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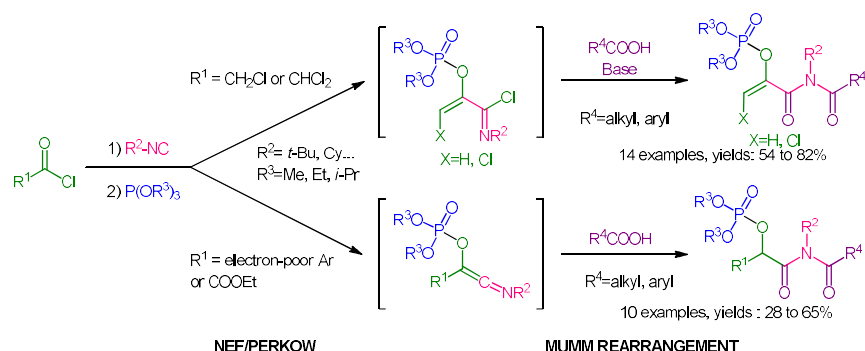
Nef/Perkow/Mumm Cascade towards Imido Phosphate Derivatives.

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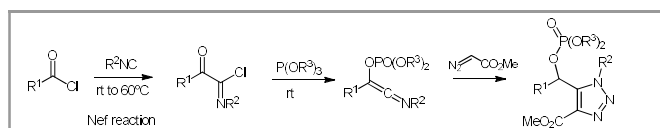
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Abstract A one-pot four-component synthesis of imido phosphates has been achieved using a Nef /Perkow sequence followed by addition of carboxylic acid derivatives. The final imido moiety is formed via a Mumm rearrangement of an intermediate imide.

Over the last decades, Ugi and Passerini reactions have been largely associated with the development of the multicomponent reaction field.¹ These reactions take advantage of the low nucleophilicity of isocyanides towards carbonyl derivatives requiring the electrophilic activation of an acidic derivative such as carboxylic acid. However the more electrophilic acyl chlorides are reactive enough to add directly with isocyanides leading to α -ketoimidoyl chlorides without any assistance (Scheme 1). Discovered by Nef in 1892,² this reaction has been little studied in comparison with the more recent Ugi and Passerini reactions.³ This is certainly associated with the lower diversity of the reaction together with an apparent reversibility of the Nef step when trying to trap the imidoyl chlorides with various nucleophiles.

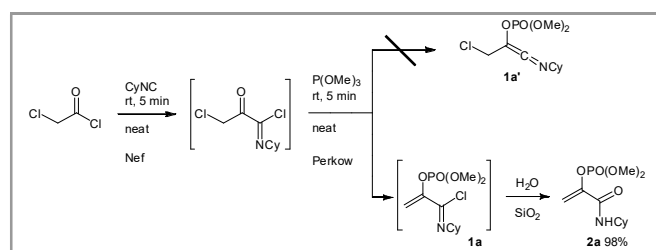


Scheme 1 Nef/Perkow sequence

In an effort to solve this problem and extend the diversity offered by the Nef isocyanide reaction, we reported a few years ago a Nef/Perkow sequence that afforded ketimine phosphates and trapped the latter in various cycloadditions with 1,3-dipoles (Scheme 1).⁴ In this context, we now wish to report a three-component one-pot Nef/Perkow/Mumm cascade leading to imido phosphate derivatives.

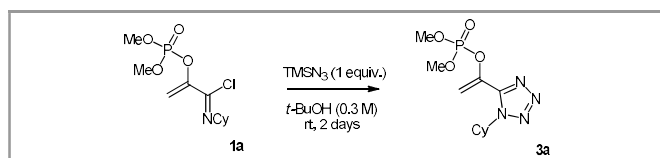
At the onset of this study, we envisioned the use of α -chloroacetyl chloride as a potential probe to evaluate the efficiency of the

Perkow reaction⁵ of α -ketoimidoyl chlorides. Indeed after Nef reaction of α -chloroacetyl chloride, the following addition of trialkylphosphite might afford two regioisomeric Perkow adducts according to the leaving group abilities of the two chlorine atoms present in the intermediate imidoyl chloride (Scheme 2). Thus, after solvent-free cyclohexyl isocyanide addition to α -chloroacetyl chloride, trimethyl phosphite was added to the resulting imidoyl chloride obtained in quantitative yield. After few minutes at room temperature, the Perkow step was over as monitored by ¹H NMR forming vinyl phosphate **1a** in almost quantitative yield without any trace of the regioisomeric ketimine phosphate **1a'**. After purification by flash chromatography on silica gel, the amide **2a** derived from the hydrolysis of imidoyl chloride **1a** was obtained with an excellent 98% isolated yield (Scheme 2).



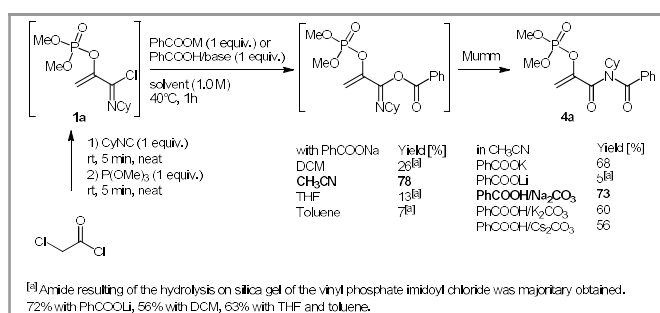
Scheme 2 Nef/Perkow sequence with chloroacetyl chloride

Besides the formation of a new vinyl phosphate derivative, the most interesting aspect of this transformation is associated with the remaining imidoyl chloride function whose potential as electrophile is not hampered by the competing α -carbonyl present in the Nef adduct.⁶ Thus simple water addition as observed in the conversion of **1a** to **2a** could be replaced by more complex nucleophilic additions as shown by the formation of the phosphorylated tetrazole **3a** obtained in 67% isolated yield under addition of trimethylsilyl azide to **1a** (Scheme 3).



Scheme 3 Nucleophilic attack on the vinyl phosphate imidoyl chloride intermediate **1a** to form the phosphorylated tetrazole **3a**

In the context of this study, we decided to focus on the addition of carboxylate salts to form imide derivatives through a Mumm rearrangement⁷ as an intermediate imidate ester (Scheme 4). Indeed, this transformation had only been reported once on Nef adducts and the formation of imide derivatives could only be observed using silver carboxylate.⁸ When sodium benzoate was added to **1a** in DCM and the mixture heated at 40°C for 1h we were delighted to observe the formation of the expected imide **4a** but the major product was the amide **2a**. The formation of the latter could be explained by remaining water in the benzoate salt or more probably by a competing anhydride formation through further attack of a second benzoate salt on the intermediate imidate before Mumm rearrangement. Rewardingly changing the solvent to acetonitrile allowed us to observe the exclusive formation of **4a** which was obtained directly from α -chloroacetyl chloride in an excellent 78% isolated yield (Scheme 4).



Scheme 4 Optimisation Nef/Perkow/Mumm rearrangement cascade towards imido vinyl phosphate **4a**

Different benzoate salts were also evaluated as well as benzoic acid/base combination to allow further extension to non commercially available carboxylates. These trials showed the superiority of the sodium salt over potassium or lithium salts whereas use of benzoic acid together with Na₂CO₃ was less satisfying than the preformed carboxylate but with still a reasonable 73% isolated yield

A set of isocyanides, trialkyl phosphites and carboxylic acids were engaged with the chloroacetyl chloride in acetonitrile with sodium carbonate to test the scope of this new one-pot Nef/Perkow/Mumm cascade. The imido vinyl phosphates **4** were isolated in moderate to good yields as shown in Table 1.

The sequence is compatible with aliphatic (Table 1, entries 7-13) and aromatic acids (Table 1, entries 1-5 and 14). The nature of the trialkyl phosphites engaged seems to have little influence on yields as shown by the close behavior of the methyl, ethyl and isopropyl phosphites (Table 1, entries 1-3). In the Nef step, cyclohexyl isocyanide react with the chloroacetyl chloride in 5 min at room temperature to give the imidoyl chloride intermediate quantitatively. When *p*-methoxy benzyl and homoveratryl isocyanides were engaged, the reaction needs to be

heated at 60°C for 1h. Though *tert*-butyl isocyanide exhibits a good reactivity in the Nef step (close to cyclohexyl isocyanide), the Perkow addition is not efficient both at rt or higher temperature probably due to the steric hindrance of the *tert*-butyl group together with potential conversion to nitrile under forcing conditions. Rewardingly, this strategy could be extended to α -dichloroacetyl chloride leading to chlorovinyl phosphate. The latter was obtained as a single stereoisomer but we couldn't determine its *cis* or *trans* nature (Table 1, entry 6).⁹ The imide structure of these adducts could be further confirmed by a single crystal X-ray analysis of **4n**.¹⁰

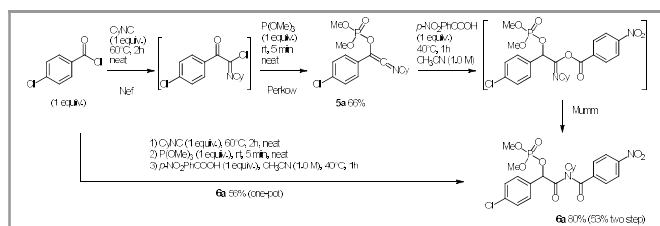
Table 1 Synthesis of imido vinyl phosphonate derivatives **4**

Entry	R ¹	R ²	R ³	R ⁴	Product	Yield [%] ^a
1	H	Cy	Me	Ph	4a	73 (78)
2	H	Cy	Et	Ph	4b	(82)
3	H	Cy	<i>i</i> -Pr	Ph	4c	(77)
4	H	<i>h</i> ver ^b	Me	Ph	4d	(79)
5	H	<i>p</i> -OMePhCH ₂	Me	Ph	4e	(65)
6	Cl	Cy	Me	Ph	4f	(69)
7	H	Cy	Me	Me	4g	61 (75)
8	H	<i>p</i> -OMePhCH ₂	Me	Me	4h	76
9	H	<i>p</i> -OMePhCH ₂	Me	ClCH ₂	4i	56
10	H	Cy	Me	CH ₂ C(Me)	4j	69
11	H	<i>p</i> -OMePhCH ₂	Me	Allyl	4k	69
12	H	Cy	Me	PhCHCH	4l	54
13	H	Cy	Me	PhCHC(Me)	4m	67
14	H	Cy	Me	<i>o</i> -iPh	4n	62

^a Yield determined for the reaction using R⁴CO₂H together with Na₂CO₃. The value in parentheses for the reaction using preformed R⁴CO₂Na.

^b For R²=*h*ver, the starting amine used in the preparation of the isocyanide partner is homoveratrylamine.

We next envisioned the extension of this strategy to less focused families of acyl chlorides. When no α -halogeno atoms are present, keteneimine phosphate derivatives are normally obtained (Scheme 1). The potential of these adducts has been mostly explored in various cycloaddition and electrocyclization processes towards triazoles and tetrazoles,⁴ indolizines,¹¹ pyridines¹² or pyrroles.¹³ Compared to the previous imidoyl chloride **1**, the keteneimine nature of the adduct might allow a direct addition of the carboxylic acid without any added base. After letting cyclohexyl isocyanide react with *p*-chlorobenzoyl chloride under neat conditions at 60°C for 2 h, trimethyl phosphite was added at rt leading to keteneimine **5a** isolated in 66% yield (by a fast chromatography on silica gel). When the latter was added to *p*-nitrobenzoic acid under the conditions optimized for **4a** (CH₃CN, 40°C, 1h) the new imido phosphate **6a** was formed in a good 80% isolated yield. As keteneimines are rather sensitive to hydrolysis a one-pot procedure was preferred adding directly the carboxylic acid to the crude keteneimine leading to a slightly better 56% yield over the whole sequence (Scheme 5).



Scheme 5 Nef/Perkow/Mumm rearrangement cascade towards imido phosphate **6a**

These one-pot conditions were adopted for the preparations of the various imides **6** from acyl chlorides as displayed in Table 2.¹⁴

Table 2 Synthesis of imido phosphate derivatives **6**

Entry	R ¹	R ²	R ³	R ⁴	Product	Yield [%]
1	<i>p</i> -ClPh	Cy	Me	<i>p</i> -NO ₂ Ph	6a	56
2	<i>p</i> -FPh	Cy	Me	Ph	6b	60
3	<i>p</i> -FPh	Cy	<i>i</i> -Pr	Ph	6c	57
4	EtO ₂ C	<i>h</i> ver	<i>i</i> -Pr	Ph	6d	51
5	EtO ₂ C	<i>t</i> Bu	<i>i</i> -Pr	Ph	6e	44
6	<i>p</i> -FPh	Cy	Me	<i>p</i> -ClPh	6f	65
7	<i>p</i> -NO ₂ Ph	Cy	Me	<i>p</i> -OMePh	6g	28
8	<i>p</i> -NO ₂ Ph	<i>h</i> ver	Me	Allyl	6h	29
9	<i>p</i> -ClPh	Cy	Me	ClCH ₂	6i	30
10	<i>p</i> -NO ₂ Ph	Cy	Me	ClCH ₂	6j	52
11	<i>p</i> -NO ₂ Ph	<i>t</i> Bu	Me	CH ₃	-	0
12	<i>p</i> -FPh	Cy	Me	CH ₂ CH ₂ CH	-	0
13	EtO ₂ C	<i>h</i> ver	Me	CH ₂ CH ₂ CH	-	0

Compared to the previous Nef/Perkow/Mumm sequence, the scope of the carboxylic acids that may be successfully added in the last step is slightly more limited: if aromatic acids (Table 2, entries 1-6) give the desired imido phosphates (**6a-6f**) with the highest yields observed for aromatics substituted by electron withdrawing groups, the addition of aliphatic acids is more problematic as shown by the lack of product formation under addition of acetic acid or cyclopropanecarboxylic (Table 2, entries 11-13). However allyl and chloroacetic acids (Table 2, entries 8-10) gave imido phosphates (**6h-6j**) in moderate yields. The higher reactivity of α -chloroacetic acid compared to acetic acid is consistent with the trend observed for aromatic derivatives. As observed previously the efficiency of the sequence does not show a strong dependence to the nature of the trialkyl phosphites added in the Perkow step (Table 2, entries 2-3).

In summary, we have further extended the synthetic applications of the Nef/Perkow sequence. According to the nature of the starting acyl chloride, the reaction may afford ketenimine as well as imidoyl chlorides. We have shown that both families of compounds may easily be engaged in a Mumm rearrangement

leading to complex imide derivatives.¹⁵ The use of the latter in further cyclizations is under study in our group.

Acknowledgment

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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- (15) **Nef/Perkow/Mumm Product 4a; Typical Procedure:** Under argon atmosphere, a mixture of chloroacetyl chloride (80 μ L, 1.0 mmol) and cyclohexyl isocyanide (124 μ L, 1.0 mmol) was stirred at room temperature for 5 minutes. Then trimethyl phosphite (118 μ L, 1.0 mmol) was added and the mixture was stirred at room temperature for 5 minutes to afford the imidoyl chloride intermediate. To a 1.0 M solution of benzoic acid (122 mg, 1.0 mmol) in CH_3CN were added sodium carbonate (106 mg, 1.0 mmol) and the imidoyl chloride intermediate (formed in situ). The mixture was stirred at 40°C for 1 hour. The resulting mixture was dissolved in DCM and washed with water. The organic layer was extracted, dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (EtOAc/DCM, 10/90) to afford **4a** as a yellow oil obtained in 73% yield (278 mg, 0.73 mmol). Rf: 0.59 (5/5 DCM/AcOEt). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.63 (d, $J_{\text{HH}} = 8.1$ Hz, 2H), 7.52 (t, $J_{\text{HH}} = 7.3$ Hz, 1H), 7.41 (dd, $J_{\text{HH}} = 8.1, 7.3$ Hz, 2H), 5.43 (dd, $J_{\text{HH,HP}} = 3.0, 2.0$ Hz, 1H), 5.22 (dd, $J_{\text{HH,HP}} = 3.0, 2.0$ Hz, 1H), 4.42-4.34 (m, 1H), 3.70 (d, $J_{\text{HP}} = 11.4$ Hz, 6H), 2.11-2.02 (m, 2H), 1.84-1.81 (m, 4H), 1.66-1.63 (m, 1H), 1.39-1.18 (m, 3H). ^{13}C NMR (100.6 MHz, CDCl_3) δ (ppm) 173.6, 166.8 (d, $J_{\text{CP}} = 8.1$ Hz), 147.7 (d, $J_{\text{CP}} = 8.1$ Hz), 136.7, 132.7, 129.3, 128.7, 108.4 (d, $J_{\text{CP}} = 3.7$ Hz), 58.8, 55.1 (d, $J_{\text{CP}} = 6.6$ Hz), 30.3, 26.2, 25.2. ^{31}P NMR (161.9 MHz, H_3PO_4) δ (ppm) -4.8. HRMS: calculated for $\text{C}_{18}\text{H}_{24}\text{NO}_6\text{P}$ 381.1341, found 381.1326. IR (neat) ν (cm^{-1}) 3033, 2960, 2936, 2859, 1707, 1659, 1631, 1450, 1329, 1280, 1187, 1044.
- Nef/Perkow/Mumm Product 6a; Typical Procedure:** Under argon atmosphere, a mixture of p-chlorobenzoyl chloride (128 μ L, 1.0 mmol) and cyclohexyl isocyanide (124 μ L, 1.0 mmol) was stirred at 60°C for 2 hours. Then trimethyl phosphite (118 μ L, 1.0 mmol) was added and the mixture was stirred at room temperature for 5 minutes to afford the keteneimine intermediate. To a 1.0 M solution of the keteneimine (formed in situ) in CH_3CN was added p-nitrobenzoic acid (167 mg, 1.0 mmol) and the mixture was stirred at 40°C for 1 hour. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc/DCM, 5/95) to afford **6a** as a yellow oil obtained in 56% yield (292 mg, 0.56 mmol). Rf: 0.71 (7/3 DCM/AcOEt). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.26 (d, $J_{\text{HH}} = 9.1$ Hz, 2H), 7.67 (d, $J_{\text{HH}} = 9.1$ Hz, 2H), 7.38-7.33 (m, 4H), 6.09 (d, $J_{\text{HP}} = 7.8$ Hz, 1H), 3.80 (d, $J_{\text{HP}} = 11.4$ Hz, 3H), 3.73-3.66 (m, 1H), 3.58 (d, $J_{\text{HP}} = 11.4$ Hz, 3H), 2.15-2.06 (m, 1H), 2.01-1.92 (m, 1H), 1.77-1.72 (m, 3H), 1.55-1.44 (m, 2H), 1.09-1.04 (m, 3H). ^{13}C NMR (100.6 MHz, CDCl_3) δ (ppm) 172.9, 171.6 (d, $J_{\text{CP}} = 5.1$ Hz), 150.0, 140.6, 135.7, 133.1 (d, $J_{\text{CP}} = 5.9$ Hz), 129.3, 129.3, 129.1, 124.0, 77.2 (d, $J_{\text{CP}} = 4.4$ Hz), 60.5, 54.9 (d, $J_{\text{CP}} = 5.9$ Hz), 54.5 (d, $J_{\text{CP}} = 5.9$ Hz), 30.4, 29.2, 26.2, 26.1, 24.8. ^{31}P NMR (161.9 MHz, H_3PO_4) δ (ppm) 0.3. IR (neat) ν (cm^{-1}) 2938, 2859, 1716, 1688, 1530, 1348, 1300, 1044, 909, 855.
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