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Isocyanide-Based Two-Step Three-Component Keteneimine Formation

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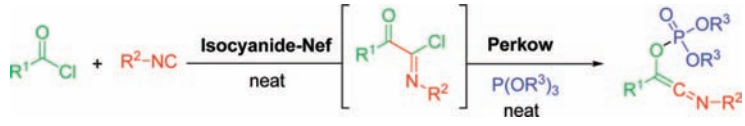
ABSTRACT



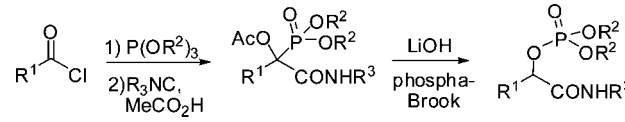
The addition of isocyanides to acyl chlorides (Isocyanide-Nef reaction) leads to imidoyl chlorides which can later be treated with trialkylphosphites to afford new keteneimines in a Perkow-type reaction. The whole sequence may be performed without any solvent, and the resulting keteneimine may easily be converted to phosphorylated tetrazoles and triazoles.

The concept of "ideal synthesis" covers issues of low costs, good yields, environmental acceptability and easy performance of a synthetic process.[1] The development of new solvent-free, rapid sequences that result in versatile structures is also an important step on the way to the "ideal synthesis". Multiple component reactions (MCRs) fulfill some of these aims as they lead in a single step to complex structures that can be further transformed in post condensation reactions.

In the field of multiple component reactions, we recently disclosed a new 3-component Passerini reaction using acyl phosphonates as formal aldehyde partners.[2] The resulting phosphonates were directly treated with LiOH to form α-amido-phosphates in a phospha-Brook type reaction (Scheme 1).

Starting from the same three components (isocyanides, acyl chlorides and phosphites), we envisioned that the scope of this sequence could be extended by altering the order of addition of the reactants. The synthetic interest of isocyanides

Scheme 1. Passerini/Phospha-Brook Sequence



is generally associated with their interaction with carbonyl derivatives as disclosed in the Passerini and Ugi reactions.[3] First published by Nef,[4] the acyl chloride-isocyanide condensation has been less studied. It gives imidoyl chloride intermediates that can be hydrolyzed or trapped to form various cyclic adducts.[5] Acyl bromides[6] and highly electrophilic carboxylic derivatives such as trifluoroacetic anhy-

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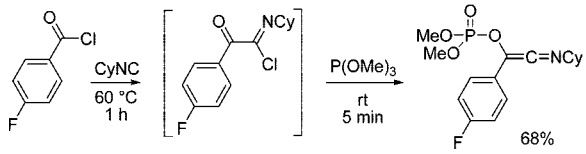
dride[7] were shown to be more efficient than the corresponding chlorides.

To test the behavior of phosphites with α-keto imidoyl chlorides, cyclohexyl isocyanide was condensed with para-fluorobenzoyl chloride in a solvent-free Isocyanide-Nef reaction. When the corresponding imidoyl chloride, formed in 1 h at 60 °C, was treated with trimethyl phosphite, the new ketenimine **1a** was formed in a 68% yield after 5 min at room temperature (Scheme 2).

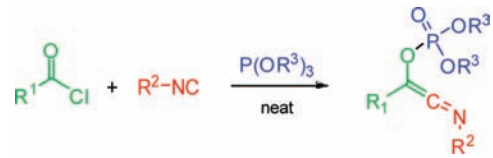
Scheme 2. Addition of Phosphites on Imidoyl Chlorides



The formation of this ketenimine may be explained by a Perkow reaction[8] of the Isocyanide-Nef adduct behaving as an α-halocarbonyl compound.[9,10] Different acyl chlorides, isocyanides and phosphites behave similarly as shown in Table 1. Simple aliphatic acyl chlorides (propionyl, hydrocinnamoyl) failed to undergo this sequence. When reacted with cyclohexylisocyanide, these acyl chlorides are quantitatively converted into imidoyl chlorides, but the following step does not give any adduct with phosphites at room temperature. Raising the temperature leads to the degradation of the Isocyanide-Nef adducts. Aromatic acyl chlorides (Table 1, entries 1−7) give the desired ketenimines (**1a**−**1g**) in moderate to good isolated yields. *tert*-Butyl isocyanide was only efficiently coupled with ethyl oxalyl chloride (Table 1, entry 10), reaction with aromatic acyl chlorides failed to give Isocyanide-Nef adducts in our hands. Benzylic isocyanides failed to undergo this sequence as the Isocyanide-Nef-adducts decomposed under these conditions. With the more reactive ethyl or methyl oxalyl chloride (Table 1, entries 8−11), both steps are efficiently performed within 5 min at room temperature.

Ketenimines are usually very sensitive to nucleophilic attacks and have to be generated in situ.[11] The presence of an electron-donating phosphate group makes these particular ketenimines less prone to hydrolysis, allowing them to be purified under a flash column on silica gel. The higher yields obtained with isopropyl substituted phosphites over methyl

Table 1. Isocyanide-Nef-Perkow Sequence Resulting to Ketenimines



entry	R^1	R^2	R^3	product (yield %)[a]
1	*p*-F-Ph	Cy	Me	**1a** (68)
2	″	″	Et	**1b** (59)
3	″	″	*i*-Pr	**1c** (75)
4	″	$(CH_2)_2Ar^b$	″	**1d** (62)
5	Ph	Cy	Me	**1e** (41)
6	″	″	*i*-Pr	**1f** (64)
7	*m*-Me-Ph	″	″	**1g** (59)
8	COOEt	″	″	**1h** (100)
9	″	$(CH_2)_2Ar^b$	″	**1i** (88)
10	″	*t*-Bu	″	**1j** (100)
11	COOMe	$(CH_2)_2OAllyl$	Et	**1k** (54)

[a] Isolated yields. [b] Ar = 3,4-dimethoxyphenyl.

and ethyl ones are probably associated to the increased stability toward hydrolysis of the bulkier and less polar resulting ketenimine. The direct hydrolysis of the crude mixture can be performed using TFA at room temperature; **1i** was thus converted to the corresponding amidophosphate in a 69% isolated yield over three steps. This amidophosphate is similar to the products obtained by the Arbuzov/Passerini/saponification/phospha-Brook sequence as disclosed in our previous study (Scheme 1).[2]

The ketenimine formation from isocyanides has already been disclosed and usually involves isocyanide addition to carbenoid intermediates. Besides few studies involving couplings with metal-free carbenes[12] most studies on ketenimine formation from isocyanides have been reported with Fisher-type carbene complexes.[13] We have thus performed here a formal addition of an O-phosphoryl substituted carbene onto an isocyanide without any assistance of a metal.

The synthetic scope of this new reaction is highly increased by the potential of the postcondensations involving ketenimines. Besides the obvious hydrolysis, more interesting heterocycle formations could be reached using these ketenimines as reactive intermediates. For instance, under

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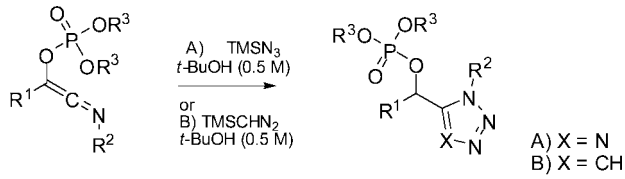
addition of trimethylsilyl azide in *tert*-butanol, these keteneimines give phosphorylated tetrazoles in fair to good yields (Table 2, entries 1−4). Considering the biological significance of tetrazoles,[14] the phosphorylated moiety of these previously unknown tetrazoles will probably increase their biological interest. Alternatively, [3 + 2] cycloadditions with trimethylsilyl diazomethane may be achieved with the formation of new triazoles in moderate to good yields (Table 2, entries 5−8). As far as we know, none of these β-phosphato- tetrazoles or triazoles have already been described.

Table 2. Triazoles and Tetrazoles Formation from Keteneimines



entry	keteneimine	adduct	yield (%)[a]
1	**1c**	**2a** (X = N)	58
2	**1h**	**2b** (X = N)	73
3	**1g**	**2c** (X = N)	61
4	**1j**	**2d** (X = N)	55
5	**1h**	**2e** (X = CH)	79
6	**1d**	**2f** (X = CH)	50
7	**1g**	**2g** (X = CH)	52
8	**1k**	**2h** (X = CH)	57

[a] Isolated yields.

In summary, we have developed a new, solvent-free, two-step three-component synthesis of keteneimines. The diversity offered by this process is further enhanced by the electrophilic nature of keteneimines which allows further additions of nucleophilic components. This was demonstrated by the preparation of small libraries of O-phosphorylated triazoles and tetrazoles.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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