Cyclopropylphosphine oxides, new reagents for the synthesis of five-membered heterocycles

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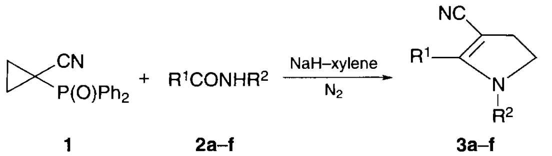
Cyclopropylphosphine oxides react with the salts of *N*-alkylamides, *N*-arylamides and phthalimide to produce dihydropyrrole derivatives in moderate to good yields.

Cyclopropylphosphonium salts react with the salts of α-carbonyl nucleophiles *via* a ring opening reaction and intramolecular Wittig–Horner reaction to form five-membered ring compounds.[1,2] However, these reagents are very difficult to prepare,[3–5] and the reactions are usually very slow. There is, to our knowledge, no report on the reaction of these reagents with salts of amides.

On the other hand, cyclopropylphosphine oxides, such as (1-cyanocyclopropyl)diphenylphosphine oxide **1**[6] and (1-ethoxycarbonylcyclopropyl)diphenylphosphine oxide **9**[7] can be easily prepared from the corresponding methylenephosphine oxides and 1,2-dibromoethane under phase-transfer catalysed conditions. We report here the reaction of these reagents and the salts of *N*-alkylamides, *N*-arylamides and phthalimide.

When (1-cyanocyclopropyl)diphenylphosphine oxide **1** was heated at 130–165 °C in xylene under nitrogen with sodium salts of *N*-monosubstituted amides **2**, reaction took place rapidly to produce the corresponding 2,3-dihydropyrroles **3**† in good yields (Scheme 1, Table 1).

This reaction may proceed *via* a ring-opening reaction and ensuing intramolecular Wittig–Horner reaction. For example, when the sodium salt of *N*-pentylacetamide and **1** were refluxed in benzene, the ring-opened product **4**† was isolated (Scheme 2).



a $R^1 = H$, $R^2 = C_5H_{11}$
b $R^1 = Me$, $R^2 = C_4H_9$
c $R^1 = Me$, $R^2 = C_5H_{11}$
d $R^1 = Me$, $R^2 = Ph$
e $R^1 = Et$, $R^2 = C_4H_9$
f $R^1 = Et$, $R^2 = Ph$

Scheme 1

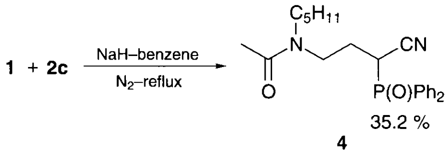
Table 1 Reaction of **1** and the sodium salts of *N*-monosubstituted amides **2**

Entry	R^1	R^2	T/°C[a]	t/h	Product **3**	Yield (%)[b]
1	H	C_5H_{11}	165	1	**a**	54.8
2	Me	C_4H_9	160	4	**b**	78.5
3	Me	C_5H_{11}	155–160	4	**c**	60.0
4	Me	Ph	130	3	**d**	55.9
5	Et	C_4H_9	140	2	**e**	45.4
6	Et	Ph	140	3	**f**	57.5

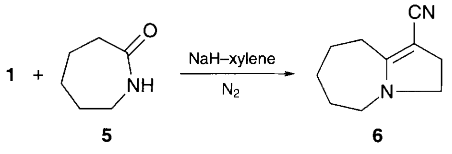
[a] Bath temperature. [b] Isolated yield.

Sodium salts of *N*-butyl- and *N*-phenyl-benzamide reacted with **1** in xylene without formation of the desired products, perhaps because the carbonyl groups in the ring-opened products are too inert to undergo further intramolecular Wittig–Horner reaction, and instead decompose under the reaction conditions. Reaction of unsubstituted amides such as acetamide and propionamide with **1** did not yield the corresponding dihydropyrroles either.

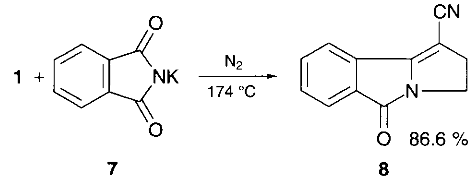
Caprolactam **5** reacted with **1** to form pyrrolo[1,2-*a*]azepine derivative **6**† in a yield of 24.7% (Scheme 3). The sodium salt of phthalimide did not react under similar conditions, but when the potassium salt of phthalimide **7** and **1** were heated directly at 174 °C under nitrogen, the desired product **8**† was isolated in high yield (Scheme 4). (1-Ethoxycarbonylcyclopropyl)-diphenylphosphine oxide **9** reacted similarly with **7** to produce the expected product **10** and *ca.* 30% dehydrogenated product **11**† (Scheme 5).



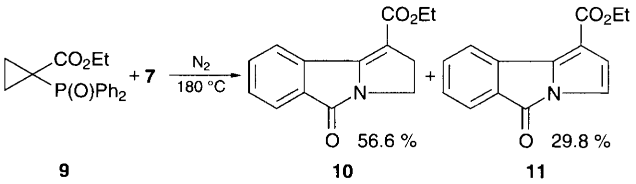
Scheme 2



Scheme 3



Scheme 4



Scheme 5

In summary, cyclopropyldiphenylphosphine oxides were found to react readily with the sodium salts of *N*-alkyl- and *N*-aryl-amides and the potassium salt of phthalimide to give dihydropyrrole derivatives through a ring-opening reaction and ensuing intramolecular Wittig–Horner reaction, in moderate to good yields, thus proving that they are novel reagents for the synthesis of these compounds.

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Footnote

† All new compounds were fully characterized by spectral means and/or microanalysis.

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