Isocyanide Addition to Acylphosphonates: A Formal Passerini Reaction of Acyl Chlorides

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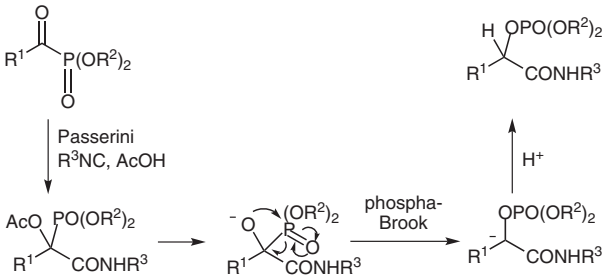
Abstract: Acylphosphonates behave as carbonyl components in Passerini reactions with isocyanides and carboxylic acids. Under saponification, the adducts undergo a phospha-Brook rearrangement to form α-amidophosphates. As acylphosphonates are quantitatively formed from carboxylic derivatives, this new reductive procedure allows acyl chlorides to react as aldehydes in a Passerini-type reaction.

Key words: phosphonate, isocyanide, multicomponent reaction, Passerini reaction

The synthetic interest in isocyanides is traditionally associated with their interaction with aldehydes and ketones as disclosed in the Ugi and Passerini reactions.[1] Discovered much earlier by Nef,[2] the reaction of isocyanides with acyl chlorides is, however, less documented.[3] Reinvestigated more recently by Ugi,[3a] this reaction gives imidoyl chloride intermediates which can be either hydrolyzed to ketoamides or trapped to form various cyclic adducts. In contrast to the Ugi and Passerini reactions, the interaction between isocyanides and acyl chlorides often requires heating to give adducts in moderate yield due to partial polymerization under these conditions.[4] More efficient Nef-type reactions could be obtained with highly electrophilic acid derivatives such as trifluoroacetic anhydride[5] or acyl bromides which were shown to be more reactive than the corresponding chlorides.[3b]

We envisioned that the choice of a leaving group less prone to nucleophilic displacement on the acyl moiety could allow the acyl derivative to react as a ketone with isocyanides in a Passerini-type reaction. The removal of the leaving group could then be performed directly from the Passerini adduct. Interesting work in this direction has been achieved recently with acyl cyanides. Indeed, the cyano group allows the starting material to react as an activated ketone, the resulting cyano amide being selectively reduced to an amine in a further step.[6]

Following our studies on α-hydroxyphosphonate–phosphate rearrangement (phospha-Brook),[7] we surmised that a Passerini reaction of acylphosphonate could settle the proper functionalities for efficient phospha-Brook rearrangements (Scheme 1).



Scheme 1 Passerini reaction coupled with phospha-Brook rearrangement

Acylphosphonate **2a** was quantitatively formed under treatment of acyl chloride **1a** with trimethyl phosphite in a solvent-free Arbuzov-type reaction. Toluene was then added to **2a**, followed by cyclohexylisocyanide (**3a**) and acetic acid (**4a**). After 24 hours under an argon atmosphere at room temperature, the Passerini adduct **5a** was formed in a 74% isolated yield showing that the carbon–phosphorous bond is relatively stable in the process (Table 1).

Different acyl chlorides **1a**–**f** behaved similarly with various isocyanides and carboxylic acids forming hydroxyphosphonoamide derivatives **5a**–**n** in moderate to good yields. Aliphatic as well as aromatic acyl chloride reacted under these additions. The aromatic acyl chlorides (entries 12–14) were, however, less efficient and the addition with isocyanides required heating for the reaction to reach completion. The formation of aryl-substituted phosphonates such as **5l**, **5m** or **5n** was most noteworthy as these compounds have never been prepared before (the related esters are unknown as well). Dimethyl acylphosphonates were the most efficient acyl intermediates; the diethyl and diisopropyl analogues gave adducts in lower yields probably due to steric factors.

α-Hydroxyphosphonate derivatives are interesting compounds displaying both pharmaceutical and agrochemical activities.[8] These compounds are usually prepared by basic treatment of carbonyl derivatives with dialkyl phosphites.[9] These additions are highly efficient except for carbonyl derivatives substituted with electron-withdrawing groups; in these latter cases, phosphate derivatives are easily obtained along with the expected phosphonates.[10] Indeed, under basic treatment, hydroxyphosphonates may undergo a 1,2-shift of the phosphoryl group to give phosphates. Close to the Brook rearrangement of silyl derivatives, this phosphoryl migration discovered more than 50

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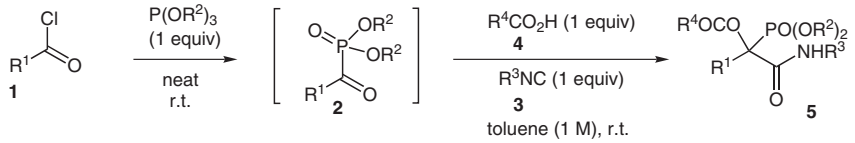
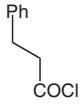
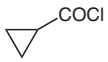
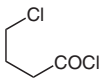
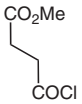
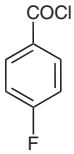
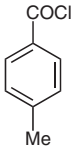
years ago is often coined as the phospha-Brook (PB) rearrangement (Scheme 1).[11]

This equilibrium is shifted toward the phosphate only if anion-stabilizing groups are tethered to the carbon bearing the phosphonate.

The phospha-Brook rearrangement is observed when simple acylphosphonates are treated with nucleophiles such as dialkyl phosphite[12] and cyanide anion.[13] By using trimethylsilyl cyanide, the intermediate oxyphosphonates can be trapped as silyloxycyanophosphonates before any

Table 1 Preparation of Hydroxyphosphonoamide Derivatives **5a–n** from Acyl Chlorides **1a–f**

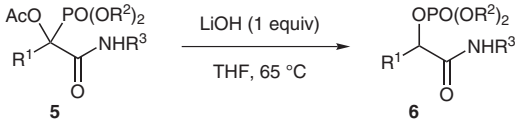


Entry	R^1COCl	R^2	R^3NC	R^4CO_2H	5 [Yield (%)]
1	 **1a**	Me	CyNC **3a**	AcOH **4a**	**5a** (74)[a]
2	**1a**	Et	**3a**	**4a**	**5b** (61)[a]
3	**1a**	Et	**3a**	$ClCH_2CO_2H$ **4b**	**5c** (58)[a]
4	**1a**	Et	*t*-BuNC **3b**	**4a**	**5d** (63)[a]
5	**1a**	*i*-Pr	**3a**	**4a**	**5e** (67)[a]
6	**1a**	*i*-Pr	*t*-OctNC **3c**	**4a**	**5f** (59)[a]
7		*i*-Pr	**3b**	**4a**	**5g** (40)[a]
8	 **1c**	*i*-Pr	**3b**	**4a**	**5h** (56)[a]
9	**1c**	Me	**3a**	**4a**	**5i** (78)[a]
10	 **1d**	Me	**3b**	**4a**	**5j** (73)[a]
11	**1a**	Et	**3b**	Me_3CCO_2H **4c**	**5k** (59)[a]
12	 **1e**	Et	**3b**	**4a**	**5l** (56)[b]
13	**1e**	Me	**3a**	**4a**	**5m** (76)[b]
14	 **1f**	Et	**3b**	**4a**	**5n** (54)[b]

[a] Equimolar amount of phosphite was added to neat acyl chloride. After 1 h at r.t., evaporation of residual alkyl chloride was followed by the addition of toluene (1 M) and an equimolar amount of isocyanide and carboxylic acid. The Passerini adduct was obtained after 24 h at r.t.
[b] The Passerini reaction was performed at 80 °C for 24 h.

phospha-Brook rearrangement.[14] Isocyanides behave similarly in conjunction with carboxylic acids. Under saponification conditions, release of the alkoxide should trigger the rearrangement. Indeed, when phosphonates **5** were treated with one equivalent of LiOH in THF and the mixture was heated at 65 °C, the new amidophosphates **6** were formed in quantitative yield (Table 2).

Table 2 Phospha-Brook Rearrangement



R^1	R^2	R^3	Yield
$PhCH_2CH_2$	Et	*t*-Bu	quant
$PhCH_2CH_2$	Me	Cy	quant
$PhCH_2CH_2$	*i*-Pr	Cy	quant
4-MeC_6H_4	Et	*t*-Bu	quant

In conclusion, we have used acyl chlorides as formal aldehyde partners in a Passerini-type reaction with isocyanides and phosphoric acids.[15] To the best of our knowledge, Passerini reactions with phosphoric acid derivatives have never been described in the literature. In allowing the preparation of amidophosphonates, important phosphoryl analogues of amino acids, this new strategy extends the scope of the Passerini reaction. Further interactions of phosphonates with isocyanides are under study in our research group.

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(15) **General Procedure for the Formation of Phosphonate 5**: To acyl chloride **1** (2 mmol) was added neat trialkyl phosphite (1 equiv). The mixture was stirred under argon for 30 min. Toluene (1 M), isocyanide (1 equiv) and carboxylic acid (1 equiv) were then successively added. The mixture was stirred for 24 h under argon at r.t. (for alkyl acyl chlorides) or at 80 °C (for aromatic acyl chlorides). The solvent was then removed under reduced pressure to afford Passerini products after purification by flash column chromatography on silica gel. Data for **5a**: mp 72–74 °C; R_f (EtOAc–PE, 50:50): 0.1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.33 (m, 2 H), 7.18–7.24 (m, 3 H), 6.73 (d, *J* = 8.3 Hz, 1 H), 3.84–3.88 (m, 1 H), 3.88 (d, J_{H-P} = 10.8 Hz, 3 H), 3.84 (d, J_{H-P} = 10.6 Hz, 3 H), 2.69–2.80 (m, 1 H), 2.56–2.69 (m, 3 H), 2.18 (s, 3 H), 1.91–1.99 (m, 2 H), 1.68–1.78 (m, 2 H), 1.59–1.66 (m, 1 H), 1.33–1.47 (m, 2 H), 1.17–1.32 (m, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.1 (d, J_{C-P} = 5.9 Hz), 165.2 (d, J_{C-P} = 4.4 Hz), 141.4, 129.0, 128.9, 126.5, 83.3 (d, J_{C-P} = 152.2 Hz), 55.1 (d, J_{C-P} = 6.6 Hz), 54.5 (d, J_{C-P} = 7.3 Hz), 49.1, 35.6, 33.2, 33.1, 30.5 (d, J_{C-P} = 7.3 Hz), 25.9, 25.1, 21.6. IR (thin film): 3328, 3027, 2987, 1749, 1669, 1531, 1259, 1222, 1020 cm^{-1}. HRMS: *m/z* calcd for $C_{20}H_{30}NO_6P$: 411.1811; found: 411.1810.
Typical Procedure for the Conversion of 5a to 6a: To a solution of LiOH (1 mmol) in anhyd THF (0.25 M) was added **5a** (1 equiv). The mixture was heated for 2 d at 65 °C under argon. After evaporation of the solvent under reduced pressure, the remaining salts were removed by washing the

residue with a 1:1 mixture of CH_2Cl_2 and PE followed by filtration. Evaporation of the solvent gave **6a** as a yellow oil in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.30 (m, 2 H), 7.13–7.22 (m, 3 H), 6.46 (d, *J* = 7.6 Hz, 1 H), 4.70–4.78 (m, 1 H), 3.80 (d, J_{H-P} = 10.9 Hz, 6 H), 3.75–3.83 (m, 1 H), 2.65–2.76 (m, 2 H), 2.16–2.25 (m, 2 H), 1.83–1.94 (m, 2 H), 1.65–1.76 (m, 2 H), 1.55–1.65 (m, 1 H), 1.27–1.43 (m, 2 H), 1.10–1.27 (m, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 168.5 (d, J_{C-P} = 4.4 Hz), 141.1, 128.9, 128.8, 126.5, 78.2 (d, J_{C-P} = 6.6 Hz), 55.2 (d, J_{C-P} = 6.6 Hz), 55.1 (d, J_{C-P} = 6.6 Hz), 48.5, 35.3 (d, J_{C-P} = 4.4 Hz), 33.4, 33.2, 30.8, 25.8, 25.1. IR (thin film): 3298, 2932, 2856, 1668, 1536, 1452, 1267, 1051 cm^{-1}. HRMS: *m*/*z* calcd for $C_{18}H_{28}NO_5P$: 369.1705; found: 369.1700.