Nef–Perkow–Mumm Cascade towards Imido Phosphate Derivatives

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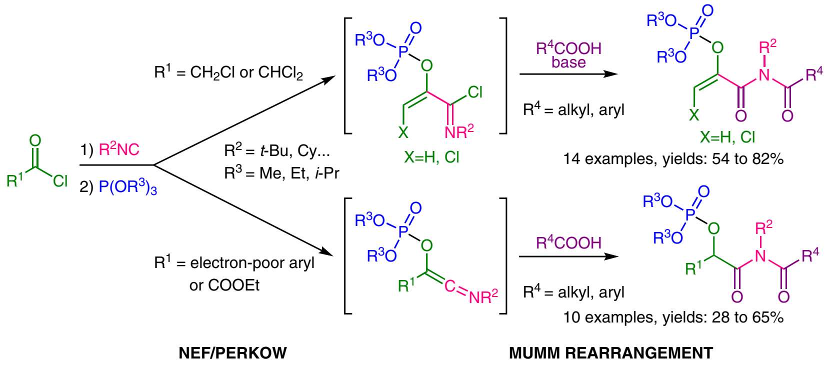

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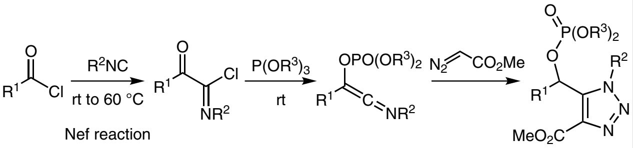
Abstract A one-pot, four-component synthesis of imido phosphates has been achieved using a Nef–Perkow sequence followed by addition of carboxylic acid derivatives. The final imido moiety is formed via a Mumm rearrangement of an intermediate imidate.

Key words vinyl phosphate, keteneimine, isocyanide, Nef reaction, Perkow reaction, Mumm rearrangement

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 to 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.

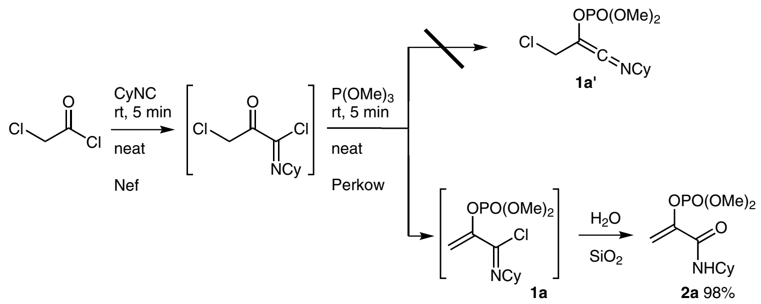


Scheme 1 Nef–Perkow sequence

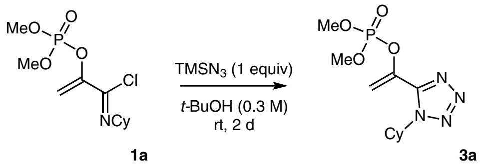
In an effort to solve this problem and extend the diversity offered by the Nef isocyanide reaction, we reported a few years ago a Nef–Perkow sequence that afforded ketenimine phosphates and trapped the latter in various cycloadditions with 1,3-dipoles (Scheme 1).[4] In this context, we now wish to report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

At the onset of this study, we envisaged the use of α-chloroacetyl chloride as a potential probe to evaluate the efficiency of the Perkow reaction[5] 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 a few minutes at room temperature, the Perkow step was complete, as monitored by ^{1}H NMR spectroscopy, forming vinyl phosphate **1a** in almost quantitative yield without any trace of the regioisomeric ketenimine 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).

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 an 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** into **2a**, could be replaced by more complex nucleophilic additions as shown by the formation of the phosphorylated tetrazole **3a** obtained in 67% isolated yield on addition of trimethylsilyl azide to **1a** (Scheme 3).



Scheme 2 Nef–Perkow sequence with chloroacetyl chloride



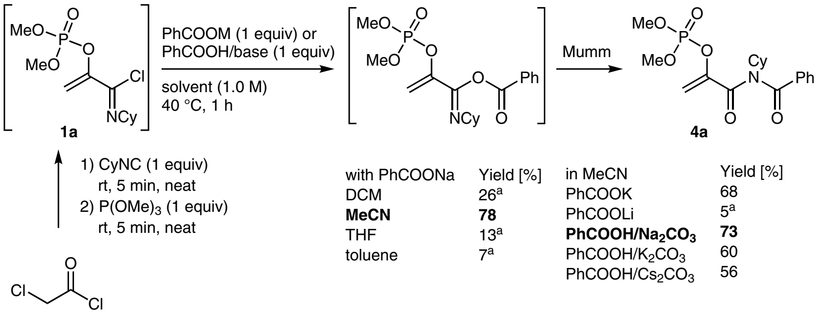
Scheme 3 Nucleophilic attack on the vinyl phosphate imidoyl chloride intermediate **1a** to form the phosphorylated tetrazole **3a**

In the context of this study, we decided to focus on the addition of carboxylate salts to form imide derivatives through a Mumm rearrangement[7] of an intermediate imidate ester (Scheme 4). Indeed, this transformation has only been reported once on Nef adducts and the formation of imide derivatives could only be observed when using silver carboxylates.[8] However, when sodium benzoate was added to **1a** in dichloromethane and the mixture heated at 40 °C for one hour 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 residual 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** that was obtained directly from α-chloroacetyl chloride in an excellent 78% isolated yield (Scheme 4).

Different benzoate salts were also evaluated as well as benzoic acid/base combinations to allow further extension to noncommercially available carboxylates. These trials showed the superiority of sodium salts over potassium or lithium salts whereas use of benzoic acid together with $Na_2CO_3$was less efficient than using the preformed carboxylate but still gave a reasonable 73% isolated yield.

A range of isocyanides, trialkyl phosphites, and carboxylic acids were examined with chloroacetyl chloride in acetonitrile in the presence of 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 used 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 reacts with chloroacetyl chloride in five minutes at room temperature to give the imidoyl chloride intermediate quantitatively. When *p*-methoxy benzyl and homoveratryl isocyanides were used, the reaction needs to be heated at 60 °C for one hour. Although *tert*-butyl isocyanide exhibits good reactivity in the Nef step (close to that of cyclohexyl isocyanide), the Perkow addition is not efficient both at room or higher temperature probably due to the steric hindrance of the *tert*-butyl group together with potential conversion into a

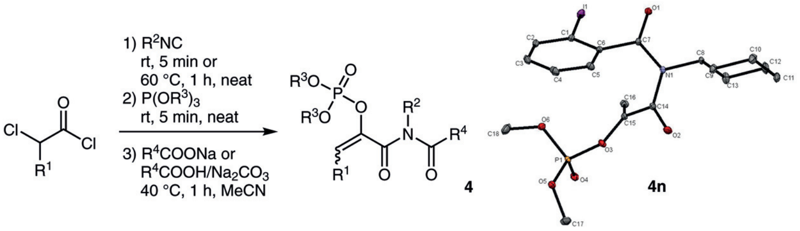


with PhCOONa	Yield [%]
DCM	26[a]
MeCN	**78**
THF	13[a]
toluene	7[a]

in MeCN	Yield [%]
PhCOOK	68
PhCOOLi	5[a]
PhCOOH/Na_2CO_3	**73**
PhCOOH/K_2CO_3	60
PhCOOH/Cs_2CO_3	56

Scheme 4 Optimization Nef–Perkow–Mumm rearrangement cascade towards imido vinyl phosphate **4a**. [a] Amide resulting of the hydrolysis on silica gel of the vinyl phosphate imdioyl chloride was majoritary obtained; 72% with PhCOOLi, 56% with CH_2Cl_2, 63% with THF and toluene.

Table 1 Synthesis of Imido Vinyl Phosphonate Derivatives **4**

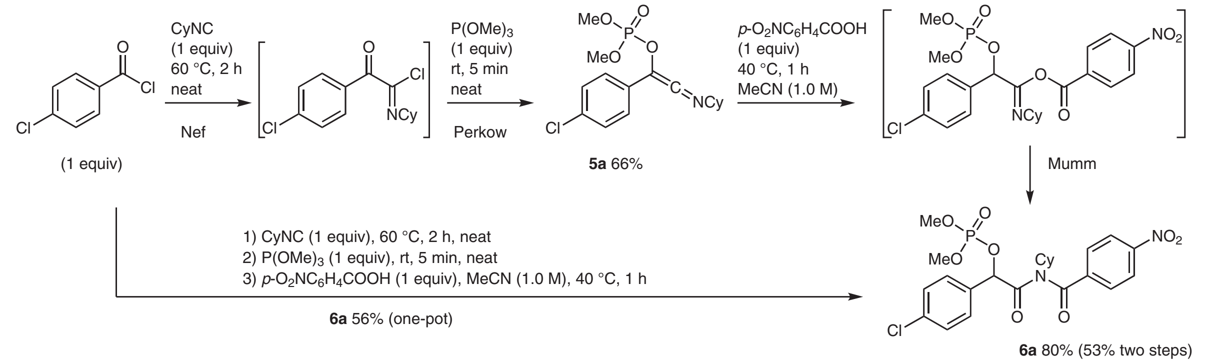


Entry	R^1	R^2	R^3	R^4	Product	Yield (%)[a]
1	H	Cy	Me	Ph	**4a**	73 (78)
2	H	Cy	Et	Ph	**4b**	(82)
3	H	Cy	*i*-Pr	Ph	**4c**	(77)
4	H	hver[b]	Me	Ph	**4d**	(79)
5	H	*p*-$MeOC_6H_3CH_2$	Me	Ph	**4e**	(65)
6	Cl	Cy	Me	Ph	**4f**	(69)
7	H	Cy	Me	Me	**4g**	61 (75)
8	H	*p*-$MeOC_6H_3CH_2$	Me	Me	**4h**	76
9	H	*p*-$MeOC_6H_3CH_2$	Me	$ClCH_2$	**4i**	56
10	H	Cy	Me	$CH_2C(Me)$	**4j**	69
11	H	*p*-$MeOC_6H_3CH_2$	Me	allyl	**4k**	69
12	H	Cy	Me	PhCHCH	**4l**	54
13	H	Cy	Me	PhCHC(Me)	**4m**	67
14	H	Cy	Me	*o*-IPh	**4n**	62

[a] Yield determined for the reaction using R^4CO_2H together with Na_2CO_3. The value in parentheses for the reaction using preformed R^4CO_2Na.
[b] For R^2 = hver, the starting amine used in the preparation of the isocyanide partner is homoveratrylamine.

nitrile under forcing conditions. Rewardingly, this strategy could be extended to α-dichloroacetyl chloride leading to a chlorovinyl phosphate. The latter was obtained as a single stereoisomer but we could not 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]

We next envisaged extending this strategy to other acyl chlorides. When no α-halogeno atoms are present, ketenimine phosphate derivatives are normally obtained (Scheme 1). The potential of these adducts has been mostly explored in various cycloaddition and electrocyclization processes to furnish triazoles and tetrazoles,[4] indolizines,[11] pyridines,[12] and pyrroles.[13] Compared to the previous imidoyl chloride **1**, the ketenimine nature of the adduct might allow a direct addition of the carboxylic acid without any added base. After allowing cyclohexyl isocyanide to react with *p*-chlorobenzoyl chloride under neat conditions at

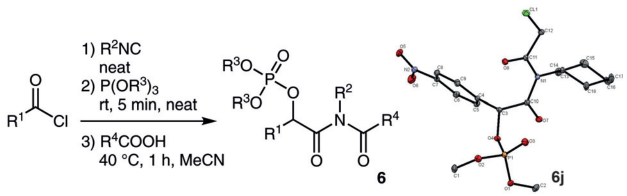


Scheme 5 Nef–Perkow–Mumm rearrangement cascade towards imido phosphate **6a**

60 °C for two hours, trimethyl phosphite was added at room temperature leading to ketenimine **5a** isolated in 66% yield (by rapid chromatography on silica gel). When the latter was added to *p*-nitrobenzoic acid under the conditions optimized for **4a** (MeCN, 40 °C, 1 h) the new imido phosphate **6a** was formed in a good 80% isolated yield. As ketenimines are rather sensitive to hydrolysis a one-pot procedure was preferred adding the carboxylic acid directly to the crude ketenimine leading to a slightly better 56% yield over the whole sequence (Scheme 5).

These one-pot conditions were adopted for the preparation of 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	*p*-ClC_6H_4	Cy	Me	*p*-$O_2NC_6H_4$	**6a**	56
2	*p*-FC_6H_4	Cy	Me	Ph	**6b**	60
3	*p*-FC_6H_4	Cy	*i*-Pr	Ph	**6c**	57
4	EtO_2C	hver	*i*-Pr	Ph	**6d**	51
5	EtO_2C	*t*-Bu	*i*-Pr	Ph	**6e**	44
6	*p*-FC_6H_4	Cy	Me	*p*-ClC_6H_4	**6f**	65
7	*p*-$O_2NC_6H_4$	Cy	Me	*p*-$MeOC_6H_4$	**6g**	28
8	*p*-$O_2NC_6H_4$	hver	Me	allyl	**6h**	29
9	*p*-ClC_6H_4	Cy	Me	$ClCH_2$	**6i**	30
10	*p*-$O_2NC_6H_4$	Cy	Me	$ClCH_2$	**6j**	52
11	*p*-$O_2NC_6H_4$	*t*-Bu	Me	Me	–	0
12	*p*-FC_6H_4	Cy	Me	CH_2CH_2CH	–	0
13	EtO_2C	hver	Me	CH_2CH_2CH	–	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. Aromatic acids (Table 2, entries 1–6) give the desired imido phosphates **6a–f**, with the highest yields observed when the aromatic ring is substituted with electron-withdrawing groups; whereas the addition of aliphatic acids is more problematic as shown by the lack of product formation on addition of acetic acid or cyclopropanecarboxylic acid (Table 2, entries 11–13). However allyl and chloroacetic acids (Table 2, entries 8–10) gave imido phosphates **6h–j** 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 and 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 ketenimines as well as imidoyl chlorides. We have shown that both families of compounds may readily undergo a Mumm rearrangement leading to complex imide derivatives.[15] The use of the latter in further cyclizations is under investigation in our group.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590856.

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(14) CCDC 1550095 contains the supplementary crystallographic data for compound **6j**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(15) **Nef–Perkow–Mumm Product 4a – Typical Procedure**

Under an argon atmosphere, a mixture of chloroacetyl chloride (80 μL, 1.0 mmol) and cyclohexyl isocyanide (124 μL, 1.0 mmol) was stirred at rt for 5 min. Then trimethyl phosphite (118 μL, 1.0 mmol) was added, and the mixture was stirred at rt for 5 min to afford the imidoyl chloride intermediate. To a 1.0 M solution of benzoic acid (122 mg, 1.0 mmol) in MeCN were added Na_2CO_3 (106 mg, 1.0 mmol) and the imidoyl chloride intermediate (formed in situ), and the mixture was stirred at 40 °C for 1 h. The resulting mixture was dissolved in DCM and washed with H_2O. 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 yellow oil in 73% yield (278 mg, 0.73 mmol). R_f = 0.59 (DCM/EtOAc, 5:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J_{HH} = 8.1 Hz, 2 H), 7.52 (t, J_{HH} = 7.3 Hz, 1 H), 7.41 (dd, J_{HH} = 8.1, 7.3 Hz, 2 H), 5.43 (dd, $J_{HH,HP}$ = 3.0, 2.0 Hz, 1 H), 5.22 (dd, $J_{HH,HP}$ = 3.0, 2.0 Hz, 1 H), 4.42–4.34 (m, 1 H), 3.70 (d, J_{HP} = 11.4 Hz, 6 H), 2.11–2.02 (m, 2 H), 1.84–1.81 (m, 4 H), 1.66–1.63 (m, 1 H), 1.39–1.18 (m, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.6, 166.8 (d, J_{CP} = 8.1 Hz), 147.7 (d, J_{CP} = 8.1 Hz), 136.7, 132.7, 129.3, 128.7, 108.4 (d, J_{CP} = 3.7 Hz), 58.8, 55.1 (d, J_{CP} = 6.6 Hz), 30.3, 26.2, 25.2 ppm. ^{31}P NMR (161.9 MHz, H_3PO_4): δ = –4.8 ppm. HRMS: *m/z* calcd for $C_{18}H_{24}NO_6P$: 381.1341; found: 381.1326. IR (neat): 3033, 2960, 2936, 2859, 1707, 1659, 1631, 1450, 1329, 1280, 1187, 1044 cm^{-1}.

Nef–Perkow–Mumm Product 6a – Typical Procedure

Under an argon atmosphere, a mixture of *p*-chlorobenzoyl chloride (128 μL, 1.0 mmol) and cyclohexyl isocyanide (124 μL, 1.0 mmol) was stirred at 60 °C for 2 h. Then trimethyl phosphite (118 μL, 1.0 mmol) was added, and the mixture was stirred at rt for 5 min to afford the ketenimine intermediate. To a 1.0 M solution of the keteneimine (formed in situ) in MeCN was added *p*-nitrobenzoic acid (167 mg, 1.0 mmol), and the mixture was stirred at 40 °C for 1 h. 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 yellow oil in 56% yield (292 mg, 0.56 mmol). R_f = 0.71 (DCM/EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, J_{HH} = 9.1 Hz, 2 H), 7.67 (d, J_{HH} = 9.1 Hz, 2 H), 7.38–7.33 (m, 4 H), 6.09 (d, J_{HP} = 7.8 Hz, 1 H), 3.80 (d, J_{HP} = 11.4 Hz, 3 H), 3.73–3.66 (m, 1 H), 3.58 (d, J_{HP} = 11.4 Hz, 3 H), 2.15–2.06 (m, 1 H), 2.01–1.92 (m, 1 H), 1.77–1.72 (m, 3 H), 1.55–1.44 (m, 2 H), 1.09–1.04 (m, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.9, 171.6 (d, J_{CP} = 5.1 Hz), 150.0, 140.6, 135.7, 133.1 (d, J_{CP} = 5.9 Hz), 129.3, 129.3, 129.1, 124.0, 77.2 (d, J_{CP} = 4.4 Hz), 60.5, 54.9 (d, J_{CP} = 5.9 Hz), 54.5 (d, J_{CP} = 5.9 Hz), 30.4, 29.2, 26.2, 26.1, 24.8 ppm. ^{31}P NMR (161.9 MHz, H_3PO_4): δ = 0.3 ppm. IR (neat): 2938, 2859, 1716, 1688, 1530, 1348, 1300, 1044, 909, 855 cm^{-1}.