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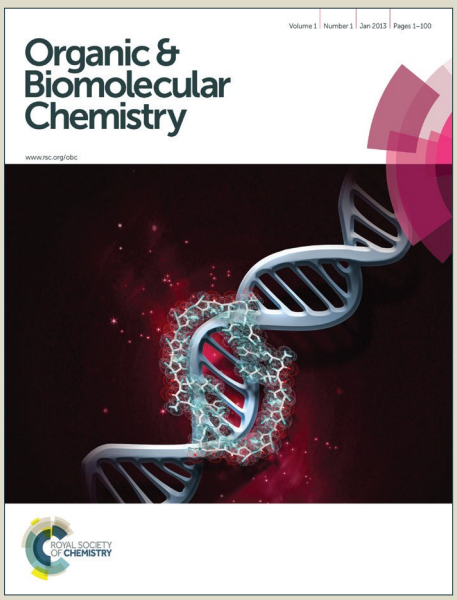

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ARTICLE

Phosphinic Acid-Promoted Addition Reaction of Isocyanides to (*Z*)-Hydroximoyl Chlorides: Efficient Synthesis of α-(Hydroxyimino)amides

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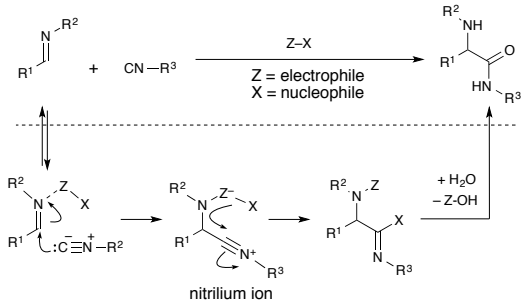
The reaction of (*Z*)-hydroximoyl chlorides with isocyanides promoted by phosphinic acid in the presence of triethylamine proceeds smoothly to afford α-(hydroxyimino)amides in good to high yields. Phosphinic acid plays an important role in effectively promoting the reaction. A wide range of (*Z*)-hydroximoyl chlorides and isocyanides were found to be suitable for this reaction.

Introduction

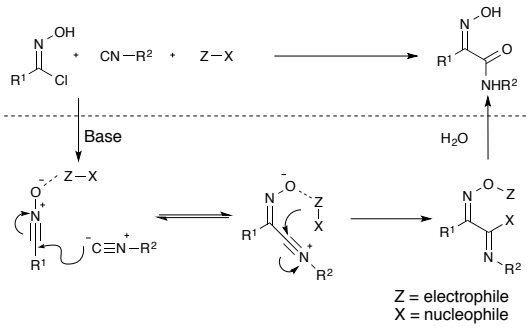
α-(Hydroxyimino)amides have long attracted significant attention due to their biological activity, and because they are important building blocks in natural product synthesis and drug discovery[1]. In particular, α-(hydroxyimino)amides have been reported to be effective zinc chelating moieties in a series of potent HDAC inhibitors[1a]. In addition, α-(hydroxyimino)amides are very useful building blocks for the precursor of α-ketoamide and α-aminoamide. Generally, α-aminoamide derivatives have been prepared *via* an isocyanide-based multicomponent reaction known as the Ugi reaction[2].

In general, Ugi reactions require the presence of a carboxylic acid, which activates the imine and traps a nitrilium ion to form an acyloxylated intermediate. Subsequent acyl transfer leads to the corresponding α-aminoamide. A carboxylic acid is therefore typically a necessary component of the sequence within the Ugi synthesis involving the reaction of an isocyanide with an imine. This requirement for a carboxylic acid, however, limits the applications of the reaction and prevents the synthesis of a broad range of molecules. To overcome this limitation, we reasoned that a compound Z–X, composed of an electrophile Z and a nucleophilic group X, could essentially perform the same function as the carboxylic acid in an Ugi-type reaction (Scheme 1). Based on this hypothesis, we previously developed *O*-silylative, *O*-phosphinative, and *O*-sulfinative Passerini reactions as well as borinic acid-catalyzed α-addition of isocyanide[3]. In addition, we have developed the addition of isocyanide to 1,3-dipoles, such as, 3,4-dihydroisoquinoline *N*-oxides, *C,N*-cyclic *N*-acyl azomethine imines, and azomethine ylides.[4] Based on these investigations, we have focused on the utility of nitrile oxide. Among imine analogues, nitrile oxides appear to be promising candidates for the reaction, as they possess an electronegative oxygen which can coordinate strongly to metal (Scheme 2).[5] Although (*Z*)-arylhydroximoyl chlorides have been used for isocyanide-based reactions by Tron, direct synthesis of α-(hydroxyimino)amides has not yet been achieved[6]. Herein, we report a phosphinic acid-promoted addition of isocyanides to nitrile oxide generated in situ from the corresponding (*Z*)-hydroximoyl chlorides to give the corresponding α-(hydroxyimino)amide derivatives in high yields.

Scheme 1. General Ugi-type reaction



Scheme 2. Hypothetical modified Ugi-type reaction of nitrile oxides



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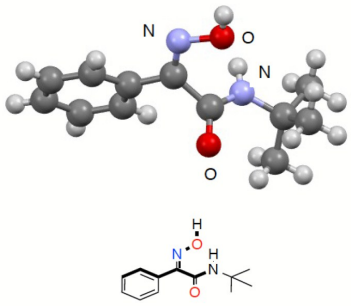
Results and discussion

Our initial attempts involved the use of (*Z*)-benzohydroximoyl chloride (**1a**) as a precursor of nitrile oxide, triethylamine[7], and *tert*-butyl isocyanide (**2a**) in the presence of TMSCl (**3a**) which was useful as a promoter of the addition reaction of isocyanide[4b], although it was not effective in this reaction. The reaction gave the desired α-(hydroxyimino)amide **4aa** in 13% yield (Table 1, entry 1). Triphenylsilanol (**3b**), diphenylborinic acid (**3c**), and 4-toluenesulfinic acid (**3d**) were subsequently used as carboxylic acid equivalents in dichloromethane[3]. However, none of these reactions were successful; the reactions either did not proceed or gave a very complex mixture of products (entries 2–4). In contrast, when the reaction was carried out in the presence of phenylphosphinic acid (**3e**) in dichloromethane[3c], the α-(hydroxyimino)amide derivative **4aa** was obtained in 51% yield (entry 5).

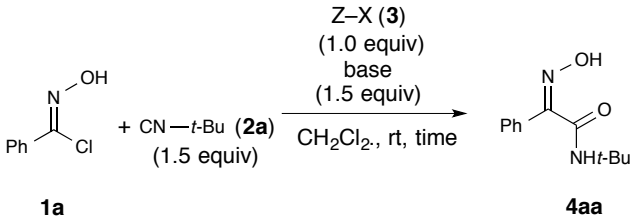
To improve the chemical yield of **4aa**, we investigated the mixing order of the reagents. After several attempts, we found that the addition of a dichloromethane solution of **1a** to a mixture of **2a** (1.5 equiv), triethylamine (1.5 equiv), and **3e** (1.0 equiv) in dichloromethane at room temperature gave **4aa** in an improved yield of 94% (entry 6). This reaction proceeded efficiently in toluene and methanol to afford **4aa** in good yields (entries 7 and 11). The use of THF, diethylether (Et_2O), or acetonitrile (MeCN) as a solvent was less effective, resulting in the formation of α-(hydroxyimino)amide **4aa** in yields of 60, 47, and 53%, respectively (entries 8–10). To generate nitrile oxide species efficiently, various types of base—DBU, pyridine, KO*t*-Bu, and K_2CO_3—were examined (entries 12–15). However, the reaction using Et_3N was the most effective. The structure of product **4aa** was determined by X-ray crystallography (Figure 1).

Figure 1. X-ray crystallographic structure of **4aa**.



Having established a method for the addition reaction of isocyanide to (*Z*)-benzohydroximoyl chloride (**1a**), we then set out to evaluate the effectiveness of phosphinic acids bearing other substituents (entries 16–19). When employing either (4-methoxyphenyl)phosphinic acid (**3f**), (4-tolyl)phosphinic acid (**3g**), or (4-chlorophenyl)phosphinic acid (**3h**), the product was obtained in good yield (entries 16–18). In the case of (4-nitrophenyl)phosphinic acid (**3i**), the reaction showed low reactivity, perhaps due to the low solubility of **3i** (entry 19)

Table 1. Reaction conditions and results for Ugi-type reactions.



1a **4aa**

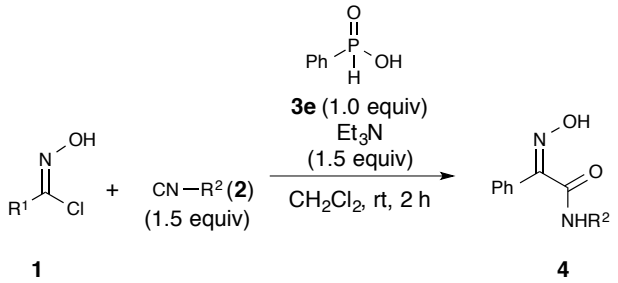
entry [a]	Z–X	base	yield of **4aa** /%
1 [b]	TMS-Cl (**3a**)	Et_3N	13
2 [b]	Ph_3Si-OH (**3b**)	Et_3N	- [c]
3 [b]	Ph_2B-OH (**3c**)	Et_3N	- [c]
4 [b]	PhS(O)-OH (**3d**)	Et_3N	- [c]
5 [b]	PhP(O)H-OH (**3e**)	Et_3N	51
6	PhP(O)H-OH (**3e**)	Et_3N	94
7 [d]	PhP(O)H-OH (**3e**)	Et_3N	77
8 [e]	PhP(O)H-OH (**3e**)	Et_3N	60
9 [f]	PhP(O)H-OH (**3e**)	Et_3N	47
10 [g]	PhP(O)H-OH (**3e**)	Et_3N	53
11 [h]	PhP(O)H-OH (**3e**)	Et_3N	75
12	PhP(O)H-OH (**3e**)	DBU	65
13	PhP(O)H-OH (**3e**)	pyridine	53
14	PhP(O)H-OH (**3e**)	KO*t*-Bu	55
15	PhP(O)H-OH (**3e**)	K_2CO_3	33
16	4-$MeOC_6H_4$ P(O)H-OH (**3f**)	Et_3N	81
17	4-MeC_6H_4P(O)H-OH (**3g**)	Et_3N	77
18	4-ClC_6H_4 P(O)H-OH (**3h**)	Et_3N	74
19	4-$O_2NC_6H_4$P(O)H-OH (**3i**)	Et_3N	57

[a] Method A (entries 1–5): To a solution of **1a** in CH_2Cl_2, Et_3N was added at 0 °C. To this reaction mixture, a solution of **2a** and **3** in CH_2Cl_2 was subsequently added and the reaction mixture was warmed to room temperature. Method B (entries 6–19): To a solution of **2a** in solvent, a solution of base and **3** in solvent were added dropwise and the mixture was stirred at 0 °C. To this mixture, a solution of **1a** in CH_2Cl_2 was added dropwise, and the reaction mixture was warmed to room temperature. [b] 1.2 equiv of **2a** and Et_3N were used. [c] Complex mixture. [d] Toluene was used as a solvent. [e] THF was used as a solvent. [f] Et_2O was used as a solvent. [g] MeCN was used as a solvent. [h] MeOH was used as a solvent.

We subsequently attempted to expand the range of isocyanides and hydroximoyl chlorides to which this Ugi-type reaction utilizing phosphinic acid **3e** might be applied, as detailed in Table 2. In these reactions, optimal molar quantities of hydroximoyl chlorides **1a–n** (1.0 equiv), triethylamine (1.5 equiv), and isocyanides **2a–f** (1.5 equiv) were used in the presence of 1.0 equiv of phenylphosphinic acid (**3e**). We found that these reaction conditions were applicable to a wide variety of hydroximoyl chlorides and isocyanides and that most reactions were completed within 2 h at room temperature. The

reaction of aliphatic isocyanides **2a**–**2e** (R^2 = *t*-Bu, *t*-Oct, *c*-Hex, Bn, and *n*-Bu) with **1a** in the presence of phenylphosphinic acid (**3e**) gave the products in good to high yields (entries 1–5). Aromatic isocyanides were also investigated, although they showed very low reactivity (entries 6–8). Even aromatic isocyanides bearing an electron-donating group at the *para* position exhibited low reactivity, with low product yield.

Table 2. Summary of reactions using isocyanides and hydroximoyl chlorides.



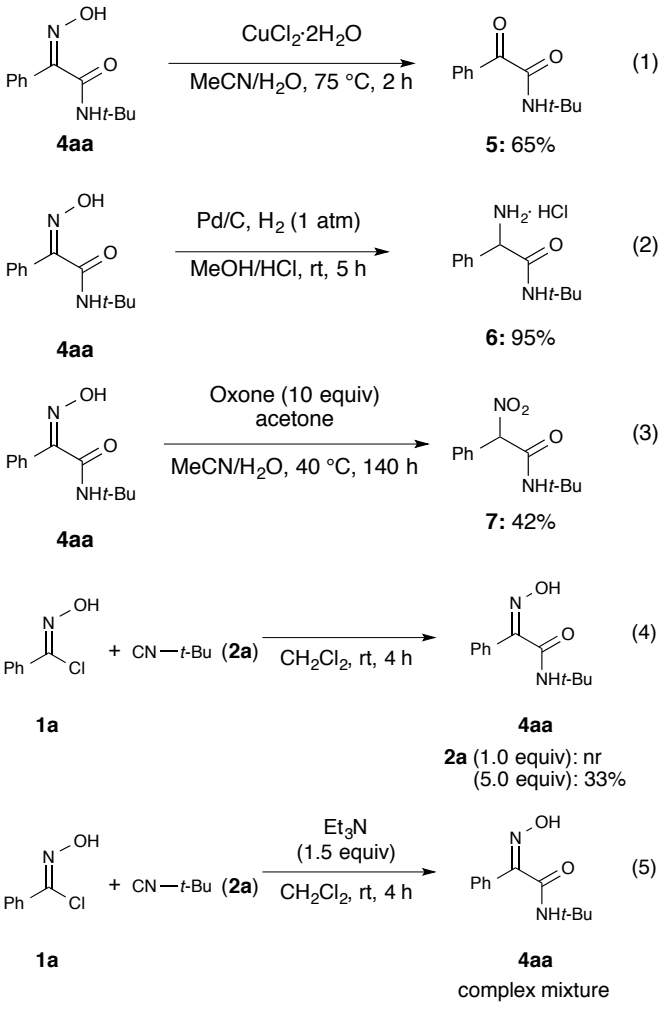
1 **4**

entry [a]	R^1	R^2	yield / %
1	C_6H_5 (**1a**)	*t*-Bu (**2a**)	94 (**4aa**)
2	C_6H_5 (**1a**)	*t*-Oct (**2b**)	84 (**4ab**)
3	C_6H_5 (**1a**)	*c*-Hex (**2c**)	94 (**4ac**)
4	C_6H_5 (**1a**)	Bn (**2d**)	87 (**4ad**)
5	C_6H_5 (**1a**)	*n*-Bu (**2e**)	94 (**4ae**)
6	C_6H_5 (**1a**)	Ph (**2f**)	- [b]
7	C_6H_5 (**1a**)	4-$MeOC_6H_4$ (**2g**)	- [b]
8	C_6H_5 (**1a**)	4-$Me_2NC_6H_4$(**2h**)	- [b]
9	1-Naphthyl (**1b**)	*t*-Bu (**2a**)	67 (**4ba**)
10	2-Naphthyl (**1c**)	*t*-Bu (**2a**)	40 (**4ca**)
11	4-MeC_6H_4 (**1d**)	*t*-Bu (**2a**)	85 (**4da**)
12	4-$MeOC_6H_4$ (**1e**)	*t*-Bu (**2a**)	92 (**4ea**)
13	3-$MeOC_6H_4$ (**1f**)	*t*-Bu (**2a**)	81 (**4fa**)
14	2-$MeOC_6H_4$ (**1g**)	*t*-Bu (**2a**)	55 (**4ga**)
15	4-ClC_6H_4 (**1h**)	*t*-Bu (**2a**)	79 (**4ha**)
16	2-pyridyl (**1i**)	*t*-Bu (**2a**)	49 (**4ia**)
17	2-thienyl (**1j**)	*t*-Bu (**2a**)	88 (**4ja**)
18	2-phenylethenyl(**1k**)	*t*-Bu (**2a**)	82 (**4ka**)
19	$BnCH_2$ (**1l**)	*t*-Bu (**2a**)	88 (**4la**)
20	*i*-Pr (**1m**)	*t*-Bu (**2a**)	54 (**4ma**)
21	*t*-Bu (**1n**)	*t*-Bu (**2a**)	74 (**4na**)

[a] Reactions were carried out following Method B in Table 1. [b] Complex mixture.

Next, the reactivity of various hydroximoyl chlorides **1** as a precursor of nitrile oxides in conjunction with *tert*-butyl isocyanide (**2a**) was examined *via* the reaction of 1.5 equiv of **2a** in the presence of 1.0 equiv of phenylphosphinic acid (**3e**). 1- and 2-naphthyl-substituted hydroximoyl chlorides (**1b** and **1c**) were found to be good substrates, and the products **4ba** and **4ca** were obtained in 67% and 40% yields, respectively (entries 9 and 10). Hydroximoyl chlorides with an electron-donating group on the aromatic ring were all reactive, furnishing the corresponding products in good to high yields (entries 11–14). The reaction was also applicable to hydroximoyl chlorides with an electron-withdrawing group on the aromatic ring, affording the product in 79% yield (entry 15). Hydroximoyl chlorides substituted with a heterocyclic ring were also good substrates for the reaction, affording the corresponding products in 49% and 88% yield, respectively (entries 16 and 17). When (*Z*)-*N*-hydroxycinnamimidoyl chloride (**1k**) was used as a substrate, the reaction proceeded smoothly to give the product **4ka** in 82% yield (entry 18). Aliphatic hydroximoyl chlorides **1l**, **1m**, and **1n** gave the products in 88%, 54%, and 74% yields, respectively (entries 19–21).

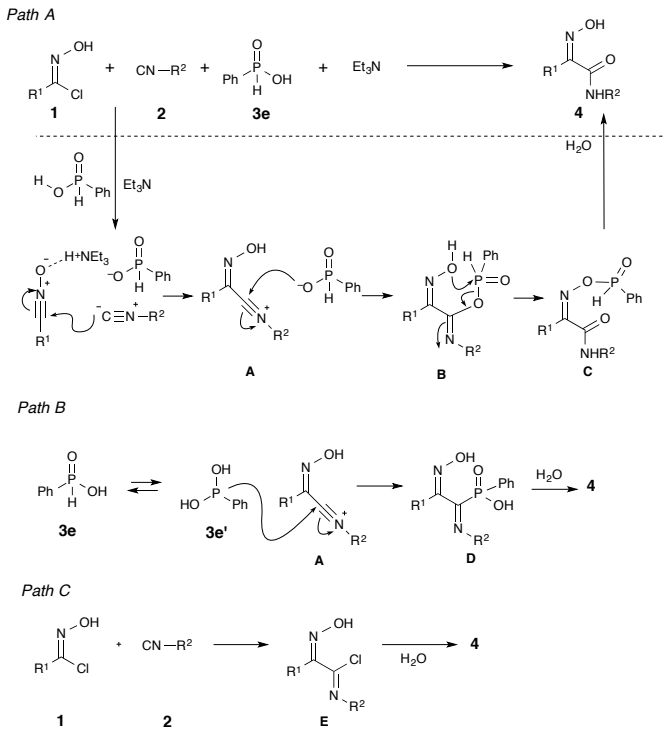
α-(Hydroxyimino)amide derivatives could be transformed



to the corresponding α-ketoamides. We demonstrated the hydrolysis of **4aa** using copper chloride to afford α-ketoamide **5** in 65% yield (eq. 1)[6a]. In addition, we found that α-(hydroxyimino)amide derivatives could be used as precursors of α-aminoamide and α-nitroamide derivatives. For example, α-aminoamide **6** was obtained in high yield under simple hydrogenation conditions (eq. 2). The oxidation reaction to form α-nitroamide was difficult due to the instability of the product **7**, and a complex mixture of products was obtained. Finally, we found that oxidation of **4aa** was successful using Oxone at 40 °C in $MeCN/H_2O$ for 140 h, affording the desired α-nitroamide **7** in 42% yield (eq. 3)[8].

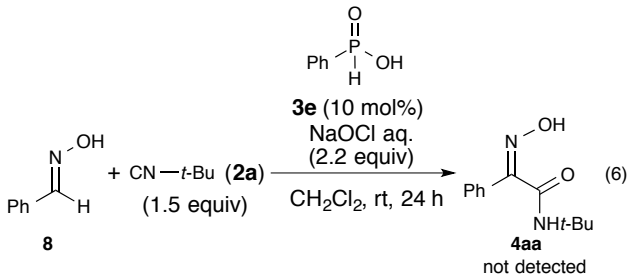
To reveal the reaction mechanism, we conducted a series of controlled experiments. Although the addition of 1.0 equiv of **2a** to (*Z*)-benzohydroximoyl chlorides (**1a**) in the absence of phenylphosphinic acid (**3e**) and triethylamine at room temperature did not proceed in CH_2Cl_2 over a period of 4 h, the desired product **4aa** was obtained in 33% yield by using 5.0 equiv of **2a** (eq. 4). In addition, when the reaction of **1a** with **2a** was attempted in the presence of triethylamine in CH_2Cl_2 at room temperature, the desired product **4aa** was not obtained at all and the reaction was complicated (eq. 5).

Scheme 3. Plausible reaction mechanisms.



Based on these results, we propose a reaction mechanism for the Ugi-type reaction, shown in Scheme 3. In Path A, the nitrile oxide, which is generated from the corresponding hydroximoyl chloride **1** by treatment with triethylamine, is activated by the acidic proton of triethylammonium salt which comes from the reaction between triethylamine and phosphinic acid **3e** (pK_a = 1.75 in H_2O) through coordination with the nitrile oxide oxygen. Subsequently, nucleophilic attack of the C≡N bond by isocyanide provides a nitrilium intermediate **A**, which is trapped by the phosphinate anion to afford the adduct **4** through migration of the phosphinate group onto the oxygen atom originating from the hydroxyl group of oxime. The intermediate **C** is then hydrolyzed by water to give the final product. In addition, based on the reported article by List[9], path B is also proposed: Thus, phenyl phosphonous acid **3e'** act as a Lewis base, and the nitrilium ion **A** was trapped by **3e'** to give intermediate **D**. The intermediate **D** is then hydrolyzed by water to give the final product. In the absence of **3e** and base, isocyanide is inserted into **1a** to form the α-adduct **E**, which is then hydrolyzed by water[10, 11]. As shown in eq. 4, path C proceeded very slowly and is not effective.

Considering the stability of (*Z*)-hydroximoyl chloride, we have examined the alternative reaction of benzaldoxime by oxidation with NaOCl aq. (producing the corresponding nitrile oxide in situ) in the presence of isocyanide **2a** and catalytic amount of the phenylphosphinic acid (**3e**, 10 mol %) in CH_2Cl_2. However, the desired reaction did not proceed and little amount of product **4aa** was detected (eq. 6).



Experimental Section

General

^{1}H NMR spectra were recorded on a 400 MHz NMR spectrometer. Chemical shifts *d* are reported in ppm using TMS as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (*J*) and integration. ^{13}C NMR spectra were recorded on 100 MHz NMR spectrometer. The chemical shifts were determined in the *d*-scale relative to $CDCl_3$ (*d* = 77.0 ppm). The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. HRMS (FAB positive, DART) was measured with a quadrupole mass spectrometer and TOF mass spectrometers. All melting points were measured using a micro melting point apparatus. Dehydrated solvents were purchased for the reactions and used without further desiccation.

General procedure

To a solution of **2** (0.75 mmol) in CH_2Cl_2 (3 mL), Et_3N (0.75 mmol), and phosphinic acid (0.5 mmol) were subsequently added dropwise and whole was stirred at 0 °C. To this mixture, a solution of **1** (0.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise, and the reaction mixture was warmed to room temperature. After reaction completion (monitored by TLC), satd. $NaHCO_3$ aq was added and separated. Aqueous layer was extracted with $CHCl_3$ (5 mL x 3). Combined organic layers were dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography.

(*Z*)-*N*-(*tert*-Butyl)-2-(hydroxyimino)-2-phenylacetamide (4aa)

Silica gel column chromatography (hexane/ethyl acetate = 3/1~2/1) gave **4aa** (104 mg, 94% yield) as a white solid of mp = 156.6–157.2 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.37 (s, 9H), 5.72 (brs, 1H), 7.30–7.35 (m, 3H), 7.49–7.52 (m, 2H), 10.3 (brs, 1H). ^{13}C NMR ($CDCl_3$): 28.6, 52.6, 127.5, 128.8, 130.0, 131.8, 152.6, 162.6. IR (KBr): 3310, 2970, 2950, 2890, 1640, 1550, 1430, 1360, 1270, 1060 cm^{-1}. HRMS–DART

(*m/z*): Calcd for $C_{12}H_{17}N_2O_2$ $[M+H]^+$: 221.1290. Found: 221.1285.

(*Z*)-2-(Hydroxyimino)-2-phenyl-*N*-(2,4,4-trimethylpentan-2-yl)acetamide (4ab)

Silica gel column chromatography (hexane/ethyl acetate = 4/1~1/1) gave **4ab** (117 mg, 84% yield) as a white solid of mp = 66.8–67.5 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 0.89 (s, 9H), 1.42 (s, 6H), 1.63 (s, 2H), 5.92 (s, 1H), 7.30–7.35 (m, 3H), 7.46–7.48 (m, 2H), 11.0 (brs, 1H). ^{13}C NMR ($CDCl_3$): 28.5, 31.4, 31.6, 52.7, 56.6, 127.4, 128.7, 129.9, 131.9, 152.1, 162.5. IR (KBr): 3300, 2970, 2950, 2890, 1640, 1540, 1420, 1370, 1260, 1060 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{16}H_{25}N_2O_2$ $[M+H]^+$: 277.1916. Found: 277.1910.

(*Z*)-*N*-Cyclohexyl-2-(hydroxyimino)-2-phenylacetamide (4ac)

Silica gel column chromatography (hexane/ethyl acetate = 3/1~1/1) gave **4ac** (117 mg, 94% yield) as a white solid of mp = 193.2–193.8 °C (hexane/ethyl acetate). ^{1}H NMR (acetone d_6): 1.23–2.00 (m, 10H), 3.92 (brs, 1H), 7.36–7.38 (m, 4H), 7.62–7.63 (m, 2H), 10.6 (brs, 1H). ^{13}C NMR (methanol d_4): 26.3, 26.8, 33.7, 50.1, 127.2, 129.7, 130.8, 133.7. 154.4, 166.0. IR (KBr): 3290, 2930, 2860, 1600, 1470, 1380, 1270, 1060 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{14}H_{19}N_2O_2$ $[M+H]^+$: 247.1447. Found: 247.1439.

(*Z*)-*N*-Benzyl-2-(hydroxyimino)-2-phenylacetamide (4ad)

Silica gel column chromatography (hexane/ethyl acetate = 2/1~1/1) gave **4ad** (112 mg, 87% yield) as a pale yellow solid of mp = 159.5.2–160.2 °C (hexane/ethyl acetate). ^{1}H NMR (acetone d_6): 4.64 (m, 2H), 7.25–7.47 (m, 8H), 7.63 (m, 2H), 8.04 (brs, 1H), 10.8 (brs, 1H). ^{13}C NMR (methanol d_4): 43.9, 127.3, 128.4, 128.8, 129.6, 129.7, 130.8, 133.6, 139.7, 154.3, 167.1. IR (KBr): 3320, 3160, 2840, 1640, 1600, 1430, 1370, 1240, 1080 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{15}H_{15}N_2O_2$ $[M+H]^+$: 255.1134. Found: 255.1128.

(*Z*)-*N*-Butyl-2-(hydroxyimino)-2-phenylacetamide (4ae)

Silica gel column chromatography (hexane/ethyl acetate = 2/1~1/1) gave **4ae** (104 mg, 94% yield) as a yellow solid of mp = xxxx–xxxx °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 0.85 (t, J = 7.6 Hz, 3H), 1.30 (m, 2H), 1.47 (m, 2H), 3.34 (q, J = 6.8 Hz, 2H), 6.01 (s, 1H), 7.28–7.34 (m, 3H), 7.47–7.51 (m, 2H). OH proton was not observed cleanly. ^{13}C NMR ($CDCl_3$): 13.7, 20.0, 31.2, 39.2, 127.4, 128.8, 130.0, 131.8, 152.0, 163.2. IR (KBr): 3330, 2940, 1640, 1560, 1250, 960 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{12}H_{17}N_2O_2$ $[M+H]^+$: 221.1290. Found: 221.1284.

(*Z*)-*N*-(*tert*-Butyl)-2-(hydroxyimino)-2-(naphthalen-1-yl)acetamide (4ba)

Silica gel column chromatography (hexane/ethyl acetate = 3/1~1/1) gave **4ba** (90 mg, 67% yield) as a yellow solid of mp = 135.5–136.0 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.23 (s, 9H), 5.45 (s, 1H), 7.51–7.56 (m, 4H), 7.48–7.96 (m, 4H). ^{13}C NMR ($CDCl_3$): 28.2, 52.5, 124.7, 125.4, 126.6, 127.1, 128.5, 128.6, 129.5, 130.5, 131.6, 133.7, 148.3, 163.6. IR (KBr): 3290, 2970, 1650, 1550, 1450, 1370, 1280, 1250, 990 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{16}H_{19}N_2O_2$ $[M+H]^+$: 271.1447. Found: 271.1446.

(*Z*)-*N*-(*tert*-Butyl)-2-(hydroxyimino)-2-(naphthalen-2-yl)acetamide (4ca)

Silica gel column chromatography (hexane/ethyl acetate = 3/1~1/1) gave **4ca** (33 mg, 40% yield, 0.3 mmol scale) as a yellow solid of mp = 167.3–168.1 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.38 (s, 9H), 5.85 (s, 1H), 7.36–7.43 (m, 2H), 7.60–7.73 (m, 4H), 7.90 (s, 1H), 10.1 (s, 1H). ^{13}C NMR ($CDCl_3$): 28.7, 52.6, 123.4, 126.5, 127.1, 127.6, 127.7, 128.4, 128.6, 129.1, 132.9, 133.8, 153.1, 162.9. IR (KBr): 3290, 2980, 1650, 1550, 1460, 1370, 1280, 1220, 1020, 990 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{16}H_{19}N_2O_2$ $[M+H]^+$: 271.1447. Found: 271.1448.

(*Z*)-*N*-(*tert*-Butyl)-2-(hydroxyimino)-2-(*p*-tolyl)acetamide (4da)

Silica gel column chromatography (hexane/ethyl acetate = 3/1~1/1) gave **4da** (100 mg, 85% yield) as a white solid of mp = 158.7–160.2 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.36 (s, 9H), 2.30 (s, 3H), 5.72 (s, 1H), 7.12 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 10.3 (brs, 1H). ^{13}C NMR ($CDCl_3$): 21.3, 28.7, 52.5, 127.1, 129.0, 129.5, 140.2, 152.7, 162.8. IR (KBr): 3290, 2980, 1650, 1550, 1460, 1370, 1280, 1220, 1020, 990 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{13}H_{19}N_2O_2$ $[M+H]^+$: 235.1447. Found: 235.1442.

(*Z*)-*N*-(*tert*-Butyl)-2-(hydroxyimino)-2-(4-methoxyphenyl)acetamide (4ea)

Silica gel column chromatography (hexane/ethyl acetate = 4/1~2/1) gave **4da** (116 mg, 92% yield) as a white solid of mp = 175.2–175.8 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.42 (s, 9H), 3.80 (s, 3H), 5.78 (s, 1H), 6.88 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 9.91 (brs, 1H). ^{13}C NMR ($CDCl_3$): 28.6, 52.5, 55.3, 114.2, 124.1, 128.6, 152.6, 161.0, 162.8. IR (KBr): 3360, 3200, 2970, 1650, 1600, 1550, 1510, 1460, 1380, 1240, 1180, 1060, cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{13}H_{19}N_2O_3$ $[M+H]^+$: 251.1396. Found: 251.1402.

(*Z*)-*N*-(*tert*-Butyl)-2-(hydroxyimino)-2-(3-methoxyphenyl)acetamide (4fa)

Silica gel column chromatography (hexane/ethyl acetate = 2/1~1/1) gave **4fa** (103 mg, 81% yield) as a pale yellow solid of mp = 90.4–90.9 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.42 (s, 9H), 3.80 (s, 3H), 5.78 (s, 1H), 6.94 (m, 1H), 7.11 (m, 2H), 7.26–7.39 (m, 1H). OH proton was not observed cleanly. ^{13}C NMR ($CDCl_3$): 28.6, 52.5, 55.2, 111.7, 116.1, 119.6, 129.6, 133.0, 152.8, 159.5, 162.8. IR (KBr): 3310, 3190, 2970, 1640, 1550, 1490, 1460, 1380, 1280, 1210, 1180, 1040, cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{13}H_{19}N_2O_3$ $[M+H]^+$: 251.1396. Found: 251.1399.

(*Z*)-*N*-(*tert*-Butyl)-2-(hydroxyimino)-2-(2-methoxyphenyl)acetamide (4ga)

Silica gel column chromatography (hexane/ethyl acetate = 2/1~1/1) gave **4ga** (69 mg, 55% yield) as a pale yellow solid of mp = 150.5–151.2 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.34 (s, 9H), 3.82 (s, 3H), 5.75 (s, 1H), 6.94 (d, J = 8.4 Hz, 1H), 7.02 (m, 1H), 7.36–7.43 (m, 2H). OH proton was not observed cleanly. ^{13}C NMR ($CDCl_3$): 28.4, 52.1, 55.4, 111.1, 121.4, 121.8, 131.3, 131.6, 148.4, 157.2, 162.9. IR (KBr): 3420, 3220, 2970, 1640, 1600, 1540, 1490, 1460, 1370, 1290, 1260, 1040, cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{13}H_{19}N_2O_3$ $[M+H]^+$: 251.1396. Found: 251.1401.

(*Z*)-*N*-(*tert*-Butyl)-2-(4-chlorophenyl)-2-(hydroxyimino)acetamide (4ha)

Silica gel column chromatography (hexane/ethyl acetate = 3/1~1/1) gave **4ha** (101 mg, 79% yield) as a white solid of mp = 183.3–183.9 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.40 (s, 9H), 5.73 (s, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 9.60 (brs, 1H). ^{13}C NMR ($CDCl_3$): 28.7, 52.7, 128.5, 129.0, 130.3, 136.1, 151.2, 162.1. IR (KBr): 3330, 2970, 1620, 1550, 1490, 1370, 1290, 1260, 1090, 1040 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{12}H_{16}N_2O_2Cl$ $[M+H]^+$: 255.0900. Found: 255.0904.

(*Z*)-*N*-(*tert*-Butyl)-2-(hydroxyimino)-2-(pyridin-2-yl)acetamide (4ia)

Silica gel column chromatography (hexane/ethyl acetate = 2/1~1/3) gave **4ia** (54 mg, 49% yield) as a white solid of mp = 162.5–163.3 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.41 (s, 9H), 6.30 (s, 1H), 7.51 (d, J = 5.2 Hz, 2H), 8.56 (d, J = 5.2 Hz, 2H). OH proton was not observed cleanly. ^{13}C NMR (methanol d_4): 29.1, 53.3, 121.9, 126.0, 142.7, 149.9, 150.6, 152.3, 164.9. IR (KBr): 3390, 2970, 1660, 1600, 1530, 1460, 1360, 1290, 1270, 1070 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{11}H_{16}N_3O_2$ $[M+H]^+$: 222.1243. Found: 222.1137.

(*E*)-*N*-(*tert*-Butyl)-2-(hydroxyimino)-2-(thiophen-2-yl)acetamide (4ja)

Silica gel column chromatography (hexane/ethyl acetate = 5/1~2/1) gave **4ja** (96 mg, 88% yield) as a pale yellow solid of mp = 167.2–167.6 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.39 (s, 9H), 6.01 (s, 1H), 6.97 (dd, J = 5.2, 4.4 Hz, 1H), 7.26–7.28 (m, 2H), 9.23 (brs, 1H). ^{13}C NMR ($CDCl_3$): 28.7, 52.3, 127.4, 128.1, 129.1, 134.9, 149.0, 161.0. IR (KBr): 3390, 2970, 1660, 1600, 1530, 1460, 1360, 1290, 1270, 1070 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{10}H_{15}N_2O_2S$ $[M+H]^+$: 227.0854. Found: 227.0855.

(2*Z*,3*E*)-*N*-(*tert*-Butyl)-2-(hydroxyimino)-4-phenylbut-3-enamide (4ka)

Silica gel column chromatography (hexane/ethyl acetate = 3/1~1/1) gave **4ka** (101 mg, 82% yield) as a yellow solid of mp = 105.2–105.8 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.34 (s, 9H), 6.34 (s, 1H), 6.67 (d, J = 16.4 Hz, 1H), 6.85 (d, J = 16.4 Hz, 1H), 7.18 (t, J = 6.8 Hz, 3H), 7.30 (d, J = 6.8 Hz, 2H), 10.30 (brs, 1H). ^{13}C NMR ($CDCl_3$): 28.7, 52.4, 120.7, 127.1, 128.6, 128.7, 135.8, 136.6, 154.5, 162.0. IR (KBr): 3270, 2970, 1650, 1540, 1450, 1370, 1250, 1220, 990 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{14}H_{19}N_2O_2$ $[M+H]^+$: 247.1447. Found: 247.1450.

(*Z*)-*N*-(*tert*-Butyl)-2-(hydroxyimino)-4-phenylbutanamide (4la)

Silica gel column chromatography (hexane/ethyl acetate = 2/1~1/1) gave **4la** (103 mg, 88% yield) as a white solid of mp = 124.3–124.8 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.31 (s, 9H), 2.68 (m, 2H), 2.77 (m, 2H), 7.04 (s, 1H), 7.10 (d, J = 6.8 Hz, 3H), 7.17 (d, J = 6.8 Hz, 2H), 10.1 (brs, 1H). ^{13}C NMR ($CDCl_3$): 28.6, 33.0, 33.3, 51.9, 126.1, 128.4, 128.5, 140.8, 152.5, 160.4. IR (KBr): 3190, 2980, 1640, 1610, 1550, 1450, 1390, 1370, 1220, 1140, 970 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{14}H_{21}N_2O_2$ $[M+H]^+$: 249.1603. Found: 249.1600.

(*Z*)-*N*-(*tert*-Butyl)-2-(hydroxyimino)-3-methylbutanamide (4ma)

Silica gel column chromatography (hexane/ethyl acetate = 3/1~2/1) gave **4ma** (50 mg, 54% yield) as a white solid of mp = 113.8–114.5 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.06 (d, J = 6.8 Hz, 6H), 1.36 (s, 9H), 2.93 (septet, J = 6.8 Hz, 1H), 6.59 (s, 1H), 9.60 (brs, 1H). ^{13}C NMR ($CDCl_3$): 19.7, 28.7, 30.6, 52.0, 158.3, 161.1. IR (KBr): 3380, 2970, 1630, 1540, 1460, 1390, 1370, 1230, 950 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_9H_{19}N_2O_2$ $[M+H]^+$: 187.1447. Found: 187.1449.

(*Z*)-*N*-(*tert*-Butyl)-2-(hydroxyimino)-3-methylbutanamide (4na)

Silica gel column chromatography (hexane/ethyl acetate = 5/1~3/1) gave **4na** (74 mg, 74% yield) as a white solid of mp = 155.1–155.7 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.19 (s, 9H), 1.39 (s, 9H), 5.36 (brs, 1H), 8.16 (brs, 1H). ^{13}C NMR ($CDCl_3$): 28.1, 28.8, 35.8, 52.3, 162.9, 163.0. IR (KBr): 3300, 3140, 2980, 1640, 1620, 1560, 1460, 1390, 1360, 1230, 1100 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{10}H_{21}N_2O_2$ $[M+H]^+$:201.1603. Found: 201.1607.

***N*-(*tert*-Butyl)-2-oxo-2-phenylacetamide (5)**[12]

To a solition of a-(hydroxyimino)amide **4aa** (110 mg, 0.5 mmol) in MeCN (3 mL) and H_2O (2 mL), $CuCl_2 \cdot 2H_2O$ (170 mg, 1.0 mmol) was added at room temperature. The whole was stirred under refluxing conditions and was monitored by TLC. After the reaction was completion, the solvents were removed *in vacuo*. The residue was diluted with ethylacetate and separated. The aqueous layer was extracted with ethyl acetate (5 mL x 3), and the combined organic layers were washed with brine, and dried over Na_2SO_4. Concentration and purified by silica gel column chromatography (hexane/ethyl acetate = 4/1~3/1) gave **5** (67 mg, 65% yield) as a white solid of mp = 75.8–76.2 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.39 (s, 9H), 6.86 (brs, 1H), 7.39 (t, J = 7.2 Hz, 2H), 7.53 (t, J = 7.2 Hz, 1H), 8.22 (d, J = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): 28.3, 51.6, 128.4, 131.2, 133.3, 134.1, 161.1, 188.5. IR (KBr): 3300, 3140, 2980, 1640, 1620, 1560, 1460, 1390, 1360, 1230, 1100 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1181. Found: 206.1186.

2-Amino-*N*-(*tert*-butyl)-2-phenylacetamide hydrochloride (6)

To a solition of a-(hydroxyimino)amide **4aa** (110 mg, 0.5 mmol) in HCl (conc.)/MeOH (1/4, 10 mL), 10% Pd/C (82.6 mg) was added. The reaction was stirred at room temperature under hydrogen gas (balloon) until the starting material disappeared (monited by TLC). The reaction mixture was filtered off though a bed of Celite and the filtrate was concentrated *in vacuo*. The product was obtained in 95% yield (100 mg) as a pale yellow solid of mp =189.8–190.6 °C (ethanol). ^{1}H NMR (DMSO d_6): 1.23 (s, 9H), 4.87 (s, 1H), 7.39–7.52 (m, 6H), 8.27 (brs, 1H), 8.82 (brs, 3H). ^{13}C NMR (methanol d_4): 28.8, 52.7, 58.0, 129.2, 130.5, 131.0, 135.2, 167.9. IR (KBr): 3300, 2980, 1700, 1540, 1480, 1380, 1290, 1260, 1230 cm^{-1}. HRMS–FAB (*m/z*): Calcd for $C_{12}H_{19}NO$ $[M+H]^+$:207.1497. Found: 207.1493.

***N*-(*tert*-Butyl)-2-nitro-2-phenylacetamide (7)**[8]

To a solution of oxone (1.84 g, 3 mmol) in acetone (5 mL) and H_2O (5 mL), a-(hydroxyimino)amide **4aa** (66 mg, 0.3 mmol) and phosphate buffer (5 mL, 0.05 M, pH 7.5) were subsequently added at room temperature. The whole was stirred at 40 °C for 140 h. The reaction mixture was extracted with diethyl ether (5 mL x 3) and the combined organic layers were washed with brine and dried over Na_2SO_4. Concentration and purified by silica gel column chromatography (hexane/ diethyl ether = 3/1~1/1) gave **7** (30 mg, 42% yield) as a white solid of mp = 115.6–116.4 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.34 (s, 9H), 5.90 (brs, 1H), 6.06 (s, 1H), 7.24–7.50 (m, 5H). ^{13}C NMR ($CDCl_3$): 28.3, 52.6, 93.0, 129.1, 129.3, 130.2, 130.7, 161.7. IR (KBr): 3290, 2980, 1660, 1560, 1460, 1370, 1250, 1230, 940 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{12}H_{17}N_2O_3$ $[M+H]^+$: 237.1239. Found: 237.1231.

Procedure for equation 6

To a solution of **8** (0.5 mmol) in CH_2Cl_2 (3 mL), phosphinic acid **3e** (7 mg, 0.05 mmol), **2a** (0.75 mm) in CH_2Cl_2 (3 mL) followed by NaOCl aq (1.8 mL, 5% aqueous solution), were subsequently added dropwise and whole was stirred at room temperature. After 24 h, satd. $NaHCO_3$ aq was added and separated. Aqueous layer was extracted with $CHCl_3$ (5 mL x 3). Combined organic layers were dried over Na_2SO_4, and concentrated.

Conclusions

In conclusion, the reaction of (*Z*)-hydroximoyl chlorides with isocyanides promoted by phosphinic acid in the presence of triethylamine proceeded smoothly to afford α-(hydroxyimino)amides in good to high yields. We have found that phosphinic acid plays an important role in allowing the reaction to proceed effectively. The reaction was found to be applicable to a wide range of (*Z*)-hydroximoyl chlorides and isocyanides.

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