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The Addition of Alkylzinc Iodides to 1-(Phenoxycarbonyl)pyridinium Salts

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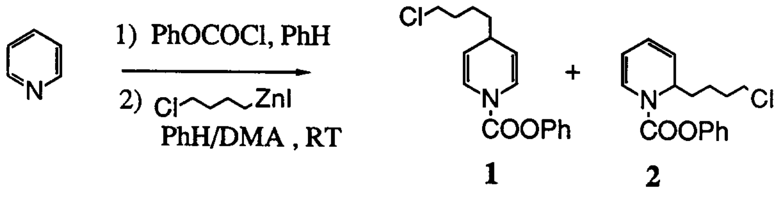
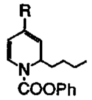
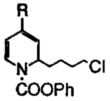
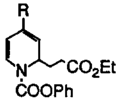
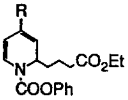
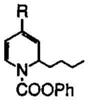
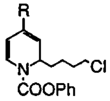
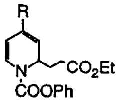
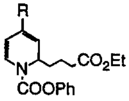
Summary: Several 1-(phenoxycarbonyl)-1,2-dihydropyridines were prepared by the addition of alkylzinc iodides to 1-(phenoxycarbonyl)pyridinium salts.

Recently, Yoshida and coworkers reported a convenient preparation of alkylzinc iodides from alkyl iodides and Zn-Cu couple.[1,2] The alkylzinc iodides are relatively mild in their reactivity and can be prepared in the presence of esters and alkyl chlorides. In the absence of a palladium catalyst, the organozinc iodides prepared in benzene-DMF were unreactive toward acid chlorides at room temperature.[1] As part of a project aimed at studying the addition of nucleophiles to 1-acylpyridinium salts,[3] we examined the reaction of various organozinc iodides with pyridines in the presence of an acyl chloride. Initial reactions using methyl or benzyl chloroformate as the acyl chloride gave little or none of the desired 1-acyldihydropyridines. However, the reaction of pyridine, phenyl chloroformate, and 4-chlorobutylzinc iodide gave a 70% yield of 1-(phenoxycarbonyl)-1,4- and 1,2-dihydropyridines 1 and 2 in a ratio of 68:32.



Substituted 1-acyldihydropyridines are useful intermediates for the synthesis of natural products.[4,5] The use of alkylzinc iodides appeared to have considerable potential for the preparation of synthetically useful 1-acyldihydropyridines that contain a functionalized side chain. To determine the scope of this synthesis, we prepared several 1-acyl-1,2-dihydropyridines 5 from various alkylzinc iodides using 4-tert-butylpyridine (3) or 4-phenylpyridine (4) and phenyl chloroformate. The results are given in the Table.

Table. Synthesis of 2-Alkyl-1-(phenoxycarbonyl)-1,2-dihydropyridines 5.

Entry	R'-ZnI[a]	R	Product[b] 5	Yield[c] %
a	n-BuZnI	t-Bu		71
b	$Cl(CH_2)_4ZnI$	t-Bu		81
c	$EtO_2C(CH_2)_2ZnI$	t-Bu		46
d	$EtO_2C(CH_2)_3ZnI$	t-Bu		35
e	n-BuZnI	Ph		71
f	$Cl(CH_2)_4ZnI$	Ph		57
g	$EtO_2C(CH_2)_2ZnI$	Ph		66
h	$EtO_2C(CH_2)_3ZnI$	Ph		47

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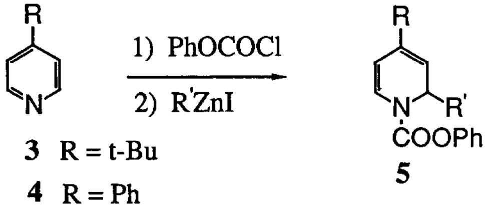
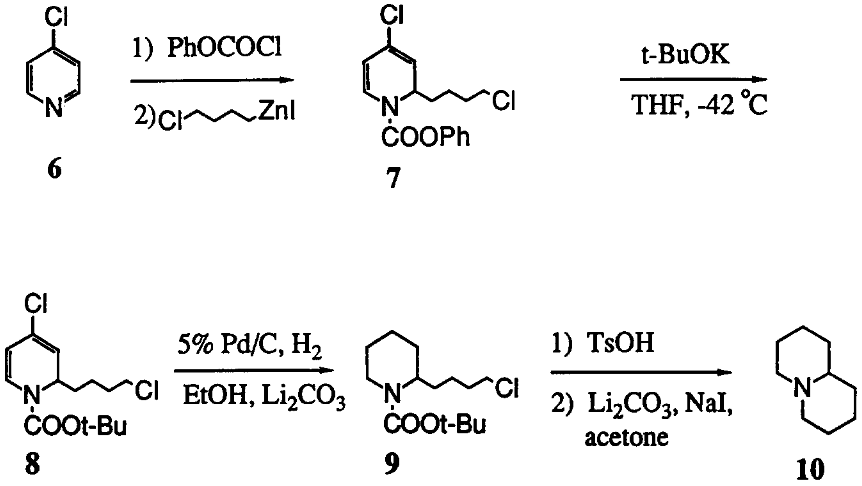
[a] Reactions were performed by slowly adding the alkylzinc iodide (benzene-DMA)[2] to the 1-(phenoxycarbonyl)pyridinium salt in benzene at kΓ. After stirring at RT for 30 min, 10% aqueous hydrochloric acid was added. Extraction with ether provided the crude products. [b] All products were clear oils and gave the expected IR and ^1H NMR spectra. Due to their instability,[6] products 5 were not submitted for elemental analysis. [c] Yields are of purified products obtained from radial-PLC (SiO_2, ethyl acetate/hexanes).



Several of the dihydropyridines 5 have the potential to be utilized as precursors to quinolizidine or indolizidine alkaloids. To demonstrate that potential, we prepared quinolizidine (10) from 4-chloropyridine (6) and 4-chlorobutylzinc iodide as shown below. The phenoxycarbony salt of 4-chloropyridine was prepared by the addition of phenyl chloroformate to 4-chloropyridine in toluene at -20°C. Addition of 4-chlorobutylzinc iodide (benzene-DMA) to this salt gave 1,2-dihydropyridine 7 in 66% yield.[7] Conversion of 7 to the N-BOC derivative 8 was accomplished using potassium tert-butoxide in THF[3d] (-42°C, 3h; 74% yield). The vinyl chloro substituent, which acted as a blocking group in the initial reaction (6 → 7), was removed by hydrogenolysis along with concomitant reduction of the dihydropyridine double bonds to give piperidine derivative 9 (87%). Removal of the N-BOC group with p-toluenesulphonic acid[8] and subsequent cyclization gave quinolizidine (10) in 60% yield. 1-Acyl-1,2-dihydropyridines of the type 5 and 7 are promising synthetic intermediates for the synthesis of quinolizidine and indolizidine alkaloids. Work is in progress to explore the synthetic utility of these heterocycles.



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