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Facile Introduction of Michael Acceptors into Nitrogen Heterocycles. A New Efficient Route to Fused α-Methylene-γ-lactams

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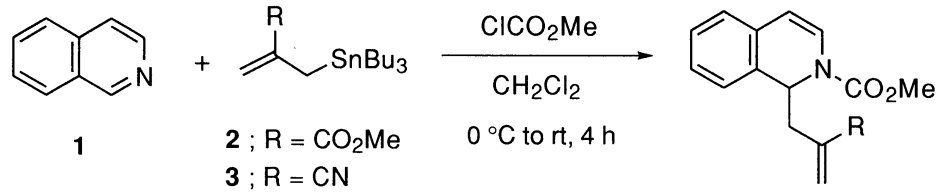
A new effective method for introduction of Michael acceptors into isoquinoline and β-carboline systems has been developed by means of tin reagents. Deprotection of the *N*-allyloxycarbonyl-1-(2-methoxycarbonyl)prop-2-enyl adducts affords novel α-methylene-γ-lactams fused with isoquinoline and β-carboline systems.

Development of effective methods for introduction of useful carbon functional groups into nitrogen heterocycles has been one of the key objectives in heterocyclic synthesis. We have reported that several kinds of tin reagents react with C=N bonds activated by a variety of acyl chlorides in a highly selective manner, providing efficient methods for introducing unsaturated carbon functional groups.[1)]

Although 2-alkoxycarbonyl- and 2-cyanoallylic tin reagents have been widely used as Michael acceptor transfer reagents in radical reactions,[2)] few nucleophilic reactions of the reagents have been reported probably due to their reduced nucelophilicity.[3)] We have recently reported that the above electron deficient allylic tin reagents show their remarkable regioselectivity in addition reactions to 4-acylpyridinium ions.[4)] We now report that 2-alkoxycarbonyl- and 2-cyanoallylic tin reagents readily react with C=N bonds incorporated in isoquinoline and β-carboline systems when activated by a variety of acyl chlorides, thus providing a convenient method to introduce the Michael acceptors into the nitrogen heterocycles. The resulting adducts may be versatile synthetic intermediates in heterocyclic synthesis.

When methyl chloroformate was added to a mixture of isoquinoline (**1**) and 2-methoxycarbonylprop-2-enyltributyltin (**2**) in dichloromethane, the addition reaction proceeded smoothly to give 2-methoxycarbonyl-1-(2-methoxycarbonyl)prop-2-enyl-1,2-dihydroisoquinoline (**4a**) in 83% yield.[5)] The similar reaction of 2-cyanoprop-2-enyltributyltin (**3**) as above gave the 1,2-adduct **4b** in 82% yield.

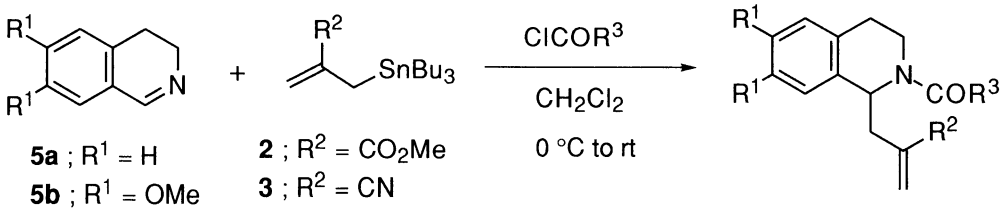


1

2 ; R = CO_2Me
3 ; R = CN

Y = 83% **4a** ; R = CO_2Me
Y = 82% **4b** ; R = CN

Furthermore, it has been found that 3,4-dihydroisoquinolines **5a** and **5b** also readily react with **2** or **3** when they are activated by a variety of acyl chlorides. The results are summarized in the Table 1.



5a ; R^1 = H
5b ; R^1 = OMe

2 ; R^2 = CO_2Me
3 ; R^2 = CN

6 ~ **14**

Table 1. Reactions of Allylic Tin Reagents (**2** and **3**) with 3,4-Dihydroisoquinolines (**5a** and **5b**) Activated by Acyl Chlorides

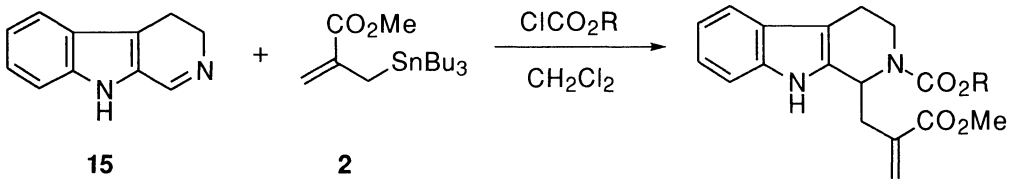
Entry	R^1	R^2	R^3	Time / h[a]	Product	Yield / %[b]
1	H (**5a**)	CO_2Me (**2**)	OMe	3	**6**	86
2	OMe (**5b**)	CO_2Me (**2**)	OMe	3.5	**7**	90
3	H (**5a**)	CN (**3**)	OMe	8	**8**	93
4	OMe (**5b**)	CN (**3**)	OMe	14	**9**	91
5	H (**5a**)	CO_2Me (**2**)	OAllyl	15	**10**	93
6	OMe (**5b**)	CO_2Me (**2**)	OAllyl	4	**11**	91
7	H (**5a**)	CO_2Me (**2**)	CH_2Br	15	**12**	80
8	H (**5a**)	CO_2Me (**2**)	$CHCl_2$	15	**13**	88
9	H (**5a**)	CN (**3**)	OAllyl	6	**14**	81

a) Reaction time at rt. b) Isolated yields.

As shown in the Table 1, Michael acceptors are readily introduced into isoquinoline systems by this simple method and a variety of acyl chlorides can be tolerated as the activating agents. Thus, α-haloacetyl groups, which may be useful functional groups, are simultaneously introduced into isoquinoline systems (entries 7 and 8).

This simple method can be also applied to the introduction of 2-methoxycarbonylallyl group into tetrahydro-β-carboline system, the 1-substituted derivatives of which are widely found in a number of indole alkaloids.[6] Thus, the reaction of **2**

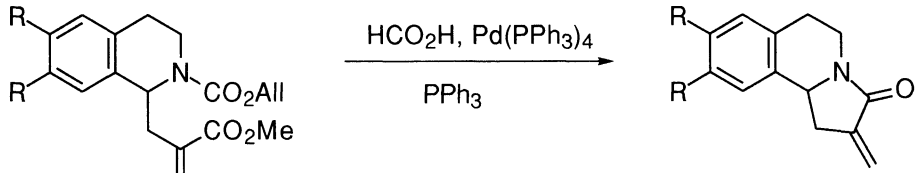
with 3,4-dihydro-β-carboline (**15**) activated by methyl chloroformate gave the adduct **16** in 85% yield. Similarly, the reaction using allyl chloroformate as the activating agent gave the adduct **17** in 84% yield.



15 **2**

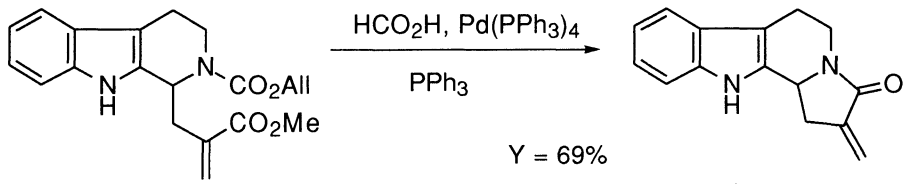
Y = 85% **16** ; R = Me
Y = 84% **17** ; R = Allyl

Next, we examined deprotection of *N*-allyloxycarbonyl groups of the adducts, because intramolecular cyclization may lead to α-methylene-γ-lactams which have been interested in their physiological activities.[7] Deprotections of the *N*-allyloxycarbonyl adducts **10**, **11**, and **17** were conducted under the usual conditions.[8] Thus, reactions of **10** and **11** with formic acid in the presence of catalytic amount of $Pd(PPh_3)_4$ and PPh_3 gave directly α-methylene-γ-lactams **18**[9] and **19** in 72 and 70% yields, respectively. Similarly, deprotection of **17** afforded a novel α-methylene-γ-lactam **20** fused with tetrahydro-β-carboline system in 69% yield.



10 ; R = H
11 ; R = OMe

Y = 72% **18** ; R = H
Y = 70% **19** ; R = OMe



17

Y = 69%

20

In summary, we have shown a new effective method for introduction of Michael acceptors into isoquinoline and β-carboline systems by means of tin reagents. Removal of *N*-allyloxycarbonyl groups affords novel fused α-methylene-γ-lactams.

References

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5) A typical experimental procedure is as follows: To a solution of **1** (138 mg, 1.07 mmol) and **2** (456 mg, 1.25 mmol) in dry CH_2Cl_2 (4 mL) was added $ClCO_2Me$ (0.10 mL, 1.3 mmol) under ice-cooling. The solution was stirred at rt for 4 h and the solvent was evaporated. The residue was chromatographed on silica gel (hexane / AcOEt = 10 / 0 to 7 / 3) to give **4a** (256 mg, 83%) as a mixture of two rotamers of the C-N bond: IR (neat) 1714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.07—6.92 (m, 4H), 6.84 6.65 (d, 1H, *J* = 7.9 Hz), 6.02 6.00 (s, 1H), 5.83 5.73 (d, 1H, *J*= 7.9 Hz), 5.49 5.35 (q, 1H, *J*= 7.6 and 5.3 Hz), 5.27 5.23 (s, 1H), 3.69 3.64 (s, 3H), 3.63 3.57 (s, 3H), 2.58—2.40 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 166.7 166.5 (s), 153.8 153.2 (s), 136.2 135.8 (s), 132.1 131.8 (s), 129.8 129.7 (s), 127.6 126.5 (d), 127.2 127.1 (d), 126.6 (t), 126.0 125.8 (d), 124.5 124.3 (d), 124.2 123.8 (d), 108.8 108.5 (d), 54.4 54.3 (d), 53.0 52.4 (q), 51.3 (q), 38.0 37.4 (t). Anal. Found: C, 66.94; H, 5.99%. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96%.

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9) Spectral and analytical data of **18**: IR (neat) 1687 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29—7.10 (m, 4H), 6.00 (s, 1H), 5.35 (s, 1H), 4.80 (t, 1H, *J* = 7.0 Hz), 4.41—4.36 (m, 1H), 3.44—3.36 (m, 1H), 3.23—3.16 (m, 1H), 3.05—2.97 (m, 1H), 2.81 (d, 1H, *J* = 16.2 Hz), 2.74—2.67 (m, 1H); ^{13}C NMR (CDCl3) δ 166.4 (s), 139.7 (s), 137.3 (s), 133.6 (s), 129.1 (d), 127.0 (d), 126.8 (d), 125.0 (d), 115.1 (t), 53.9 (d), 37.6 (t), 33.3 (t), 28.2 (t). Anal. Found: C, 78.10; H, 6.50%. Calcd for $C_{13}H_{13}NO_2$: C, 78.36; H, 6.58%.

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