Synthesis of phosphorus esters by transesterification mediated by *N*-heterocyclic carbenes (NHCs)†

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Received (in Bloomington, IN, USA) 11th July 2005, Accepted 23rd August 2005
First published as an Advance Article on the web 3rd October 2005
DOI: 10.1039/b509783e

The versatile nucleophilic organic catalysts *N*-heterocyclic carbenes (NHCs) have been shown to effectively mediate the transesterification of phosphorus esters under mild conditions; user-friendly imidazolium salts can also be employed as pre-catalysts.

Phosphorus esters are important functional groups in organic synthetic chemistry. They not only play an important role as protective groups in pharmaceuticals[1] but are also used as reagents in organic transformations (*e.g.* Wadsworth–Emmons reaction)[2] or in the development of analytical tools.[3] Moreover, on the industrial scale, *P*-esters find applications in agrochemicals as fertilizers,[4] pesticides[5] and insecticides.[6] The major means of preparation of *P*-esters involve alkyl dichlorophosphines or the Michaelis–Arbuzov reaction. While the dichlorophosphines are usually expensive, the Michaelis–Arbuzov[7] reaction suffers from low yields when hindered substrates are used. Gagné has reported on the use of alkali metal alkoxide clusters as efficient catalysts for the ester interchange reaction leading to phosphorus esters.[8] A method relying on $Ti(OR)_4$/ROH catalyzed transesterification has also been reported but suffers from long reaction times and a lack of reactivity towards phosphonates.[9] An inexpensive, metal-free, catalytic protocol for the synthesis of phosphorus esters *via* transesterification would have a significant impact on the accessibility of this class of compounds.

We previously reported on the use of *N*-heterocyclic carbenes (NHCs) as efficient transesterification catalysts for primary and secondary alcohols.[10] We have extended this methodology to now include *P*-esters as substrates, achieving excellent yields using mild conditions (Scheme 1). Phosphonate esters, which are usually unreactive using the Michaelis–Arbuzov protocol, undergo transesterification effectively with the use of various NHCs as catalysts.

Extensive works by Wanzlick,[11] Bertrand,[12] Arduengo[13] and others[14] have shown that the singlet nucleophilic carbenes are neutral compounds having a divalent carbon atom with two non-bonding electrons. Non-toxicity, a non-pyrophoric nature and tunable sterics and electronics have helped establish NHCs as versatile nucleophilic organic catalysts effectively mediating organic transformations.[15–23] The screening of various NHCs in the reaction involving dimethyl methylphosphonate (DMMP) with benzyl alcohol showed the alkyl substituted NHCs, ICy {1,3-bis(cyclohexyl)imidazol-2-ylidene}, IAd {1,3-bis(adamantyl)-imidazol-2-ylidene} and I^{t}Bu {1,3-bis(*tert*-butyl)imidazol-2-ylidene} are capable mediators in this transesterification reaction. The cyclohexyl substituted NHC, ICy, was found to be the best catalyst giving a good yield in only 2 hours (entry 1, Table 1). Better yields can be obtained on increasing the reaction time but this allows for an increase in formation of diesterified product (entry 2, Table 1). Sterically demanding, alkyl substituted NHCs, IAd and I^{t}Bu, provide moderate yields.[24] The aryl substituted NHCs, which are less nucleophilic than the alkyl substituted counterparts,[14,25] did not show activity in this transformation. Even on increasing the catalyst loading, IPr {1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene} and IMes {1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene} did not furnish the desired product.[26]

To fully exploit the potential of this reaction, we examined a wide array of conditions. The data presented in Table 2 illustrate the effect of various parameters on the efficiency of this protocol. Since transesterification is an equilibrium process, removal of products from the reaction mixture drives the reaction in the forward direction. This is achieved by use of molecular sieves (4 Å) that absorb the methanol formed in the course of the reaction and improve conversion. Initially similar conversions are observed in

Scheme 1 NHC catalyzed transesterification of *P*-esters.

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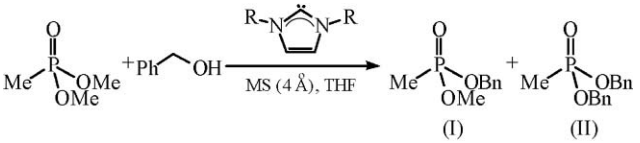
† Electronic supplementary information (ESI) available: Experimental details. See http://dx.doi.org/10.1039/b509783e

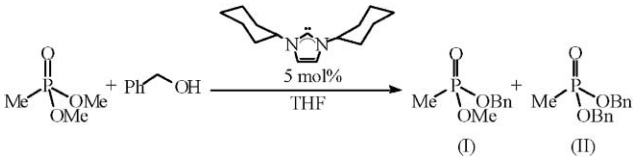
Table 1 Screening of *N*-heterocyclic carbenes[a]



Entry	Catalyst	Time (h)	Yield (%)	Product ratio (I:II)
1	R = Cyclohexyl	2	71	90:10
2	R = Cyclohexyl	8	90	75:25
3	R = Adamantyl	2	35	100:0
4	R = *tert*-Butyl	2	32	100:0
5	R = 2,6-Diisopropylphenyl	18	0	—
6	R = 2,4,6-Trimethylphenyl	18	0	—

[a] Reaction conditions: 5 mol% catalyst, 1 mmol of DMMP, 1 mmol of BnOH, 0.5 g of molecular sieves, 1 mL of THF, NMR yields (average of two runs).

Table 2 Impact of variation of reaction parameters on NHC catalyzed transesterification of *P*-esters[a]



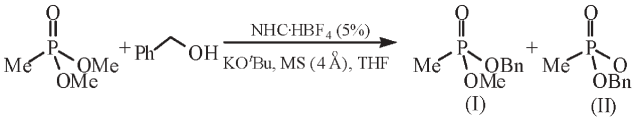
Entry	Conditions	Time (h)	Yield (%)	Product ratio (I:II)
1	No MS	2	67	100:0
2	No MS	8	70	100:0
3	With MS	2	71	90:10
4	With MS	8	90	75:25
5	$T = 40$ °C	2	87	60:40
6	2 equiv. Bn–OH	2	75	100:0
7	2 equiv. Bn–OH	36	100	45:55
8	2 equiv. Bn–OH	120	100	36:64
9	EDPP[b]	6	72	—

[a] Standard reaction conditions: 5 mol% catalyst, 1 mmol of DMMP, 1 mmol of BnOH, 0.5 g of molecular sieves (4 Å), 1 mL of THF, NMR yields (average of two runs). [b] EDPP = ethyl diphenylphosphonite: 0.5 g of molecular sieves (5 Å).

reactions with and without molecular sieves. However, on allowing the reaction to stir for longer time periods, a significant difference in conversion can be observed (entries 1–4, Table 2). Moreover, formation of only mono-esterified product in the absence of molecular sieves is indicative of the reaction being reversible under equilibrium conditions, rather than undergoing a second esterification.[27] Not surprisingly, an increase in temperature has a favorable effect on conversion. However, the selectivity suffers in this case and an increase in formation of the diesterified product is observed (entries 3 and 5, Table 2). The effect of excess alcohol was also studied. On conducting the reaction over a longer time period, quantitative conversion with loss of selectivity was observed (entries 7 and 8, Table 2). To increase the scope of the reaction, ethyl diphenylphosphonite was also tested. The reaction proceeded to furnish the product in good yield (entry 9, Table 2). Various reactions presented in Table 2 reveal simple and efficient ways to alter the final outcome of the reaction, providing flexibility to the protocol.[28]

To render the protocol more user-friendly, various commercially available, NHC pre-catalysts were also tested for activity. The use of ionic liquid, bmim·HBF_4 (*N*,*N*′-butylmethylimidazol-2-ylidene) is of particular interest since it demonstrated good conversion, with preferential formation of the mono-esterified product in >80% yield (entry 1, Table 3). The imidazolium salts of ICy, IAd and I^{t}Bu also furnished moderate to good yields under similar conditions with ICy·HBF_4 proving to be the best pre-catalyst for this transformation.[29] To achieve better selectivity in the *in situ* generated-carbene-protocol, experiments were performed with a slight change in experimental conditions. ICy·HBF_4 was employed in the usual reaction conditions without the presence of molecular sieves (entry 3, Table 3). Better selectivity was achieved under these conditions. However, product conversion suffered because of the absence of molecular sieves. The reaction did not proceed further than 55% conversion after 24 h. Interestingly, no change in selectivity was observed after allowing the reaction to proceed for 24 h.

Table 3 *In situ* generation of catalyst[a]



Entry	Catalyst precursor	Time (h)	Yield (%)	Product ratio (I:II)
1	bmim·HBF_4	6	84	81:19
2	ICy·HBF_4	3	71	70:30
3	ICy·HBF_4	3	46[b]	85:15
4	IAd·HBF_4	3	58	63:37
5	I^{t}Bu·HBF_4	12	72	60:40

[a] Reaction conditions: 5 mol% catalyst, 0.9 equiv. base, 1 mmol of DMMP, 1 mmol of BnOH, 0.5 g of molecular sieves, 1 mL of THF, NMR yields (average of two runs). [b] No molecular sieves.

An additional important use of phosphorus esters is in the manufacture of chemical nerve agents. Chemical weapons such as VX {*S*-2-(diisopropylamino)ethyl *O*-ethyl methylphosphonothioate} and GB-Sarin are various forms of *P*-esters. These agents inhibit the control of acetylcholinesterase over the central nervous system by reacting with this enzyme in an irreversible fashion.[6,30] Recent developments have brought attention to chemical weapons, especially methods for their detoxification/decommission. The usual methods of detoxification of the nerve agent VX are incineration and chemical neutralization. However, these methods suffer from limitations making them unacceptable. Chemical detoxification in particular suffers from the release of harmful side products in yields as high as 15%.[31] Moreover, the reagents have to be used in stoichiometric amounts. Metal catalyzed methods for chemical detoxification of VX nerve agent have been proposed.[32] The NHC mediated transesterification of *P*-esters could be an attractive alternative to the conventional methods of VX detoxification. Since methyl and ethyl esters are more difficult to cleave compared to benzyl esters,[27] we propose that, using the described methodology, the properties of *P*-esters can be altered to render them innocuous.[33]

In summary, an organocatalytic approach for the synthesis of phosphorus esters is described. Various parameters affecting the transformation have been examined. Applications of this method can range from synthesis of pharmaceutically important molecules to detoxification of *P*-ester nerve agents. Efforts aimed at expanding the scope of this user-friendly reaction and understanding its mechanism are presently underway.

Support of this work from the National Science Foundation is gratefully acknowledged.

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