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Synthesis of Vinyl Isocyanides and Development of a Convertible Isonitrile

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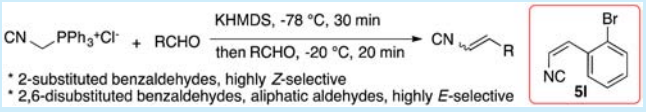
Supporting Information

ABSTRACT: The reaction of isocyanomethylenetriphenylphosphorane, generated in situ from the corresponding phosphonium salt, with a diverse set of aldehydes afforded vinyl isocyanides in good to high yields. Excellent *E*-selectivity was observed for aliphatic aldehydes and 2,6-disubstituted aromatic aldehydes, whereas *Z*-olefins were formed predominantly with *ortho*-substituted aryl aldehydes. (*Z*)-1-Bromo-2-(2-isocyanovinyl)benzene (**5l**) was found to be a truly universal isonitrile since, after Ugi reaction, the resulting secondary amide unit (RNHCO−) is convertible under both acidic and basic conditions. The application of **5l** in the synthesis of polyheterocycles is also illustrated.



Isocyanomethylenetriphenylphosphorane, synthesized in 1985 by Fehlhammer,[1] has remained a laboratory curiosity. Indeed, coordination to transition metal and subsequent [3 + 2] cycloaddition with carbon disulfide is the only reported transformation known to date.[2] This is in sharp contrast to other α-functionalized isonitriles such as Schöllkopf's diethyl isocyanomethylphophonate (**2**), isocyanoacetate **3a** (X = OR), isocyanoacetamide **3b** (X = NR_2),[3] and Van Leusen's TosMic **4**,[4] whose chemistry has been extensively exploited (Figure 1).

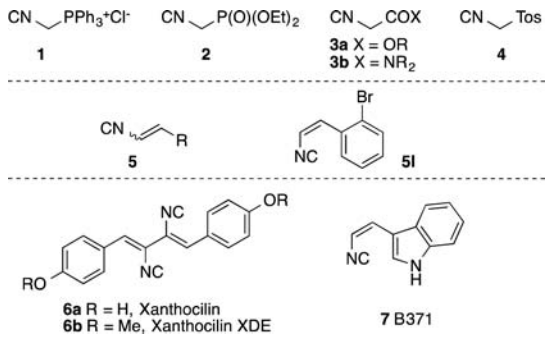


Figure 1. α-Functionalized isonitriles, vinyl isocyanides, and convertible isonitriles.

As a continuation of our research program dealing with α-functionalized isonitriles,[5] we became interested in the chemistry of Fehlhammer's phosphonium salt **1**, hypothesizing that selective manipulation of the functionalities in **1** should provide us with rich synthetic opportunities. As a prelude, we report herein that **1** is an excellent reagent undergoing the Wittig reaction with a diverse set of aldehydes to afford vinyl isocyanides **5** in good to high yields. We also document that **5** is a new class of convertible isonitriles, and in particular, **5l** is a truly universal isonitrile since the resulting secondary amide after Ugi reaction is convertible under both acidic and basic conditions.

Vinyl isocyanides such as xanthocilins (**6a**, **6b**)[6] and B371 (**7**)[7] exist in nature and display potent antimicrobial activities. Three main strategies have been developed, viz. (a) dehydration of *N*-vinylformamides,[8] (b) isomerization of allyl isocyanides,[9] and (c) condensation of α-functionalized isonitriles **2** or **3** with carbonyl compounds.[10,11] Notwithstanding its straightforwardness, the last method is not without problems due to the competitive formation of oxazolines and *N*-vinylformamides.[10,11] Therefore, the development of an efficient synthesis of vinyl isocyanides is still highly demanding, especially in light of recent developments on the elaboration of this family of building blocks to complex heterocycles.[12]

Isocyanomethyltriphenylphosphonium chloride (**1**) was synthesized on multigram scale by reaction of trimethylsilylmethyl isocyanide[13] with PPh_3 and C_2Cl_6 in THF at room temperature following Fehlhammer's procedure. We noted that highly pure reagent **1** was obtained in 70% yield by simple filtration and washing with THF when this operation was carried out in a glovebox. In view of the aforementioned importance of vinyl isocyanides, the Wittig reaction of **1** was investigated using benzaldehyde (**8a**) as a test substrate. Sodium amide, used by Fehlhammer for the generation of phosphorane from **1**, was found to be inefficient for the desired Wittig reaction (entry 1, Table 1). Therefore, a systematic survey of reaction conditions varying the base, the solvent, and the temperature was carried out,[14] and the most relevant results are summarized in Table 1. Key observations are noted below: (a) there was a significant counterion effect, with KHMDS

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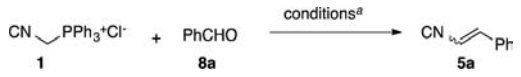
Table 1. Wittig Reaction of 1: Survey of Reaction Conditions



entry	base	t_1 (°C)	t_2 (°C)	time (h)	E/Z[b]	yield[c] (%)
1	$NaNH_2$	0	rt	72	0	trace
2	LiHMDS	−78	rt	1	54/46	10
3	LiHMDS	−78	−20	1	54/46	20
4	NaHMDS	−78	−20	1	70/30	50
5	NaHMDS[d]	−78	−20	1	70/30	8
6	KHMDS	−78	−20	0.3	70/30	57
7	KHMDS	−78	−20	0.3	70/30	70[e]

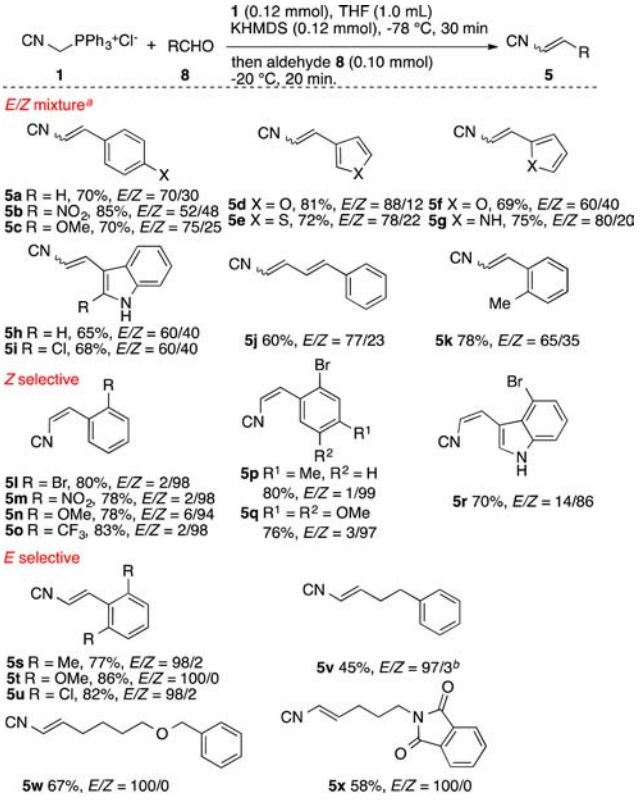
[a]Reaction conditions: **1** (0.12 mmol), THF (1.0 mL), base (0.12 mmol), at t_1 (°C) for 30 min, then add **8a** (0.10 mmol) and raise the temperature to t_2 (°C). [b]Determined by NMR. [c]Isolated yield after flash column chromatographic (FCC) purification on silica gel. [d]With 2.0 equiv of base. [e]Purification by FCC on Al_2O_3 (activity IV). The *E*/*Z* isomers were inseparable using Al_2O_3 as support.

providing the highest yield of vinyl isocyanide **5a** (entries 6, 7); (b) an excess amount of base reduced the yield of **5a** (entry 5 vs 4); and (c) flash column chromatographic (FCC) purification was better performed on Al_2O_3 support (activity IV) since partial decomposition of **5a** was observed during purification on silica gel (entry 7 vs 6).[15] Overall, the optimum conditions consisted of treatment of **1** with KHMDS at −78 °C for 30 min followed by adding **8a** and stirring the reaction mixture at −20 °C for 20 min. FCC purification on Al_2O_3 support afforded **5a** in 70% yield.

With the optimum conditions in hand, the scope of this Wittig reaction was next examined. As shown in Scheme 1, both aromatic and aliphatic aldehydes underwent Wittig reaction with phosphonium salt **1** to provide the corresponding vinyl isocyanides **5** in good to high yields. 4-Substituted benzaldehydes, regardless of the electronic nature of the substituents (NO_2, OMe, **5b**, **5c**) and heterocycles including 2- and 3-formylfuran, 3-formylthiophene, 2-formylpyrrole, 3-formylindole (**5d**−**i**), and α,β-unsaturated aldehyde **5j**, all participated in the olefination reaction to afford the corresponding vinyl isocyanides with low to moderate *E*/*Z* selectivity. Interestingly, reaction of 2-substituted benzaldehydes with **1** afforded *Z*-vinyl isocyanides in high yields with excellent *Z*-selectivity (*Z*/*E* ≥ 94/6, **5l**-**5q**). However, 2-methylbenzaldehyde was an exception as compound **5k** was formed as a mixture of two isomers (*E*/*Z* = 65/35). Reaction of 4-bromo-3-formylindole also afforded *Z*-vinyl isocyanide with a reasonable *Z* selectivity (**5r**, *E*/*Z* = 14/86). On the other hand, a highly *E*-selective olefination occurred with 2,6-disubstituted benzaldehydes to afford *E*-vinyl isocyanides in good yields (*E*/*Z* ≥ 98/2, **5s**−**u**). Aliphatic aldehydes participated in the reaction with **1** to give *E*-vinyl isocyanides with excellent selectivity (**5v**−**x**), albeit with slightly diminished yields. The above observed substrate-dependent *Z*- and *E*-selectivity is in line with that of benzylidene(triphenyl)phosphorane,[16] and therefore, we can consider isocyanomethylenetriphenylphosphorane as a semistabilized ylide.

The high synthetic efficiency and great application scope encountered in the reaction of **1** with aldehydes distinguished it from other α-functionalized isocyanides (**2**−**4**). Mechanistically, the condensation of the Schöllkopf's reagent (**2**), α-isocyanoacetate (**3a**), and α-isocyanoacetamide (**3b**) with aldehydes under basic conditions would be initiated by the aldol reaction to afford the alkoxide **9**, which could evolve in

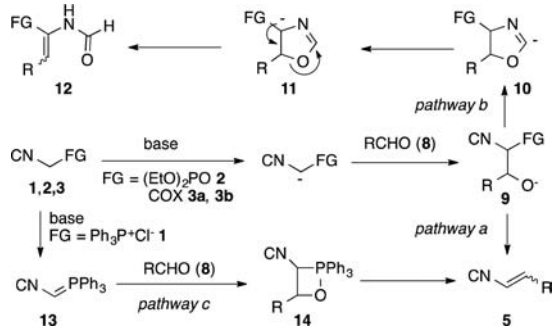
Scheme 1. Synthesis of Vinyl Isocyanides



[a]The ratio was determined by the ^1H NMR spectrum of the crude product. In some cases, the ratio changed after FCC purification. [b]After purification, the ratio became 75/25.

two different ways. The Horner−Wadsworth−Emmons reaction [R = $(EtO)_2PO$] or Knoevenagel condensation (R = COOR, or $CONR^1R^2$) pathway would provide vinyl isocyanide **5** (pathway a, Scheme 2), while intramolecular addition of the

Scheme 2. Reaction Manifold Involving the Condensation of α-Functionalized Isonitriles and Aldehydes



alkoxide to the pendant isocyano group would lead to **10** which, upon proton transfer and electrocyclic ring reversion, would afford enamide **12** (pathway b). However, the situation would be completely different with Fehlhammer's reagent **1** since it is now firmly established that oxaphosphetane **14** is formed directly from phosphorane **13** and aldehydes without the intermediacy of betaine **9** (FG = Ph_3P^+).[17] Therefore, pathway b would be impossible, and vinyl isocyanides **5** would be formed following pathway c (Scheme 2).

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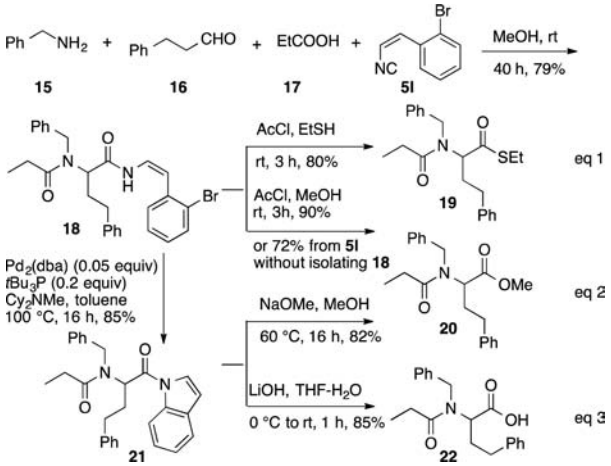
In most of the isocyanide-based multicomponent reactions including the powerful Ugi-4CR,[5] Passerini-3CR,[18] and Ugi–Smiles reaction,[19] the isonitrile (RNC) is converted to a secondary amide (RNHCO–). While the formation of secondary amide is of self-importance, its selective manipulation was nevertheless difficult due to its relatively high chemical stability. To overcome this shortcoming, a term of convertible isonitrile was advanced to define a specific family of isonitriles (RNC) in which the R residue is designed in such a way that the corresponding secondary amides (RNHCO–) are susceptible to selective functionalization under mild conditions.[20] Among them, the 1-isocyanocyclohex-1-ene, first reported by Ugi,[21] has been extensively exploited by Armstrong to conceptualize the idea of convertible isonitrile.[22] One drawback associated with this isonitrile is that it is unstable and cleavable only under strong acidic conditions, and therefore, it cannot be applied to adducts having acid-sensitive functions. Other isonitriles, convertible under acidic or basic conditions, have therefore been developed.[23−30] While all vinyl isocyanides enlisted in Scheme 1 are potentially convertible isonitriles, we were particularly interested in the vinyl isocyanide **5l** as it is stable and nonvolatile and has no disagreeable odor. In addition, we thought that it should in principle be convertible under both acidic and basic conditions. This assumption was verified as shown in Scheme 3. The Ugi four-component

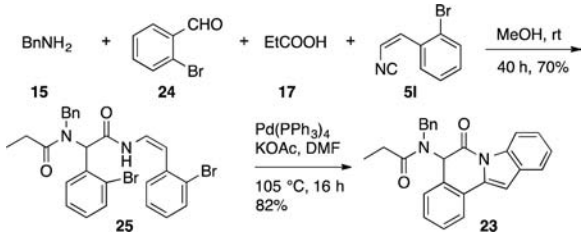
Scheme 3. Vinyl Isocyanide 5l Is a Convertible Isonitrile



reaction of benzylamine (**15**), 3-phenylpropanal (**16**), propionic acid (**17**), and **5l** in methanol afforded the adduct **18** in 79% yield (Scheme 3). No double-bond isomerization occurred in this process. Treatment of a solution of **18** in ethanethiol or in methanol with acyl chloride afforded thioester **19** (eq 1) and methyl ester **20** (eq 2) in yields of 80% and 90%, respectively. If one targeted the synthesis of **20**, then isolation of **18** would not be necessary. After completion of the Ugi reaction, simply adding AcCl and heating the reaction mixture to 55 °C provided **20** directly in 72% yield. On the other hand, intramolecular Buchwald–Hartwig *N*-arylation of **18**[31] [$Pd_2(dba)_3$, *t*-Bu_3P, Cy_2NMe, toluene, 100 °C, 16 h] afforded *N*-acylindole **21** in 85% yield. This transformation effectively converted the acid-cleavable enamide function to a base cleavable *N*-acylindole unit.[32] Indeed, treatment of **21** with NaOMe or LiOH afforded methyl ester **20** (eq 2) or carboxylic acid **22** (eq 3) in yields of 82% and 85%, respectively. Therefore, **5l** is a truly universal isonitrile as its amide equivalent is convertible under both acidic and basic conditions.

To further demonstrate the synthetic utility of vinyl isocyanide **5l**, an efficient two-step synthesis of indolo[2,1-*a*]isoquinolinone **23** was developed by an Ugi-post functionalization sequence.[33] Ugi reaction of benzylamine (**15**), 2-bromobenzaldehyde (**24**), propionic acid (**17**), and **5l** in methanol afforded the four-component adduct **25** in 70% yield (Scheme 4). Pd-catalyzed double cyclization of **25** [$Pd(PPh_3)_4$ (0.1 equiv), KOAc (2.5 equiv), DMF, 105 °C, 16 h] afforded indole **23** in 82% yield via a sequence of intramolecular *N*-arylation followed by a regioselective C–H functionalization.[34]

Scheme 4. Further Synthetic Application of Vinyl Isocyanide 5l



In conclusion, we have developed a novel and efficient synthesis of vinyl isocyanides by the Wittig reaction of isocyanomethylenetriphenylphosphorane with aldehydes. (*Z*)-1-Bromo-2-(2-isocyanovinyl)benzene (**5l**) has been identified as a truly universal isonitrile whose amide equivalent is convertible under both acidic and basic conditions. The utility of **5l** in the synthesis of polyheterocycles such as indolo[2,1-*a*]isoquinolinone has also been demonstrated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00483.

Experimental procedures, product characterization data, ^1H and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(13) This reagent is commercially available. It can be easily prepared on large scale from (chloromethyl)trimethylsilane. See the SI.
(14) Bases screened: $NaNH_2$, BuLi, Cs_2CO_3, NaH, NaOEt, LHMDS, NaHMDS, KHMDS, DBU. Solvents screened: THF, DCM, DMF.
(15) The Peterson reaction between trimethylsilylmethyl isocyanide and benzaldehyde under our optimized conditions afforded an *E*/*Z* mixture of *N*-styrylformamide in low yield.
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