives can be accessed readily from hydrazones upon heating in the presence of nucleophiles. This reactivity likely involves imino-isocyanate intermediates, and a variety of leaving groups can be used at temperatures ranging from 20 to 150 °C. Alcohols, thiols, primary, and secondary amines can be used as nucleophiles, thus providing a simple alternative to the synthesis of hydrazones via condensation on the parent carbonyl precursor and allowing late-stage derivatization.

Isocyanates (RNCO) are very important bulk chemicals (e.g., polyurethanes) and are often used as bulding blocks and derivatization reagents in organic synthesis.[1] However, many isocyanates are toxic and workers regularly exposed to them can develop sensitivity issues. Thus, for selected industrial applications (e.g., paints and coatings industries) compounds that release isocyanates in situ have been developed. Suitable carbamates (RNHCOLG, e.g., LG = OPh) thus serve as *blocked isocyanates*.[2] As part of recent efforts toward alkene amination reactions, we became interested in the reactivity of nitrogen-substituted isocyanates.[3] Surprisingly there are only a few reports on such isocyanates in the literature.[3,4]

Recently, we reported intermolecular alkene aminocarbonylation reactivity that occurs upon heating suitable hydrazones with alkenes (see below).[3b,c] Under such conditions, an imino-isocyanate intermediate is generated in situ, and complex azomethine imines possessing β-aminocarbonyl motifs are formed from simple precursors. As part of these efforts, we became interested in the formation of complex hydrazones and in surveying the impact of the nature of the leaving group on this reactivity. The synthesis of several ketohydrazones proved challenging. First, the condensation reactivity of carbazates (NH_2NHCO_2R) and semicarbazides ($NH_2NHCONR'R''$) was sensitive to the steric hindrance of ketones and required heating. Not surprisingly, some hydrazine derivatives ($NH_2NHCOLG$) decomposed under the reaction conditions, presumably via generation of the amino-isocyanate NH_2NCO.[5] Second, this approach inherently required the synthesis of hydrazine derivatives that are not commercially available. These efforts suggested that forming the hydrazone derivatives from a common hydrazone precursor would be more

(1) (a) Ulrich, H. *Chemistry and Technology of Isocyanates*; J. Wiley & Sons: Chichester, U.K., 1996. (b) Six, C.; Richter, F. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: 2012; Vol. 20, pp 63–82.

(2) For an entry in the blocked iscoyanate literature, see: (a) Wicks, D. A.; Wicks, Z. W., Jr. *Prog. Org. Coat.* **1999**, *36*, 148. (b) Wicks, D. A.; Wicks, Z. W., Jr. *Prog. Org. Coat.* **2001**, *41*, 1.

(3) (a) Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Whipp, C. J.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740. (b) Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16111. (c) Gan, W.; Moon, P. J.; Clavette, C.; Das Neves, N.; Markiewicz, T.; Toderian, A. B.; Beauchemin, A. M. *Org. Lett.* **2013**, *15*, 1890.

(4) For examples see: (Aminoisocyanates) (a) Wadsworth, W. S.; Emmons, W. D. *J. Org. Chem.* **1967**, *32*, 1279. (b) Lockley, W. J. S.; Lwowski, W. *Tetrahedron Lett.* **1974**, 4263. (c) Kurz, M.; Reichen, W. *Tetrahedron Lett.* **1978**, 1433. (Imino-isocyanates) (d) Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1982**, 766. (CONR-NCO) (e) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539. (f) Wentrup, C.; Finnerty, J. J.; Koch, R. *J. Org. Chem.* **2011**, *76*, 6024. (Amido-isocyanates) (g) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539. For reviews, see: (h) Reichen, W. *Chem. Rev.* **1978**, *78*, 569. (i) Wentrup, C.; Finnerty, J. J.; Koch, R. *Curr. Org. Chem* **2011**, *15*, 1745.

(5) Teles, J. H.; Maier, G. *Chem. Ber.* **1989**, *122*, 745.

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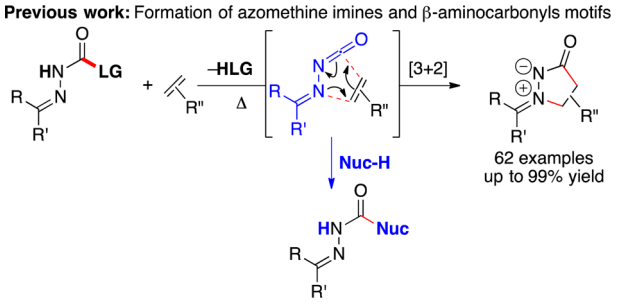
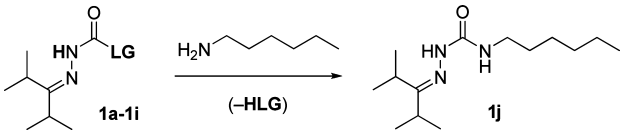
efficient. Herein, we report on the development of this reactivity and provide calibration on the in situ generation of imino-isocyanates and their reactivity with various nucleophiles.



We thus became interested in determining the ability of several hydrazone precursors to undergo an exchange reaction with *n*-hexylamine as the nucleophile. The reactivity observed with various leaving groups is presented in Table 1.

Table 1. Exchange Reaction: Impact of Hydrazone Structure (LG) with *n*-Hexylamine As Nucleophile[a]



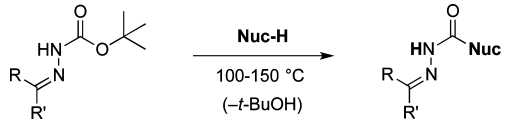
entry	**LG-H**	temp (°C)	time	yield[b] (%)
1	*n*-$C_8H_{17}SH$ (**1a**)	120	20 min	98
2	*n*-$C_8H_{17}SH$ (**1a**)	100	20 min	51
3	PhSH (**1b**)	rt	1 h	82
4	PhSH (**1b**)	rt	4 h	99 (99)
5	*t*-$BuNH_2$ (**1c**)	120	20 min	92
6	$PhNH_2$ (**1d**)	100	3 h	91
7	morpholine (**1e**)	100	1 h	99
8	*i*-Pr_2NH (**1f**)	rt	2 h	84 (84)
9	*i*-Pr_2NH (**1f**)	rt	4 h	91
10	BnOH (**1g**)	150	20 min	94
11	BnOH (**1g**)	120	20 min	38
12	*t*-BuOH (**1h**)	120	20 min	95
13	*t*-BuOH (**1h**)	100	20 min	40
14	PhOH (**1i**)	rt	20 min	91 (99)

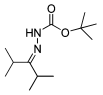
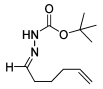
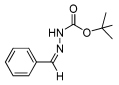
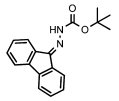
[a] Conditions: hydrazone (1 equiv), *n*-$C_6H_{13}NH_2$ (2 equiv), $PhCF_3$ (0.2 M); for reactions requiring heat, microwave irradiation was used. [b] NMR yields using internal standard; isolated yields in parentheses

As expected, the reactivity observed with *n*-hexylamine correlates well with the leaving group ability (**LGH**). Encouragingly, several hydrazone precursors reacted at room temperature [entries 3–4 (PhSH), 8–9 (*i*-Pr_2NH), and 14 (PhOH)]. The reactivity of these substrates with *n*-hexylamine at room temperature could be consistent with base catalysis, in agreement with the common use of blocked isocyanates using amines as catalysts.[2] The use of

(6) Hutchby, M.; Houlden, C. E.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 8721.

Table 2. Exchange Reaction: Nucleophile Scope Using Hydrazones Derived from NH_2NHCO_2t-Bu[a]



entry	starting material	**Nuc-H**	temp (°C)	time	yield (%) / product[b]
1		*n*-$C_6H_{13}NH_2$	120	20 min	79 **(1j)**
2		*i*-$PrNH_2$	120	20 min	83 **(1k)**
3[c]		*t*-$BuNH_2$	120	20 min	83 **(1c)**
4[c]		$PhNH_2$	120	20 min	78 **(1d)**
5[d]		*i*-Pr_2NH	150	3 min	68(99) **(1f)**
6		morpholine	120	20 min	91 **(1e)**
7		*n*-$C_8H_{17}SH$	120	3 h	82 **(1a)**
8		PhSH	120	2 h	73 **(1b)**
9[e]		BnOH	150	3 min	85 **(1g)**
10[f]		PhOH	150	3 min	27 **(1i)**
11		*i*-$PrNH_2$	100	20 min	66 **(3a)**
12		*t*-$BuNH_2$	150	30 min	75 **(3b)**
13		$PhNH_2$	150	30 min	72 **(3c)**
14		PhOH	150	2 h	0
15		PhSH	150	2 h	77 **(3d)**
16		*n*-$C_6H_{13}NH_2$	120	20 min	64 **(3e)**
17		*n*-$C_6H_{13}NH_2$	120	20 min	79 **(3f)**
18[f]		PhOH	150	5 min	18 **(3g)**

[a] Conditions: hydrazone (1.0 equiv), nucleophile (2 equiv), in $PhCF_3$ (0.2 M), microwave irradiation; time and temperature as stated above. [b] Isolated yields; NMR yield in parentheses. [c] $PhCF_3$ (0.5 M). [d] 1.0 equiv of hydrazone, 14 equiv of nucleophile, neat. [e] 5.0 equiv of nucleophile. [f] 10.0 equiv of nucleophile.

diisopropylamine as a leaving group under mild conditions was inspired by a recent report by Booker-Milburn, Lloyd-Jones et al.[6] Such room temperature reactivity is also in agreement with the pioneering work of Lubell et al. using hydrazones with a *p*-nitrophenol leaving group as building blocks for azapeptide synthesis.[7] In contrast, the use of hydrazones derived from more stable semicarbazides (entries 5–7) and carbazates (entries 10–13) required heating at 100–150 °C. For these substrates, the reactivity correlates well with leaving group ability, with sterically demanding leaving groups showing slightly increased reactivity.

After acquiring this calibration on leaving group ability, we turned our attention to the use of various nucleophiles

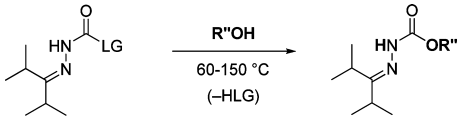
(7) (a) Sabatino, D.; Proulx, C.; Klocek, S.; Bourguet, C. B.; Boeglin, D.; Ong, H.; Lubell, W. D. *Org. Lett.* **2009**, *11*, 3650. (b) Sabatino, D.; Proulx, C.; Pohankova, P.; Ong, H.; Lubell, W. D. *J. Am. Chem. Soc.* **2011**, *133*, 12493. For an excellent review on azapeptide synthesis, see: (c) Proulx, C.; Sabatino, D.; Hopewell, R.; Spiegel, J.; Ramos, Y. G.; Lubell, W. D. *Future Med. Chem.* **2011**, *3*, 1139.

(Table 2). As discussed above, we were particularly interested in hydrazones derived from robust carbazates since these reagents can form hydrazones reliably even upon condensation onto hindered ketones. Thus, the reaction with several nucleophiles was explored on four hydrazones derived from *tert*-butylcarbazate.

Gratifyingly, reaction of these robust hydrazones with nucleophiles afforded a variety of hydrazone derivatives upon heating at 100−150 °C (Table 2). Hydrazones derived from both aldehydes and ketones proved to be excellent substrates for this exchange reaction. The reaction worked with a variety of nitrogen nucleophiles (entries 1−6, 11−13, 16, 17), thiols (entries 7−8, 15), and alcohols (entry 9; see also Table 3). Specifically, primary amines (entries 1−3, 11−12, 15, 17), aniline (entries 4 and 13), and both acyclic and cyclic secondary amines proved to be competent nucleophiles (entries 5−6). Use of *n*-octanethiol (entry 7) and thiophenol (entries 8, 15) also provided hydrazone derivatives. Only phenol proved to be a poor nucleophile, providing only little (entries 10, 18) to no (entry 14) conversion to the desired exchange product and leading to recovery of unreacted starting material. Nevertheless, hydrazone **3g** could be synthesized using this approach, and crystals suitable for X-ray crystallographic analysis were obtained (see Supporting Information for crystal structure).

Given the importance of alcohols (especially polyols) in the isocyanate industry, we then explored the use of several hydrazone precursors with these nucleophiles (Table 3). As expected, several hydrazone precursors afforded addition products upon heating in the presence of alcohols. At 150 °C, rapid exchange was observed for the use of carbazate based isocyanates (entries 1−2). Milder conditions (60−80 °C) were also developed with a semicarbazide-based hydrazone precursor (entries 3−6).[6] Notably, the reaction with 1,3-propanediol afforded the double

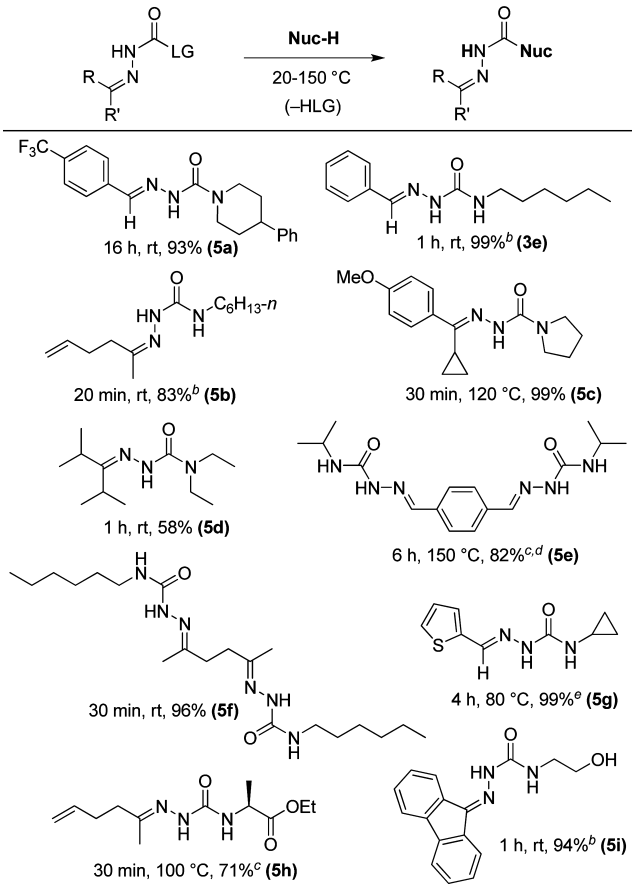
Table 3. Exchange Reaction: Impact of Hydrazone Structure Using Alcohols as Nucleophiles[a]



entry	leaving group	R″OH	temp (°C)	time	yield (%)[b]/ product
1	*t*-BuOH	BnOH	150	3 min	(85) (**1g**)
2	BnOH	*t*-BuOH	150	3 min	(80) (**1h**)
3	(*i*-Pr)$_2$NH	*n*-BuOH	60	3 h	65 (**1l**)
4[c]	(*i*-Pr)$_2$NH	*n*-BuOH	80	16 h	(95) (**1l**)
5[c]	(*i*-Pr)$_2$NH	*n*-BuOH	80	5 h	56 (**1l**)
6[d]	(*i*-Pr)$_2$NH	1,3-propanediol	80	4.5 h	62(28) (**1m**)

[a] Conditions: hydrazone (1.0 equiv), alcohol (2 equiv), in $PhCF_3$ (0.2 M), microwave irradiation. [b] NMR yield using internal standard; isolated yields in parentheses. [c] 5 equiv of alcohol [d] Hydrazone (3 equiv), alcohol (1 equiv), MeCN (0.5M), oil bath.

Scheme 1. Exchange Reaction: Synthesis of Semicarbazones[a]



[a] Conditions: hydrazone (1 equiv), amine (5 equiv), $PhCF_3$ (0.2 M), microwave irradiation if heat required. LG = OPh if performed at room temperature (rt) and LG = O*t*-Bu if heating is required. Isolated yields are reported. [b] Using 2.0 equiv of amine. [c] Using 4.0 equiv of amine. [d] MeCN (0.2 M) was used as solvent. [e] Using heating in an oil bath.

substitution product in acceptable yield (entry 6). Conceptually, this result suggests that hydrazone precursors can be used with polyols and enables further exploration of this substitution reactivity in the isocyanate industry.[2] However, additional efforts are required to indicate if the base generated as the reaction proceeds is beneficial to this substitution reaction (via catalysis, as previously discussed). Further investigations are also needed to provide support for the postulated imino-isocyanate intermediate and probe the likelihood of an alternative mechanism involving a direct substitution reaction, which could occur with activated hydrazones.

Having studied this hydrazone reactivity with several simple substrates, leaving groups, and nucleophiles, we then turned our attention to the synthesis of more complex semicarbazones (Scheme 1). The scope of this reaction was evaluated using both activated (OPh, room temperature, six examples) and unactivated (O*t*-Bu, 80−120 °C, four examples) hydrazone precursors.

Several semicarbazones were synthesized using both primary and secondary amines (Scheme 1). As observed previously (Table 2), hydrazones derived from aliphatic

and aromatic aldehydes, as well as aliphatic and aromatic ketones, were competent substrates. Double substitution reactions were also explored (due to the importance of diisocyanates in the preparation of polyurethanes[2]), and two disubstitution products were obtained. Several functional groups were also tolerated (alcohols, alkenes, esters). Overall, this reactivity proved reliable to access complex semicarbazone derivatives.

In summary, a variety of hydrazone derivatives were accessed readily simply by performing an exchange reaction using hydrazone precursors and amines, alcohols, or thiols as nucleophiles. With hydrazones derived from reactive carbazates (e.g., possessing OPh as leaving group), exchange under mild reaction conditions is possible. This reactivity provides a reliable alternative to the synthesis of hydrazones via condensation on the parent carbonyl precursor and is amenable to the formation of multiple products from a common precursor. Development of synthetic applications using rare nitrogen-substituted isocyanate precursors are under development and will be reported in due course.

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Supporting Information Available. Complete experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.