NEW CONDENSING REAGENTS: THIOPHOSPHORUS COMPOUNDS ACTIVATED BY 2-OXAZOLONE AND 2-BENZOXAZOLINONE HETEROCYCLES

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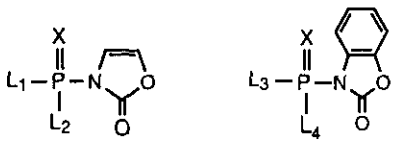
Abstract—The thiophosphorus compounds (**3** - **6**) activated by 2-oxazolone and 2-benzoxazolinone heterocycles, which have the advantages of high solubility in organic solvents and good preservability, serve well as versatile condensing reagents for one-step formation of amides including β-lactams, esters and thioesters from carboxylic acids.

The five and six-membered heterocycles such as imidazole, triazole, 2-oxazolone, 2-thiazolidinethione and 2-pyridinethiol play a crucial role in activating the carboxyl groups for acylations and condensations as the bifunctional leaving moieties.[1] Based on the excellent leaving ability of 2-oxazolone skeletons, we previously developed the types (**1**) and (**2**) of phosphorus compounds (*X=O*) *as the promising reagents for facile formation of amides* and thioesters,[2] and for the phosphorylation of alcohols.[3] Among them, highly reactive tris(2-



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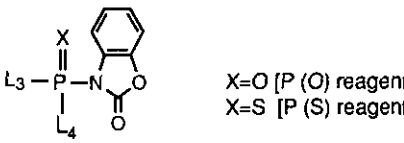

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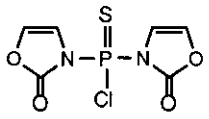
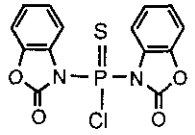
X=O [P (O) reagents]
X=S [P (S) reagents]

oxo-3-oxazolinyl) and tris(2-oxo-3 -benzoxazolinyl)phosphine oxides were found of particular use owing to their remarkable activity for the intramolecular condensation of β-amino acids to bicyclic β-lactams such as penam[4] and cepham.[5] There is, however, still ongoing need to improve the low solubility in organic solvents and the moisture lability of these compounds.

This paper describes the preparation of thiophosphorus compounds (**1**, X=S) and (**2**, X=S) activated by 2-oxazolone and 2-benzoxazolinone moieties which serve well as the condensing agents for amides, esters and thioesters. Among such types of thiophosphorus compounds examined, the derivatives activated by more than two heterocycles such as (**3-6**) were reactive enough to serve as efficient condensing agents for amides and esters. The types (**1**) and (**2**) of thiophosphonates and thiophosphinates (X=S, L_1 and/or L_2=alkoxy, aryloxy) were unsatisfactory due to their poor reactivity, in contrast to the corresponding P(O) reagents (phosphates and phosphinates) which were sufficiently powerful for the condensation of carboxylic acids with amines or alcohols.[1,2]



3 (mp 150°C)



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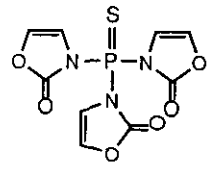
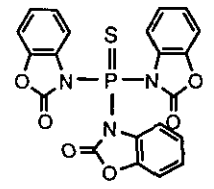


5 (mp 156°C)



6 (mp 223°C)

The reagents (**3**) and (**5**) were readily obtained as colorless crystals in 66% and 83% yield by treatment of thiophosphoryl chloride with two and three equivalent molar amounts of 2-oxazolone, respectively, in THF at room temperature. In the analogous way, 2-benzoxazolinone gave the crystalline derivatives of the reagents (**4**) and (**6**) in 34% and 70% yield, respectively. Versatility of these reagents for the direct formation of amides, esters and thioesters is shown in **Table I**, which shows the comparative data on yields obtained under the given conditions. The condensation proceeded smoothly under mild conditions as demonstrated in typical conversions of benzoic acid, except for sterically congested compounds, where longer reaction period and elevated temperature were desired to give moderate yields.

Table I Preparation of Amides, Thioesters and Esters by Thiophosphorus Reagents (**3-6**)

a) Amides(X=N) (Et_3N(2 eq.)/MeCN at room temperature for 1.5 h)

Reagent	Yield				
R(R'):	Ph(H)	$PhCH_2$(H)	$PhCH_2$($PhCH_2$)	*tert*-Bu	1-adamantyl(H)
3	71%	83%	99%	97%	94%
4	58%	76%	71%	83%	82%
5	78%	91%	95%	87%	91%
6	58%	97%	91%	83%	94%

b) Thioesters(X=S) (Et_3N(2 eq.)/MeCN at room temperature for 1.5 h)

Reagent	Yield		
R:	Bu	*sec*-Bu	*tert*-Bu*
3	93%	58%	92%
4	93%	49%	86%
5	95%	44%	40%
6	88%	33%	47%

* Et_3N(2 eq.),DMAP(1 eq.)/MeCN at room temperature for overnight.

c) Esters(X=O) (Et_3N(2 eq.),DMAP(1 eq.)/CH_2Cl_2 at room temperature for 3 h)

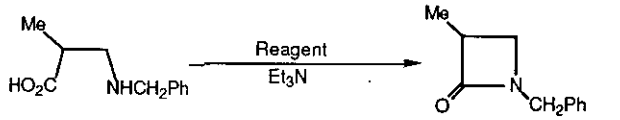
Reagent	Yield					
R: Bu	*sec*-Bu	cyclopentyl	Ph	$PhCH_2$	*tert*-Bu**
3	89%	80%	81%	83%	78%	37%
4	87%	71%	92%	91%	85%	18%

** overnight.

The reagent (**3**) was effective enough to cyclize *N*-Boc- and *N*-Benzoyl-3-aminobutyric acids into *N*-protected 2-pyrrolidones (73-76%), while it failed to give the β-lactam from *N*-Boc-2-aminopropionic acid.

Smooth intramolecular dehydration of 3-benzylaminoisobutyric acid with the P(S) reagents (**3-6**) proceeded in a boiling acetonitrile at a low concentration (~0.01 M) to give excellent yield of *N*-benzyl-3-methyl-2-azetidinone (**Table II**).

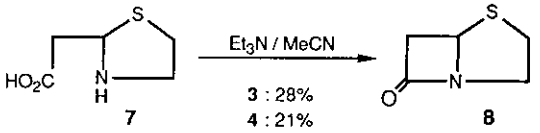
Table II Ring Closures of β-Aminopropionic Acid to β-Lactam[a]



Reagent :	3	4	5	6
Yield	96%	96%	87%	90%

a) In a boiling MeCN solution (at 0.01 M) for 4 h.

The reagents (**3**) and (**4**) were equally effective for the formation of 4-thia-1-azabicyclo-[3.2.0]heptan-7-one (**8**) (penam) from 2-thiazolidineacetic acid (**7**), but in low yield. This conversion has only one precedent [4] successfully performed by action of the P(O) reagents such as aryl bis(2-oxo-3-oxazolinyl)phosphinate and tris(2-oxo-3- oxazolinyl)phosphine oxide.



In the carboxyl activation processes, the pentacovalent thiophosphorus intermediates initially formed by coordination of the carboxylate anions at the phosphorus atom might be generally more important than other active species such as mixed anhydrides and *N*-acyloxazolides, as previously proposed for the similar type of phosphorus reagents.[1,6]

REFERENCES AND NOTES

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5. This was obtained in 61% yield from tetrahydro-1,3-thiazine-2-acetic acid. (T. Nagamatsu and T. Kunieda, unpublished result).
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