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A highly regioselective indium-mediated allylation of pyridine derivatives: synthesis of (±)-dihydropinidine from pyridine

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Abstract

The preparation of various 1-acyl-1,2-dihydropyridines with high regioselectivity by indium-mediated allylation of the corresponding 1-acylpyridinium salts is demonstrated. This is applied to the synthesis of (±)-dihydropinidines.

Keywords: allylation; 1,2-dihydropyridines; high regioselectivity; indium; (±)-dihydropinidine.

Recently, there has been considerable interest in using 1-acyl-1,2-dihydropyridines as intermediates for the synthesis of natural products.[1] It has been elegantly shown by Comins, Yamaguchi and others that dihydropyridines are useful building blocks for alkaloid synthesis.[2,3] The most straightforward method for the synthesis of substituted dihydropyridines is the addition of Grignard reagents to 1-acylpyridinium salts.[4–7] However, this method suffers from the lack of regioselectivity when pyridine is used as the starting material. For example, it has been shown[8] that in the absence of a substituent at the 4-position of the 1-acylpyridinium salt, the reaction with an allyl Grignard reagent gave a mixture of 2- and 4-substituted dihydropyridines (Scheme 1). Furthermore, functional groups such as an ester or alcohol are not compatible with Grignard reagents. An alternative method using allyl tributylstannane has also been employed with limited success.[9] Thus, it would be an advantage to use an organometallic reagent that reacts regioselectively with pyridine without affecting other functional groups such as an ester.

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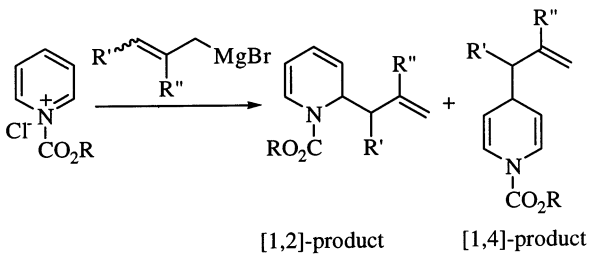
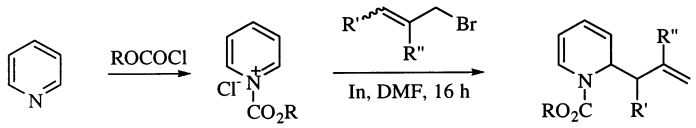


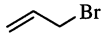
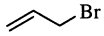
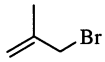
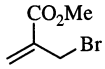
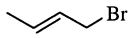
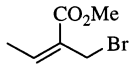
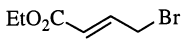
Scheme 1.

In this paper, we show that allylic indium reagents can react with 1-acylpyridinium salts to afford the corresponding 2-substituted 1,2-dihydropyridines in good yields with complete regioselectivity. In fact, to the best of our knowledge, this is the first example of the reaction of allylic indiums with pyridinium salts.

The indium-mediated allylation reactions of two different pyridinium salts with various allylic bromides were investigated (Eq. (1)). The results are summarized in Table 1. In all cases, except for the allylation reaction on the 1-ethoxycarbonylpyridinium salt (entry 1), the reactions

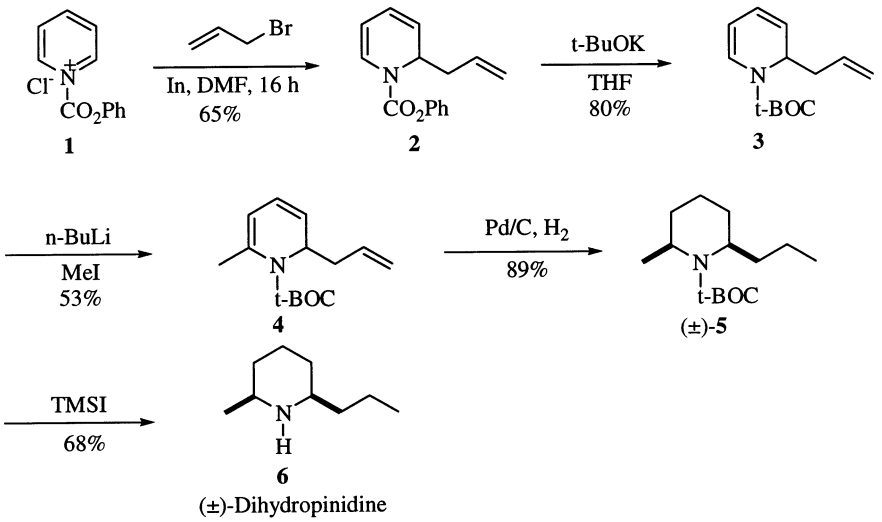
Table 1
Allylation reactions of pyridine



Entry	R	Halides	Conditions[a]	Yield (%),[b] selectivity
1	Et		In, DMF, 16 h	23
2	Ph		In, DMF, 16 h	65
3	Ph		In, DMF, 16 h	68
4	Ph		In, DMF, 16 h	70
5	Ph		In, DMF, 16 h	75 (30:70)[c]
6	Ph		In, DMF, 16 h	75 (40:60)[c]
7	Ph		In, DMF, 16 h	70 (38:62)[c]

[a] For experimental, refer to typical experimental procedure (Ref. 10).
[b] Purified yield.
[c] Relative stereochemistry not assigned.

proceeded smoothly to afford the corresponding products in moderate to high yields. Interestingly, it was found that the indium-mediated allylations of pyridine in the presence of phenyl chloroformate gave exclusively 2-substituted 1,2-dihydropyridines in DMF at room temperature. No 1,4-product was observed from ^{1}H NMR analysis. With these results in hand, we applied this strategy to the synthesis of *cis*-2,6-disubstituted piperidines. The well-characterized alkaloid (±)-dihydropinidine, which occurs naturally as (+)-dihydropinidine,[11] was chosen as the target for this study (Scheme 2).



Scheme 2. The ^{1}H and ^{13}C NMR data for compound **6**[15] are identical to the reported[16] data

Product **2** which was obtained previously was treated with potassium *t*-butoxide in THF to afford the *N*-Boc derivative **3** in 80% yield. Treatment of **3** with *n*-BuLi and MeI gave dihydropyridine **4** in 53% yield. Catalytic hydrogenation of **4** with 10% Pd/C and lithium carbonate in ethyl acetate afforded **5** in 89% yield.[12] Finally, subjecting **5** to TMSI furnished the target compound **6** in 68% yield.[12] As far as we know, this is the first method for the synthesis of (±)-dihydropinidine using pyridine as the starting material, though there have been other methods applied for the synthesis of (+)- or (−)-dihydropinidine[13] and (±)-dihydropinidine.[14] Therefore, this new strategy should be amenable to the synthesis of numerous *cis*-2,6-dialkylpiperidines.

In conclusion, we have found that indium-mediated allylation of pyridinium salts with various allylic halides affords the products in moderate to good yields with exclusive 2-regioselectivity. The efficiency of this new method has been demonstrated with a short and efficient synthesis of (±)-dihydropinidine. Efforts to develop an asymmetric version of this reaction are in progress.

Acknowledgements

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10. Typical experimental procedure: Use entry 2 in Table 1 as the example. (a) Preparation of 1-acyl-pyridinium salts: To a solution of pyridine (0.41 mL, 5 mmol) in DMF (3 mL) was added phenylchloroformate (0.63 mL, 5 mmol) at 0°C. The resulting mixture was stirred at that temperature for a few minutes. The salt solution was immediately used for the subsequent allylation reactions. (b) Allylation reactions on the 1-acyl-pyridinium salts prepared: To a solution of allyl bromide (1.27 mL, 15 mmol) in DMF (12 mL) was added indium (1.15 g, 10 mmol) at room temperature. The resulting mixture was stirred at room temperature for 4 hours. The prepared allyl bromide indium suspension was added to the freshly prepared 1-phenoxycarbonylpyridinium salt **1**. The resulting mixture was stirred for 16 hours at room temperature. Subsequently, the reaction mixture was extracted thrice with hexane:ether 1:1 (3×20 mL). The combined organic solution was washed with water (3×20 mL) and then dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to obtain the crude product as an oil. The crude product was purified by flash silica gel column chromatography with hexane: ether 8:1 to afford 0.74 g of the pure 1-(phenoxycarbonyl)-2-(2-propenyl)-1,2-dihydropiridine **2** (65% yield).
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15. ^{1}H and ^{13}C NMR data for compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.63–2.52 (m, 1H), 2.49–2.40 (m, 1H), 1.75–1.66 (m, 1H), 1.61–1.50 (m, 2H), 1.31–0.83 (m, 11H), 1.01 (d, $J=6.02$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.7, 52.3, 39.5, 34.3, 32.1, 24.7, 22.9, 19.0, 14.1; ^{1}H NMR (300 MHz, C_6D_6): δ 2.62–2.53 (m, 1H), 2.52–2.42 (m, 1H), 1.80–1.72 (m, 1H), 1.62–1.49 (m, 2H), 1.47–1.22 (m, 8H), 1.09 (d, $J=6.27$ Hz, 3H), 1.03–0.93 (m, 3H); ^{13}C NMR (75 MHz, C_6D_6): δ 56.8, 52.4, 39.9, 34.7, 32.4, 25.2, 23.1, 19.1, 14.3.

16. ^{1}H and ^{13}C NMR for the reported (±)-dihydropinidine as shown in Ref. 12: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68–2.56 (m, 1H), 2.55–2.45 (m, 1H), 1.76 (m, 1H), 1.60 (m, 2H), 1.55–0.80 (m, 8H), 1.06 (d, 3H, $J=6.6$ Hz), 0.91 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.8, 52.5, 39.7, 34.4, 32.2, 24.9, 23.1, 19.1, 14.3; ^{1}H NMR (300 MHz, C_6D_6): δ 2.52–2.42 (m, 1H), 2.40–2.32 (m, 1H), 1.69 (m, 1H), 1.48 (m, 2H), 1.35–0.80 (m, 8H), 0.99 (d, 3H, $J=6.3$ Hz), 0.88 (t, 3H, $J=6.3$ Hz); ^{13}C NMR (75 MHz, C_6D_6): δ 57.1, 52.7, 40.1, 34.8, 32.5, 25.4, 23.2, 19.3, 14.6.