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Synthesis of 2-Imino-1,3,4-thiadiazoles from Hydrazides and Isothiocyanates via Sequential Oxidation and $P(NMe_2)_3$-Mediated Annulation Reactions

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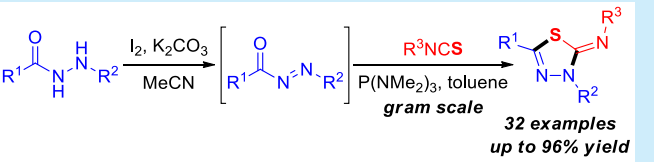
ABSTRACT: A $P(NMe_2)_3$-mediated annulation reaction of *N*-acyldiazenes with isothiocyanates, producing 2-imino-1,3,4-thiadiazoles, is reported. This reaction proceeds well with crude *N*-acyldiazenes derived from the oxidation of hydrazides by iodine and permits the sequential synthesis of products directly from hydrazides without purification of the less stable *N*-acyldiazene intermediates. The reaction does not require transition metals and is a simple, scalable operation with broad substrate scope.

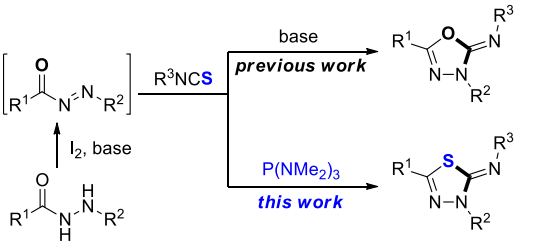


1,3,4-Thiadiazoles are important heterocyclic compounds with a wide range of applications in medicinal, agricultural, and materials chemistry.[1] Their derivatives bearing an amino or imino group display a broad spectrum of pharmaceutical and biological properties[2] including antimicrobial,[3] antitubercular,[4] anticancer,[5] anti-inflammatory/analgesic,[6] antidepressant,[7] and antioxidant activities.[8] Consequently, much effort has been devoted to the synthesis of this class of compounds. To date, however, methods to prepare 2-imino-1,3,4-thiadiazoles still rely on the reactions of hydrazonoyl halides or cyanides with sulfur-containing reagents[9] such as thioureas, isothiocyanates, dithiocarbamates, KSCN, 3-thioxo-[1,2,4]-triazepin-5-ones, or Erlenmeyer thioazlactones. Therefore, new approaches to the synthesis of 2-imino-1,3,4-thiadiazole derivatives remain highly desirable and will benefit the drug discovery community.

N-Acyldiazenes are synthons that are useful for the construction of diverse heterocyclic skeletons in the presence of *N*-heterocyclic carbenes (NHC)[10] or other catalysts.[11] Previously, we reported a practical method for the preparation of *N*-acyldiazenes by iodine-mediated oxidation of hydrazides under basic conditions. The reaction of these *N*-acyldiazenes with isothiocyanates leads to 2-imino-1,3,4-oxadiazoline products via desulfurization of isothiocyanates.[12] Continuing our research in this area, we describe here a new annulation reaction of *N*-acyldiazenes and isothiocyanates promoted by $P(NMe_2)_3$ for the synthesis of 2-imino-1,3,4-thiadiazolines via deoxidization of *N*-acyldiazenes (Scheme 1).

The required *N*-acyldiazene (**2a**) was readily obtained by I_2-mediated oxidation of hydrazide **1a** according to our previously reported procedure.[12] Among commonly used organophosphine (PR_3) reagents (entries 1−4, Table 1), $P(NMe_2)_3$ is the most effective one for the annulation of **2a** with an isothiocyanate (**3a**) to produce the 2-imino-1,3,4-thiadiazoline (**4a**) (entry 4). The structure of compound **4a** was confirmed

Scheme 1. Synthesis of Nitrogen-Containing Heterocyclic Compounds by Annulation of *N*-Acyldiazenes and Isothiocyanates



by X-ray crystallography (see Notes). Solvent screening (entries 4−11) suggested that toluene (entry 11) was the optimal medium for this transformation. Complete consumption of the *N*-acyldiazene (**2a**) involves at least 2.0 equiv of the isothiocyanate (**3a**) and 2.2 equiv of $P(NMe_2)_3$ (entry 13 vs entries 11, 12, 14). Further studies of the reaction showed that the optimum reaction temperature was 20 °C (entry 13 vs entries 15−18). Considering the poor stability of the *N*-acyldiazene (**2a**), we sought to probe the feasibility of the synthesis of **4a** from a hydrazide (**1a**) without purification of the intermediate (**2a**). Upon the completion of the first step, an oxidation, the reaction was quenched, extracted, and concentrated to give the crude **2a**, which was then directly subjected to the second-step annulation conditions. The

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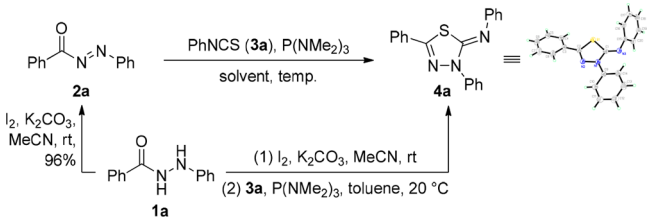
Table 1. Optimization of Reaction Conditions[a]



entry	3a (equiv)	PR_3 (equiv)	solvent	temp. (°C)	time (h)	yield (%)[b]
1	1.0	PPh_3 (1.1)	1,4-dioxane	20	4	6
2	1.0	PBu_3 (1.1)	1,4-dioxane	20	4	0
3	1.0	$P(OMe)_3$ (1.1)	1,4-dioxane	20	4	18
4	1.0	$P(NMe_2)_3$ (1.1)	1,4-dioxane	20	4	45
5	1.0	$P(NMe_2)_3$ (1.1)	DMSO	20	4	5
6	1.0	$P(NMe_2)_3$ (1.1)	MeCN	20	4	30
7	1.0	$P(NMe_2)_3$ (1.1)	CH_2Cl_2	20	4	23
8	1.0	$P(NMe_2)_3$ (1.1)	THF	20	4	19
9	1.0	$P(NMe_2)_3$ (1.1)	MeOH	20	4	13
10	1.0	$P(NMe_2)_3$ (1.1)	DMF	20	4	34
11	1.0	$P(NMe_2)_3$ (1.1)	toluene	20	4	55
12	1.8	$P(NMe_2)_3$ (2.0)	toluene	20	4	76
13	2.0	$P(NMe_2)_3$ (2.2)	toluene	20	1	81
14	2.2	$P(NMe_2)_3$ (2.4)	toluene	20	1	81
15	2.0	$P(NMe_2)_3$ (2.2)	toluene	0	3	63
16	2.0	$P(NMe_2)_3$ (2.2)	toluene	10	1.5	75
17	2.0	$P(NMe_2)_3$ (2.2)	toluene	30	1	56
18	2.0	$P(NMe_2)_3$ (2.2)	toluene	40	1	48
19[c]	**2.0**	**$P(NMe_2)_3$ (2.2)**	**toluene**	**20**	**1**	**67% (69%)**[d]

[a]Reaction conditions unless specified otherwise: A prestirred mixture (0.5 h, 20 °C) of **3a** (1 mmol) and $P(NMe_2)_3$ (1.1 mmol) in toluene (6 mL) was treated with purified **2a** in toluene (4 mL). [b]Isolated yields. [c]Synthesis from **1a** omitting purification of **2a**. [d]Yield of a gram-scale reaction (5 mmol) is given in parentheses.

expected product (**4a**) was formed successfully, although with a slightly decreased overall yield (entry 19). In the following study, most of the products were generated in equal or better yields, compared to those of the stepwise reactions (*cf.* **4b**−**4g** in Scheme 2) by the sequential synthesis. This sequential approach was conveniently conducted on a gram scale (entry 19), and the reaction conditions selected were optimal for the investigation of the substrate scope.

To probe the substrate scope of the reaction, a variety of isothiocyanates (**3**) were reacted under the optimal reaction conditions described above. As shown in Scheme 2, this synthetic protocol is compatible with phenyl isothiocyanates substituted on the phenyl ring by both electron-donating groups (EDG) or electron-withdrawing groups (EWG). These substrates were all smoothly converted into the expected products (**4b**−**4j**) in moderate to excellent yields by the $P(NMe_2)_3$-promoted annulation with the crude *N*-acyldiazene (**2a**) derived from the oxidation of the hydrazide (**1a**). The formation of the products was favored by the presence of EWG at the *para*-position of the phenyl ring (**4d**−**4g**), which may stabilize the corresponding intermediates during the transformation (*cf.* Scheme 3). The steric hindrance from the 2,6-dichlorophenyl group could be responsible for the decreased yield of **4j**. In addition, the reaction of benzoyl isothiocyanate with crude **2a** afforded the product (**4k**) in a satisfactory yield. No desired 2-imino-1,3,4-thiadiazoline was formed in the reaction of an aliphatic isothiocyanate substrate, probably due to the poor stability of the corresponding intermediates (*cf.* Scheme 3).

In light of these encouraging results, the substrate **1a** was replaced by various hydrazides (**1**) to further probe the scope of the reaction (Scheme 2). Upon completion of the first-step oxidation by iodine, each of the resulting *N*-acyldiazenes (**2**) was transformed into the corresponding products **4** under the standard annulation conditions. This reaction tolerated both EDGs and EWGs at R^1 or R^2 on either phenyl ring (**4m**−**4t**, **4aa**−**4af**). Moreover, 2-imino-1,3,4-thiadiazolines bearing a *β*-naphthyl- (**4u**) or a 2-furanyl (**4v**) group were also synthesized from the corresponding hydrazides. This synthetic method is successful with hydrazide substrates bearing aliphatic substituents at either the R^1 or R^2 position (**4w**−**4z**, **4ag**).

On the basis of these experimental results and previously reported reactions mediated by $P(NMe_2)_3$,[13] we propose a plausible mechanism for the annulation of *N*-acyldiazene **2** and isothiocyanate **3** leading to product **4** (Scheme 3). The different selectivity of the present reaction from our previous work[12] is mainly owing to the umpolung of the isothiocyanate in the presence of $P(NMe_2)_3$. Presumably, the prestirring of substrate **3** with $P(NMe_2)_3$ gives a complex (**A**). The dipolar form (**A′**), of this species reacts with the *N*-acyldiazene (**2**) to generate an intermediate with a 7-membered ring (**B**). Subsequently, the sulfur atom in **B** attacks the carbon atom of the endocyclic imine, leading to a plausible 5−4 bicyclic structure (**C**). Finally, decomposition of the four-membered ring in **C** yields the 2-imino-1,3,4-thiadiazole product (**4**) by releasing one molecule of hexamethylphosphoramide (HMPA). Another possible pathway is the attack of oxygen atom on the exocyclic imine (in intermediate **B**) eventually

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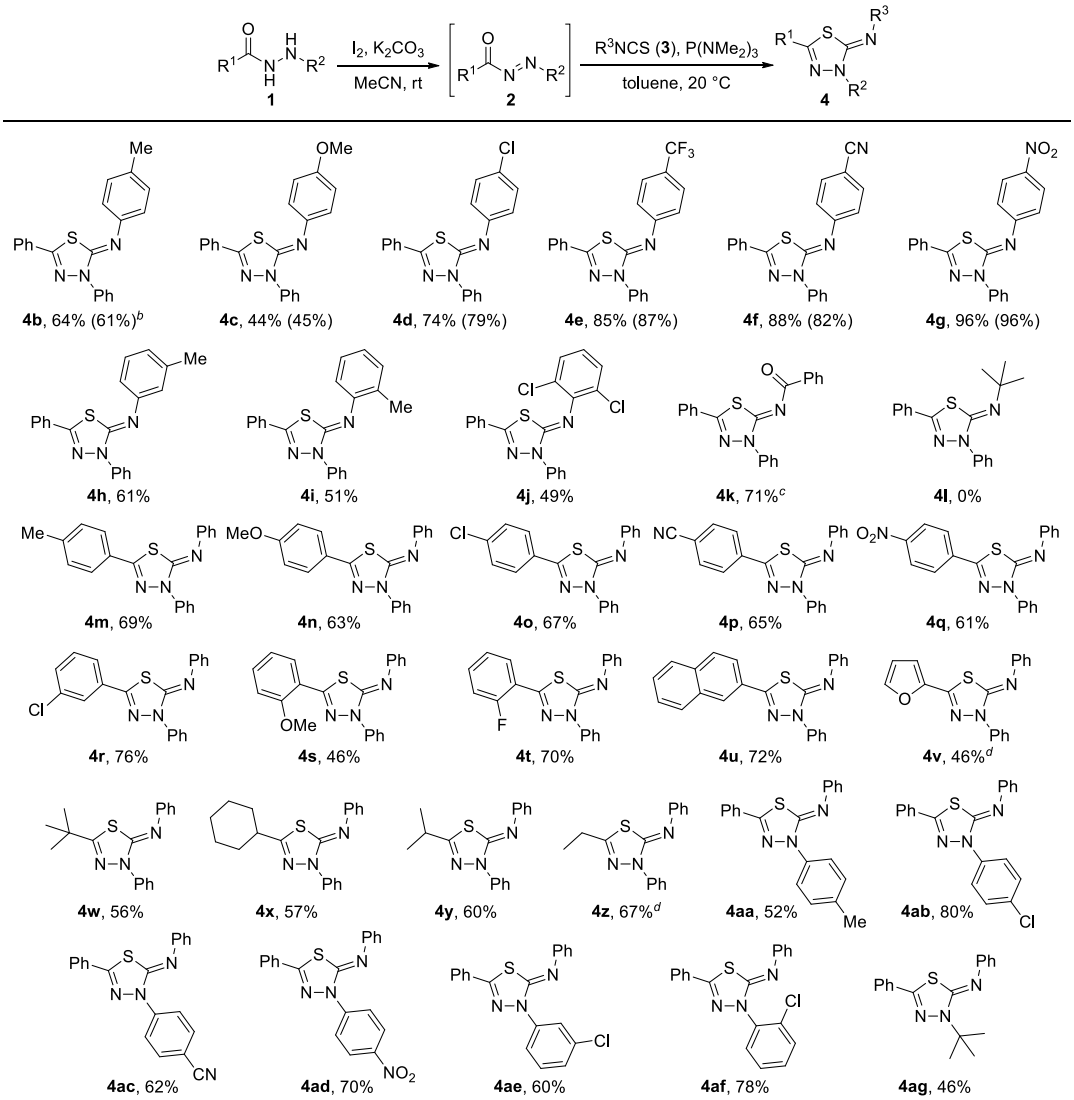
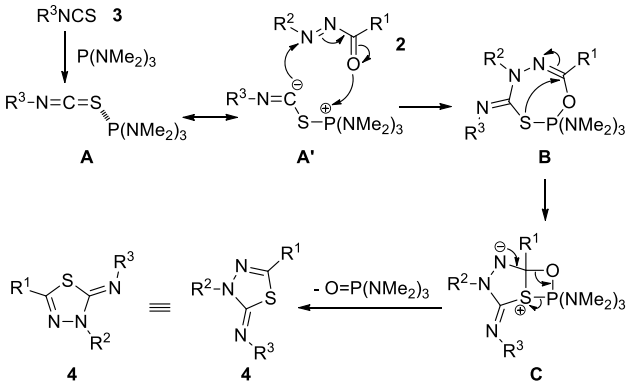
Scheme 2. Substrate Scope[a]



[a]Reaction conditions: (1) **1** (0.5 mmol), I_2 (0.6 mmol), K_2CO_3 (1.5 mmol), MeCN (5 mL), rt (25 °C); (2) a prestirred mixture (0.5 h, 20 °C) of **3** (1 mmol) and $P(NMe_2)_3$ (1.1 mmol) in toluene (6 mL) was treated with crude **2** in toluene (4 mL) (isolated yields are given). [b]Yields of the reactions using purified **2a** are given in parentheses. [c]With 2.5 equiv of **3k** and 2.75 equiv of $P(NMe_2)_3$. [d]Yields of the reactions using purified **2**.

Scheme 3. Proposed Mechanism



resulting in the formation of a 2-imino-1,3,4-oxadiazoline byproduct. However, no such byproducts were observed during this transformation probably due to the higher nucleophilicity of sulfur than that of oxygen.

In summary, we have developed a new method for the synthesis of 2-imino-1,3,4-thiadiazoles from readily accessible hydrazide and isothiocyanate substrates. This synthetic process involves oxidation of the hydrazide by iodine followed by $P(NMe_2)_3$-mediated annulation of *N*-acyldiazene intermediates and isothiocyanates. It does not require transition metals and is operationally simple, requires no purification of the less stable *N*-acyldiazenes, and can be conveniently conducted on a gram scale.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01393.

Experimental details, characterization data, and NMR spectra of compounds **4** (PDF)

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Accession Codes

CCDC 1997797 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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