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Nef-Perkow Cascade towards Imidazo Phosphate Derivatives.

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ABSTRACT

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Keywords: Vinyl phosphate hydroamination isocyanide Nef Perkow A one-pot four-component synthesis of imidazo phosphates has been achieved using a Nef /Perkow sequence followed by addition of propargylamine to form an intermediate amidrazone. The latter is not isolated but directly cyclized to imidazo phosphate derivatives in the presence of silver carbonate.

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The last two decades witnessed impressive developments activating triple bounds towards intra and intermolecular nucleophilic additions. Hydroamination of alkynes in particular has attracted considerable attention leading to the disclosure of many different catalysts for efficient preparation of 5 and 6-membered ring nitrogen heterocycles.¹ Thus, imidazole derivatives (monocyclic and fused systems) may be easily prepared from propargylamines via their analogous amidines followed by cyclization.² Imidazoles are widely represented among natural compounds and synthetic drugs, their hydrogen bonding properties are associated with strong binding properties to biological receptors and they have found important applications as anticancer and antifungal agents.³

Following our interest in the Nef-isocyanide reaction (addition of acylchlorides to isocyanides forming α -ketoimidoyl chlorides),⁴ we envisioned that this reaction could be coupled with an hydroamination step to form imidazole derivatives.⁵ However the most straightforward preparation of amidine by adding the amine to the Nef adducts usually fails due to a faster addition on the more electrophilic α -carbonyl group leading to simple amides and recovery of the isocyanide.⁶ To circumvent the problems associated with the competition between the imidoyl chloride and the ketone, we proposed several years ago to treat the Nef adducts by phosphites in a Nef/Perkow sequence leading to ketenimines⁷ or imidoyl chloride enol phosphates⁸ according to the nature of the starting acyl chloride (Scheme 1). We further confirmed that the Nef/Perkow adducts could act as electrophiles towards carboxylate anions to form imide derivatives via a Mumm rearrangement (Scheme 1).⁸ We now wish to report the result of our study on the addition of propargylamine to Nef/Perkow adducts.



Scheme 1. Isocyanide based Nef/Perkow/Mumm sequence .

We selected chloroacetyl chloride **1a**, cyclohexyl isocyanide **2a** and triisopropyl phosphite **3a** to start our study. These inputs efficiently coupled in our previous Nef/Perkow/Mumm cascade.⁸ Following the solvent-free Nef/Perkow step, the intermediate imidoyl chloride **4a** was not isolated but propargylamine were directly added, together with some solvent to the crude reaction mixture. A base and various metal salts as catalysts were added as well. The results of this optimization study are reported in Table 1. Whereas we could not isolate any trace of the expected imidazole **5a** after simple addition of propargylamine and DIPEA to intermediate imidoyl chloride **4a**, we were delighted to observe the formation of **5a** in a moderate yield when the addition was performed in the presence of silver salts. Best conditions were obtained using acetonitrile with DIPEA as a base and silver carbonate as catalyst (20 mol%).

Cl 1	1) Cy- neat, Cl a 2) (<i>i</i> -Pr neat	-N [±] =C [−] 2a rt, 5 min rO) ₃ P 3a , rt, 5 min	$\begin{array}{c} & & \\ O \\ O$	$\begin{array}{c} 0, 0\\ 0 &$
Entry	Base	Solvent	Cat. (mol%)	Yield (%) ^a
1	DIPEA	MeCN	Ag ₂ CO ₃ (20)	64
2	DBU	MeCN	Ag ₂ CO ₃ (20)	45
3	TEA	MeCN	Ag ₂ CO ₃ (20)	40
4	DIPEA	DMF	Ag ₂ CO ₃ (20)	40

Table 1. Optimization table for imidazole 5a.

5	DIPEA	Toluene	Ag ₂ CO ₃ (20)	28
6	DIPEA	MeCN	AgOTf (20)	35
7	DIPEA	MeCN	Cu(OTf) ₂ (20)	12
8	DIPEA	MeCN	SPhosAuNTf ₂ (1)	17
9	DIPEA	MeCN	Y(OTf) ₃	trace
10	DIPEA	MeCN	none	0

^{*a*} Isolated yields.

The optimized conditions were used to study the scope of different isocyanides, phosphites and chloroacetyl chlorides and the results are summarized in Table 2 (Entries 1-9).

Table 2. Imidazole 5 from acylchlorides 1, isocyanides 2 andphosphites 3.

	1) R ² —N [±] neat, rt, ℃I 2) (R ³) ₃ P neat, rt,	EC ² 2 5 min 3 5 min {₹ R ¹	O, OR ³ O P OR ³ CI NR ² 4 -	$\begin{array}{c c} H_2N & O, OR^3\\ \hline Base & O' OR^3\\ \hline Cat. & & & \\ Solvent, 60 \ ^{\circ}C & R^1 & R^2 & 5 \end{array}$
Entry	R^1	R^2	R^3	Yield (%)
1	CH ₂ Cl	<i>t</i> -Bu	<i>i</i> -Pr	5b (33)
2	CH ₂ Cl	$(CH_2)_2Ar$	<i>b i</i> -Pr	5c (53)
3	CH_2Cl	CH_2Ar^c	<i>i</i> -Pr	5d (29)
4	CH ₂ Cl	Су	Et	5e (45)
5	CH ₂ Cl	(CH ₂) ₂ Ar	^b Et	5f (56)
6	$CHCl_2$	Су	<i>i</i> -Pr	5g (48, Z:E=2:1)
7	$CHCl_2$	(CH ₂) ₂ Ar	<i>b i</i> -Pr	5h (48, Z:E=2:1)
8	CHClCH ₃	Су	<i>i</i> -Pr	5i (70, Z:E=5:1)
9	CHClCH ₃	(CH ₂) ₂ Ar	<i>i</i> -Pr	5j (49, Z:E=3.7:1)

^{*a*} Isolated yields. ^{*b*} Ar =3,4-(MeO)₂C₆H₄. ^{*c*} Ar =4-MeOC₆H₄.

The nature of the starting phosphite does not seem to have a strong influence on the yields as triethyl and triisopropyl phosphites afford both **5** in moderate yields. Even though the latter may be considered as rather low, it must be stressed that the sequence involves several synthetic steps. Besides first a Nef and Perkow reaction, intermediate amidine formation then cyclization and final aromatization occurs in a single operation in one-pot. The lower yields observed with *tert*-butyl and 4-methoxybenzyl isocyanides may be explained by steric reasons and possible isomerizations previously observed for benzylic isocyanides in the Nef reaction.⁹ Beside chloroacetyl chloride **1a** (Table 2, entries 1-5), we have used dichloroacetyl chloride **1b** (Table 2, entries 6,7) as well as 2-chloropropionyl chloride **1c** (Table 2, entries 8,9) which lead to mixtures of alkenes as classically observed in Perkow reactions.¹⁰ When **1b** and **1c** were used the Z alkene was always obtained as the major isomer, its geometry could be determined considering the ³J_{P-H} coupling constant with the vinylic proton.¹⁰

Following the successful use of aromatic acyl chlorides in our previous Nef/Perkow/Mumm study,⁸ we also examined the possible formation of benzimidazoles from p-fluorobenzoyl chloride. In this case, the Nef/Perkow steps lead to the intermediate formation of ketenimines. In contrast to what was observed with carboxylic acids,⁸ the ketenimine intermediate **6a** failed to give any adduct with propargylamine under conditions close to the ones optimized for chloroacetyl chlorides (Scheme 2, DIPEA was not used in this case). Longer reaction times and higher temperatures led to the decomposition of the Nef/Perkow intermediate. The lack of reactivity of **6a** towards the amines was quite surprising considering the known reactivity of ketenimines towards amines.¹¹ Reasoning that the phosphate moiety of **6a** might lower its electrophilic nature and prevent it to react with the amine, we next examined the behavior of a more electrophilic starting acyl chloride (ethyl oxalyl chloride). Rewardingly, the expected imidazole formation could now be observed in moderate overall yields (Scheme 2, **7b** and **7c**).



Scheme 2. Imidazoles 7 from Nef/Perkow ketenimines 6

In conclusion, we have disclosed a three-steps four-component formation of imidazoles from phosphites, acyl chlorides, isocyanides and propargylamine. The work further demonstrates the potential of Nef/Perkow adducts which may act as electrophiles towards amines if highly electron-deficient acylchlorides are used as starting material. The extension of this strategy to less electrophilic ketenimine intermediates is still under study.

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.