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Ethyl (tributylstannyl)acetate: A Versatile Reagent for the Carboethoxymethylation of Functionalized Pyridines

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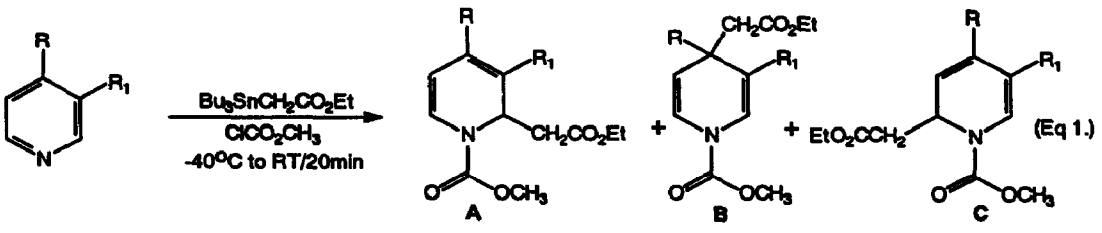
Abstract: Ethyl (tributylstannyl)acetate adds chemoselectively to acylpyridinium salts to yield a variety of dihydropyridines with diverse functional groups. These compounds are useful precursors for the preparation of a variety of N-heterocycles. The regiochemistry of the reaction is addressed and the results are rationalized based on the HSAB principle.

As part of a program directed toward the synthesis of N-heterocycles from dihydropyridines,[1] we were confronted with the problem of introducing a carboethoxymethyl group regio- and chemoselectively onto a functionalized pyridine ring system. There have been isolated reports of the addition of a carboethoxymethyl group to an unsubstituted pyridine ring employing either the Reformatsky reagent derived from ethyl bromoacetate or the titanium enolate of ethyl acetate, to yield a mixture of 1,2 and 1,4 dihydropyridines in moderate yield (58% and 68%) and selectivity (ratio of 1,2 and 1,4 dihydropyridines is 2:1).[2a,b] However, chemoselectivity is a problem with these reagents because of their tendency to add to reactive functional groups like the carbonyl group which are substituted on the pyridine ring (*vide infra*).

In tackling this problem, we were drawn toward a report by Yamaguchi et. al.,[3] who demonstrated that allyltin reagents are sufficiently nucleophilic to add to acylpyridinium salts in a regio and chemospecific manner. We wish to report here that ethyl (tributylstannyl)acetate[4] is an effective reagent in adding to acylpyridinium salts having reactive functional groups to produce a variety of useful N-heterocycles in high yield.

The general reaction is illustrated in Eq 1. A solution of a substituted pyridine and ethyl (tributylstannyl)acetate in THF at -40°C was treated with methyl chloroformate. The reaction mixture was stirred at -40°C for 20 min, then at room temperature for 15 min followed by an aq. ammonia quench. The mixture was concentrated under reduced pressure and purified by flash chromatography[5] to yield the corresponding carboethoxymethyl dihydropyridines (Table 1).



(Eq 1.)

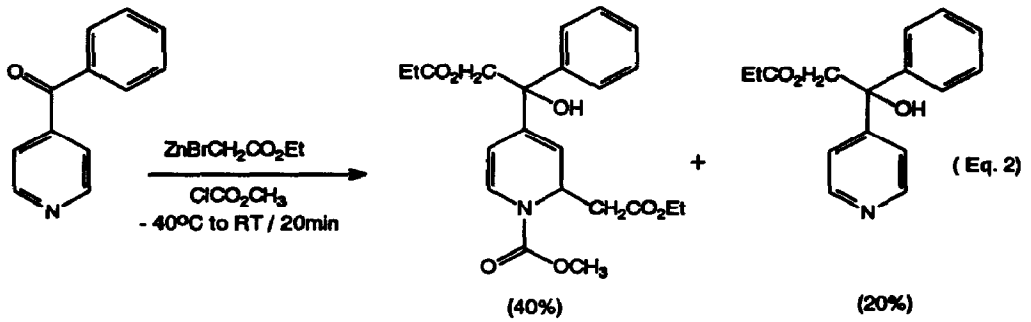
Table 1[a]

Entry		Yield (%)[b]	Ratio A:B:C[c]
1	R = R_1 = H	87	75 (65):25 (21): 0
2	R = COPh; R_1 = H	85	100 : 0 : 0
3	R = CO_2Et; R_1 = H	90	100 : 0 : 0
4	R = CN; R_1 = H	92	100 : 0 : 0
5	R = H; R_1 = Br	90	52 (47): 48 (43): 0
6	R = CHO; R_1 = H	10	0 : 100 : 0
7	R = H; R_1 = CHO	80	32 : 46 (37) : 22[d]

[a]All compounds gave satisfactory spectral data. [b]Overall yields. [c]Numbers in parenthesis refer to isolated yields of each component. [d]Combined yield of A and C isolated as a mixture was 43%. Ratio of A, C is based on the integration of the methoxy signal in the ^1H NMR spectrum.

As is evident from Table 1, ketone, aldehyde, cyano, ester and bromo groups remain unaffected during the course of the reaction. Interestingly, while functionalization of pyridine-3-carboxaldehyde occured in high yield (but with low regioselectivity), the reaction of pyridine-4-carboxaldehyde with ethyl (tributylstannyl)acetate led to extensive decomposition of the reaction mixture. We were only able to isolate and characterize the 1,4 addition product, in 10% yield from this reaction (Table 1, entry 6). This is in contrast to ethyl isonicotinate and 4-cyano pyridine which produced the 1,2 addition adducts in high yields (Table 1, entries 3, 4).

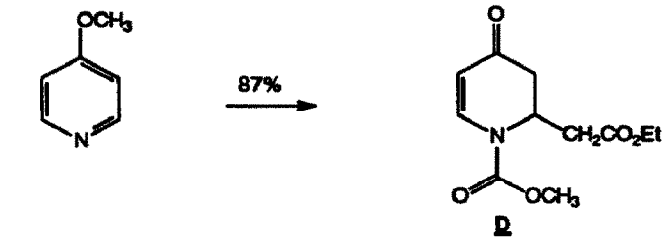
Treatment of 4-benzoylpyridine with ethyl (tributylstannyl)acetate led to the desired 1,2 dihydropyridine in very high yield (Table 1, entry 2). This is in contrast to the Reformatsky reagent generated from ethyl bromoacetate and zinc, which yielded none of the desired 1,2 addition product on reaction with 4-benzoylpyridine. Instead, products corresponding to the addition of the reagent to both the acylpyridinium salt (1,2 addition) as well as to the carbonyl group were isolated (Eq. 2). Treatment of the acylpyridinium salt of 4-benzoylpyridine with the titanium enolate of ethyl acetate[2b] gave none of the desired product. Attempted reaction of 4-benzoylpyridine with ethyl (trimethylsilyl)acetate and methyl chloroformate also did not lead to the expected products. This was expected in view of the greater nucleophilicity of tin nucleophiles over silicon nucleophiles.[6]



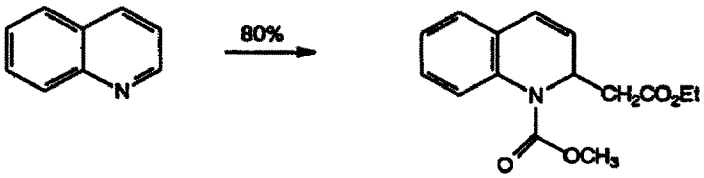
The regiochemistry of the addition of ethyl (tributylstannyl)acetate to acylpyridinium salts can be rationalized based on the hard and soft acid base (HSAB) principle.[7] For example the reaction of ethyl (tributylstannyl)acetate with pyridine and methyl chloroformate yielded a 3:1 mixture of 1,2 and 1,4 dihydropyridines (Table 1, entry 1). This indicates that ethyl (tributylstannyl)acetate lies between the "hard" alkenyl, alkynal and allyl tin reagents which undergo 1,2 addition[3] and the "soft" organocuprates which undergo 1,4 addition.[8,9] Therefore the reactivity of this reagent on the hard and soft acid base (HSAB) scale[10] is similar to that of primary Grignard reagents which give a mixture of 1,2 and 1,4 dihydropyridines when added to acylpyridinium salts.[8]

The "ortho directing effect", proposed by Sundberg et. al.,[11] may explain the formation of 1,2 and 1,4 dihydropyridine products observed in the reaction with 3-bromopyridine (Table 1, entry 5, electron donating "Br" substituent) and the poor regioselectivity observed for pyridine-3-carboxaldehyde (Table 1, entry 7, electron withdrawing formyl substituent).

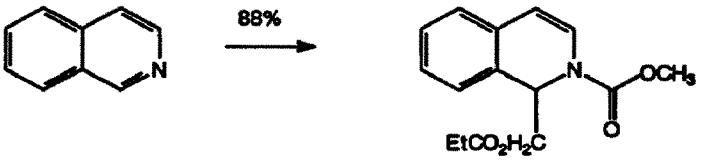
4-Methoxypyridine, a starting material widely used by Comins et. al., for the synthesis of a variety of N-heterocycles[12] gave the useful pyridone D when its acylpyridinium salt was treated with ethyl (tributylstannyl)acetate (Eq. 3).[13] In addition, the reaction of quinolinium and isoquinolinium salts with ethyl (tributylstannyl)acetate led to the corresponding dihydroquinoline and isoquinoline adducts in very high yields (Eq. 4, 5).



D (Eq. 3)



(Eq. 4)



(Eq. 5)

In conclusion, we have demonstrated that ethyl (tributylstannyl)acetate is a versatile reagent for the carboethoxymethylation of functionalized pyridines. This reagent can be made in bulk quantities, is very stable and can be stored for long periods of time unlike the corresponding Reformatsky reagent, which is not chemoselective, is moisture sensitive and has to be generated and used immediately.

These functionalized dihydropyridines, quinolines and isoquinolines can be manipulated to generate a variety of N-heterocycles, such as those belonging to the indolizidine and quinolizidine group of alkaloids.[14] These studies are in progress and will be reported in due course.

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13. Experimental procedure for the preparation of 2-carboethoxymethyl-1-(methoxycarbonyl)-2,3-dihydropyridine-4-one (compound D) (Eq. 3): To a solution of 4-methoxypyridine (0.5 g, 4.58 mmol) and ethyl (tributylstannyl)acetate (1.72 g, 4.58 mmol) in THF (10 ml) was added methyl chloroformate (0.36 ml, 4.58 mmol) over a period of 5 min. The reaction mixture was stirred at -40^{0}C for 20 min and warmed to room temperature over a period of 20 min. A solution of aq. 10% HCl was added to the reaction mixture and it was stirred at room temperature for a further 10 min. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate (20 ml) and water (10 ml). The ethyl acetate layer was dried over sodium sulfate, filtered concentrated and purified by flash chromatography employing hexane/ethyl acetate (9.5:0.5-8:2) to yield compound D as a syrup (957 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.8 (s,1H), 5.35 (s, 1H), 5.1 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.8 (s, 1H), 2.88 (dd, J = 16.9 Hz, 6.7 Hz, 1H), 2.5 - 2.7 (m, 3H), 1.26 (t, J = 7.1 , 2H).
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