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Letter

# Catalyst-free Hydrophosphinylation of Isocyanates and Isothiocyanates under Low-Added-Solvent Conditions

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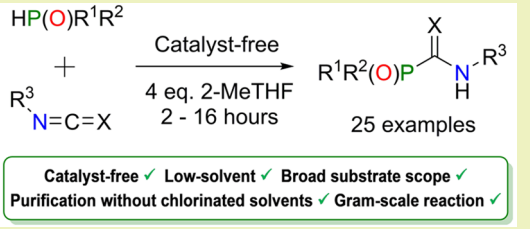
**ABSTRACT:** A catalyst-free, low-solvent method for the hydrophosphinylation of isocyanates and isothiocyanates is reported. A range of phosphorus nucleophiles including secondary phosphine oxides $HP(O)R_2$ (R = Ph, $^iPr$), phosphites $HP(O)(OR)_2$ (R = Me, Et), and methyl phenylphosphinate were tested. The procedure tolerated isocyanates and isothiocyanates featuring a wide range of substituents and, with use of 4 equiv of 2-methyltetrahydrofuran (2-MeTHF), solid substrates can be utilized. Twenty-five compounds were prepared with improved functional group tolerance compared to previous methods allowing access to new compounds (16 are novel). Facile scale up and simple reaction conditions make this a straightforward and practical methodology for obtaining phosphorus analogues of ureas and thioureas, which are challenging to synthesize by other methods.




**KEYWORDS:** *hydrophosphinylation, hydrophosphonylation, atom-efficient, metal-free, heterocumulene, carboxamide, thiocarboxamide*



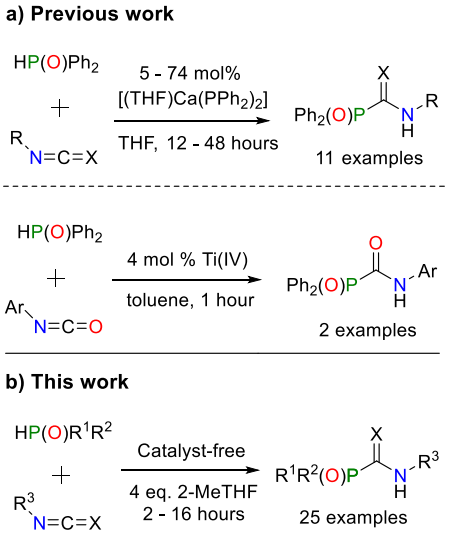
## INTRODUCTION

Organophosphorus compounds are of considerable importance due to their applications as medicines[1,2] (antiviral and anticancer agents), agrochemicals[3] (pesticides and herbicides), ligands in catalysis,[4,5] and industrial additives[6,7] (e.g., polymers and fire retardants). Classical syntheses of these compounds suffer from the use of stoichiometric additives, the need for protecting groups, and poor functional group tolerance. This has prompted research into the direct addition of P−H (hydrophosphination) or P(O)−H (hydrophosphinylation) bonds to C═X (X = C, O, N, S) unsaturated bonds, which has the potential to be 100% atom-efficient.[8]

While alkene and alkyne substrates have been thoroughly explored,[9−14] heterocumulenes are comparatively underutilized. There are several reports of catalytic hydrophosphination with heterocumulenes,[15−28] and one catalyst-free example.[29] Hydrophosphinylation of heterocumulenes is significantly rarer, with very few literature examples.[30−33] This is despite hydrophosphinylation providing an atom economical route to air-stable phosphorus derivates of guanidines, ureas, and thioureas, which have potential applications as ligands,[34−36] in the purification of lanthanide containing waste,[37−39] in medicine,[40,41] and as organic synthons.[42]

In previous work, the Ca(II)-mediated hydrophosphinylation of isocyanates or isothiocyanates afforded the corresponding phosphinylcarboxamides or phosphinylthiocarboxamides (note these compounds are also known as carbamoylphosphine oxides or thiocarbamoylphosphine oxides, respectively) in moderate yields (Scheme 1a, top).[30] However, the procedure required long reaction times (12−48 h) and high catalyst loadings for some aryl substrates (ca. 74 mol %). A

**Scheme 1. (a) Previous Catalytic Examples for the Hydrophosphinylation of Isocyanates and Isothiocyanates by Westerhausen et al.[30] (top) and Panda et al.[33] (bottom) and (b) Reactivity Presented in This Work[a]**




[a]X = O or S; $R^1$, $R^2$ = aryl, alkyl, alkoxy; $R^3$ = aryl, alkyl.

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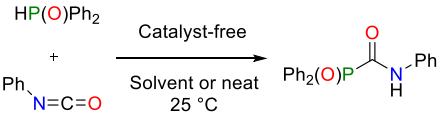
Ti(IV) catalyst gave high yields for two aryl isocyanate substrates[33] but showed no tolerance toward isothiocyanates (Scheme 1a, bottom). Additionally, both reactions suffer from the use of toxic chlorinated solvents in the workup.

Herein, we report the first catalyst-free, low-solvent hydrophosphinylation method that is applicable to a broad range of isocyanates and isothiocyanates. This method is highly atom economical, utilizes 2-MeTHF as a bioderived solvent, and uses no chlorinated solvents in the workup. The reactions proceed at room temperature or with mild heating (60 °C) and do not require additional stoichiometric reagents. This method, therefore, aligns with several of the 12 Principles of Green Chemistry. In addition, similar or better yields are obtained compared to the previously reported catalytic methods.[30−33] The functional group tolerance and simple reaction conditions make this an excellent practical route to phosphinylcarboxamides and phosphinylthiocarboxamides. We also report 16 novel compounds prepared by this methodology (see ESI S3 for characterization data).

## RESULTS AND DISCUSSION

**Hydrophosphinylation of Isocyanates with Diphenylphosphine Oxide.** Our initial experiments showed that the reaction of phenyl isocyanate (PhNCO) with diphenylphosphine oxide ($HP(O)Ph_2$) proceeded smoothly without additives (Table 1), despite previous literature suggesting that this reaction does not occur without a catalyst.[30,31,43] The reaction could be performed in concentrated solutions (ca. 0.2 M, Table 1, entries 1−6) or neat (entry 7). Neat reactions were faster but gave variable yields, possibly due to issues with sample homogeneity.[44] Reactions in air gave low conversions (entry 8). To allow for the use of solid substrates, a near-neat method using 4 equiv of THF (entry 9) or 2-MeTHF (entry 10) was employed.

**Table 1. Optimization of the Hydrophosphinylation of Phenyl Isocyanate under Catalyst-Free Conditions**[a]




| Entry | $HP(O)Ph_2$: Ph-NCO | Solvent | Time (h) | Conv. (%)[b] |
|---|---|---|---|---|
| 1 | 1.0:1.0 | $C_6D_6$ | 8 | 70 |
| 2 | 1.0:1.2 | $C_6D_6$ | 8 | 73 |
| 3 | 1.0:1.5 | $C_6D_6$ | 8 | 73 |
| 4 | 1.0:2.0 | $C_6D_6$ | 8 | 71 |
| 5 | 1.5:1.0 | $C_6D_6$ | 8 | 71 |
| 6 | 1.0:1.2 | THF | 8 | 76 |
| 7 | 1.0:1.2 | Neat | 3 | 72 |
| 8 | 1.0:1.2 | Neat[c] | 3 | 38 |
| 9 | 1.0:1.2 | THF[d] | 3 | 80 |
| 10 | 1.0:1.2 | 2-MeTHF[d] | 3 | 80 |

[a]Reaction conditions: 1.0 equiv (0.10 mmol) of reactant, 0.5 mL of solvent, and 25 °C under a nitrogen atmosphere unless otherwise stated. [b]Conversion determined by $^1$H NMR spectroscopy using an internal standard (mesitylene, 1.0 equiv). [c]Reaction performed in air. [d]Approximately 4 equiv of solvent used.

A variety of functionalized isocyanates were also tested (Table 2). The reaction tolerated aromatic isocyanates with electron-donating and electron-withdrawing substituents (4-Me, 2-F, 4-Br, and 4-OMe substituted). All these reactions afforded pure product in reasonable yields (62−82% by $^1$H NMR spectroscopy, 55−66% isolated, Table 2). However, 4-$NO_2C_6H_4NCO$ was not as well tolerated, proceeding with low conversions (49% by NMR spectroscopy) and significant byproduct formation. For a discussion of this byproduct and a proposed mechanism for its formation, see ESI S4.2 and S4.3. The reaction has been scaled up to gram scale (1.55 g of $HP(O)Ph_2$) using PhNCO without issue, with a higher isolated yield than the test-scale reaction (74% vs 64%; ESI S2.1.4).

High conversions were achieved with a range of primary and secondary alkyl isocyanates at 60 °C ($^i$Pr, Et, $^n$Pr, $^n$Hex, Cy; 82−91% by NMR spectroscopy, 65−82% isolated). The very bulky $^t$BuNCO required longer reaction times (8 h) to reach moderate conversions (61% by NMR spectroscopy, 48% isolated), and increasing the reaction temperature to 80 °C did not improve conversion. The chain length of primary isocyanates did not appear to affect conversion. The benzyl functionality was tolerated, giving **1l** in 56% isolated yield, while the heterocyclic furfuryl isocyanate afforded **1n** in 35% isolated yield. No uretdione [-NRC(O)-]$_2$ (dimerization) or isocyanurate [-NRC(O)-]$_3$ (cyclotrimerization) byproducts were detected, even with aryl isocyanates, for which some examples are known to dimerize at room temperature without a catalyst.[45] Significantly, all products (except **1f**) were purified by washing with small quantities of ethanol (ESI, S2.1.3).

These hydrophosphinylation reactions parallel recent work on the catalyst-free hydrophosphination of alkenes, alkynes, and iso(thio)cyanates.[29,46,47] However, our methodology shows broader substrate scope than these reports and, crucially, does not require column chromatography for purification, leading to a significant reduction in waste compared to these processes.

**Hydrophosphinylation of Isothiocyanates with Diphenylphosphine Oxide.** Recently, Li et al. reported the hydrophosphinylation of PhNCS by $HP(O)Ph_2$ to afford $Ph_2P(O)C(S)NH(Ph)$.[48] This reaction was carried out neat at 60 °C, but we found that addition of 2-MeTHF (4 equiv) afforded the product (**2a**) in excellent yields (90% isolated yield) and eliminated the need for heating (Table 2).

Subsequently, a range of aryl isothiocyanates featuring electron-donating and -withdrawing substituents (4-Me, 4-Cl, and 4-OMe substituted) were tested, with all giving the expected product in excellent isolated yields (**2b−2d**, 90−95%, Table 2). Like 4-$NO_2C_6H_4NCO$, 4-$NO_2C_6H_4NCS$ gave low conversions with significant byproduct formation (ESI, S4.2 and S4.3), although a pure sample of the product (**2e**) was obtained (ESI, S2.1.3; 31% isolated). Secondary alkyl isothiocyanates required heating (60 °C, 6 h) for high conversions, although the yields are significantly lower than the corresponding alkyl isocyanates. The less bulky allyl isothiocyanate, by contrast, proceeded with near quantitative conversion (**2h**, 95% by NMR spectroscopy).

**Hydrophosphinylation and Hydrophosphonylation with Other P(O)−H Nucleophiles.** Since all previous reports of hydrophosphinylation of isocyanates and isothiocyanates were limited to secondary aryl phosphine oxides,[30−33] we tested diisopropylphosphine oxide ($HP(O)^iPr_2$) as a substrate (Table 3). Reactions with PhNCO (affording **3a**) and $^i$PrNCO (affording **3c**) proceeded at 60 °C with modest isolated yields (41% and 61% respectively, Table 3). Reaction with PhNCS at 60 °C afforded **3b** in very high isolated yield (95%). However,


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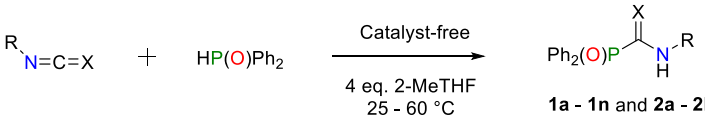
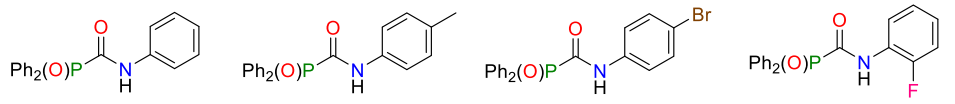
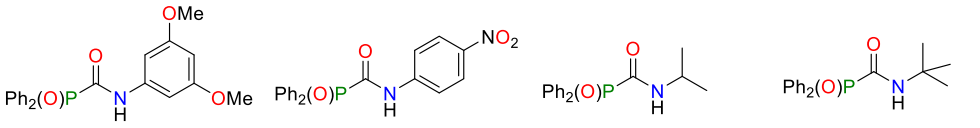
**Table 2. Hydrophosphinylation of Isocyanates and Isothiocyanates with Diphenylphosphine Oxide**[a]

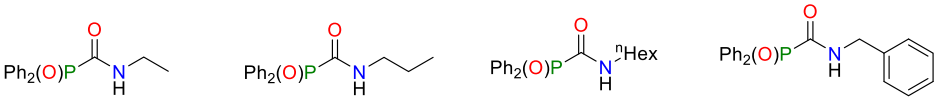


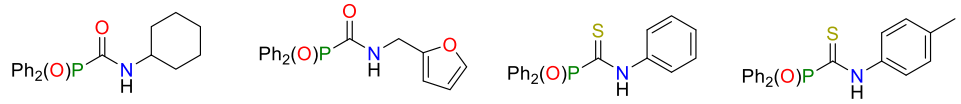
**1a**: 25 °C, 3h, 64 % (80 %) **1b**: 25 °C, 3h, 66 % (82 %) **1c:** 25 °C, 4h, 55 % (62 %) **1d**: 25°C, 4h, 61 % (75 %)



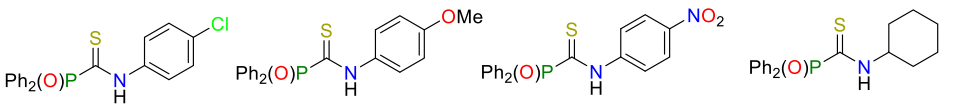
**1e**: 25 °C, 4h, 63 % (74 %) **1f**: 25 °C, 4h, (49 %) **1g**: 60 °C, 6h, 67 % (84 %) **1h**: 60 °C, 8h, 48 % (61 %)



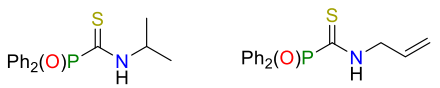
**1i**: 60 °C, 6h, 71 % (84 %) **1j**: 60 °C, 6h, 73 % (86 %) **1k**: 60 °C, 6h, 65 % (82 %) **1l**: 60 °C, 6h, 56 % (69 %)



**1m**: 60 °C, 6h, 82 % (91 %) **1n**: 60 °C, 6h, 35 % (50 %) **2a**: 25 °C, 2h, 90% (95%) **2b**: 25 °C, 2h, 95% (99%)



**2c**: 25 °C, 2h, 90% (94%) **2d**: 25 °C, 2h, 92% (98%) **2e**: 60 °C, 6h, 31% (50%) **2f**: 60 °C, 6h, 42% (57%)



**2g**: 60 °C, 6h, 40% (65%) **2h**: 60 °C, 4h, 82% (95%)

[a]Reaction stoichiometry: **1a**, **1b**, **1d**, **1g**−**1m** isocyanate (1.2 equiv) and $HP(O)Ph_2$ (1.0 equiv); **1c**, **1e**−**1f**, **2a**−**2h** iso(thio)cyanate (1.0 equiv) and $HP(O)Ph_2$ (1.0 equiv), 1.0 equiv = 0.30 mmol. NMR spectroscopic yield (in brackets) determined by $^1H$ NMR spectroscopy using an internal standard (mesitylene, 1.0 equiv).

the reaction with $^i$PrNCS proceeded with low conversions (36%), and the product (**3d**) was not obtained pure.

The methodology was then expanded to hydrophosphonylation, the addition of a $HP(O)(OR)_2$ (R = alkyl or aryl) unit across a double bond (Table 3). Kaboudin and Zahedi have previously described the catalytic hydrophosphonylation of isocyanates with $CaCl_2$, which required chlorinated solvents and column chromatography in the workup.[49] Initial reactions with PhNCO and $HP(O)(OEt)_2$ in 2-MeTHF showed no conversion at 25 °C and <5% conversion at 60 °C. However, performing the reaction neat at 60 °C increased conversion to 87% (ESI, S2.3.1). Purification of the phosphonyl carboxamide (**4a**) from residual $HP(O)(OEt)_2$ by washing (ethanol) and recrystallization afforded **4a** in ∼87% purity (by $^{31}P$ NMR spectroscopy). Column chromatography (utilizing the method of Kaboudin and Zahedi)[49] resulted, in our hands, in partial decomposition of the product. Attempts at vacuum distillation also decomposed **4a**. Similar difficulties in removing residual P(V) starting material occurred with $HP(O)(OMe)_2$ and HP(O)Ph(OMe), although products of ≥97% purity (by $^{31}P$ NMR spectroscopy) could be obtained in moderate yield in both cases (Table 3, **4b** and **4c**, ESI S3.4). The use of less electrophilic substrates (PhNCS, $^i$PrNCO, $^i$PrNCS) resulted in very low conversions (<0.1−20%, ESI S2.3.2).

**Improvements and Considerations on the Sustainability of the Synthesis of Phosphinylcarboxamides.** While isocyanates or isothiocyanates are generally toxic and potential irritants,[50,51] it should be recognized that the addition of $HP(O)Ph_2$ to isocyanates or isothiocyanates is the most atom efficient methodology for the synthesis of phosphinylcarboxamides or phosphinylthiocarboxamides, avoiding the use of stoichiometric reagents or low atom economic processes.[52,53] Isocyanates can be generated *in situ*,[54−58] but this uses additional stoichiometric reagents or metal catalysts to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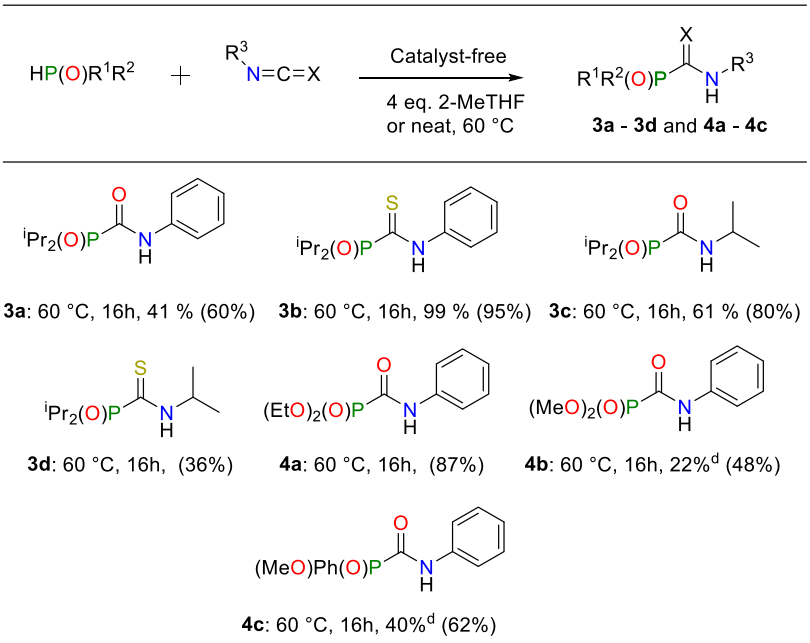
ACS Sustainable Chem. Eng. XXXX, XXX, XXX−XXX

**Table 3. Hydrophosphinylation and Hydrophosphonylation of Isocyanates and Isothiocyanates with $HP(O)^iPr_2$, $HP(O)(OEt)_2$, $HP(O)(OMe)_2$, and HP(O)Ph(OMe)[a,b,c]**




[a]Reaction stoichiometry: iso(thio)cyanate (1.0 equiv) and $HP(O)R^1R^2$ (1.0 equiv), 1.0 equiv = 0.105 mmol (**3a–c**) or 0.232 mmol (**4a–c**). [b]Reaction performed in 4 equiv of 2-MeTHF (**3a–d, 4c**) or neat (**4a,b**). [c]NMR spectroscopic yield (in brackets) determined by $^1H$ NMR spectroscopy using an internal standard (mesitylene, 1.0 equiv). [d]Final isolated product ≥97% pure (by $^{31}P$ NMR spectroscopy).

activate the isocyanate precursors. It is worth noting that the majority of organophosphorus P(V) derivatives are originally derived from toxic and pyrophoric white phosphorus. However, there is intense interest in improving the sustainability of routes to organophosphorus P(V) derivatives (e.g., avoiding $P_4$), which will only enhance the sustainability of our reported methodology.[59−61] Our development of routes to lower toxicity P(V) species, such as phosphonate derivatives, also offers improvements over previous syntheses using P(III) derivatives.

In order to quantify the improvement in the sustainability of our synthetic methodology to phosphinylcarboxamides over the current catalytic methods, we have compared it to the E-factor values for hydrophosphinylation reactions of aryl isocyanates from the literature examples (see ESI, S5). The Ca(II) mediated reaction by Westerhausen et al. gives an E-factor of 142.5, and the Ti(IV) mediated reaction by Panda et al. gives a value of 154.2 (some values for solvent purification are estimated as values are not given by the authors.).[30,33] Comparatively, our work shows a significant improvement with an E-factor of 9.1. Additionally, our procedure eliminates the use of toxic dichloromethane for purification, instead utilizing ethanol and avoiding column chromatography. Moreover, our methodology avoids the use of catalysts entirely, whereas near-stoichiometric catalyst loading was required for some substrates in previous methodologies.[30] Other substantial improvements can be seen in short reaction times for all substrates and easily scalable reactions. Overall, this is a significant improvement in sustainability for the synthesis of phosphinylcarboxamides, justifying the use of isocyanate and isothiocyanate substrates.

**Mechanistic Proposal.** To test for the formation of radicals, a radical inhibitor (1,4-cyclohexadiene or cumene) was added to the reaction of $HP(O)Ph_2$ with *p*-tolyl isocyanate (ESI, S4.1). The reaction was not influenced by either radical inhibitor and the expected product was detected in high yield in both cases.

We propose a mechanism involving the equilibrium between $HP(O)R_2$ and its P(III)−OH tautomer.[62−65] The isocyanate or isothiocyanate undergoes attack by the P(III)−OH nucleophile, followed by a proton transfer to reform the P═O bond (ESI, S4.2).[66] This mechanistic proposal is analogous to the initial steps of the mechanism proposed by Li and co-workers.[48]

## CONCLUSIONS

We have developed a catalyst-free methodology for the hydrophosphinylation of isocyanates and isothiocyanates by $HP(O)Ph_2$ and $HP(O)^iPr_2$. These reactions can be performed neat, but the addition of 4 equiv of 2-MeTHF improves yields and allows for the use of solid substrates. This methodology has enabled the synthesis of 16 new compounds and substantially improved upon the limited substrate scope of the previous research. All but two of the 25 phosphinylcarboxamide and phosphinylthiocarboxamide products were readily purified by washing with ethanol. The protocol is practical and can be scaled up to gram scale with improved yields. Although attempts at hydrophosphonylation were less successful, it was possible to obtain products of high purity for the reactions of $HP(O)(OMe)_2$ or HP(O)Ph(OMe) with PhNCO.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.1c02907.



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Full experimental details for the synthesis, characterization, and crystallographic data (PDF)
Crystallographic structures (CIF)

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### Notes

The authors declare no competing financial interest.

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