Tetrahedron Letters,Vol.29,No.15,pp 1785-1788,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

REGIO- AND CHEMOSELECTIVE ADDITION OF ALKYNYLTIN REAGENTS TO THE 2-POSITION OF 3-ACYLPYRIDINES ACTIVATED BY METHYL CHLOROFORMATE: SELECTIVE SYNTHESIS OF 2,3-DISUBSTITUTED 1,2-DIHYDROPYRIDINES

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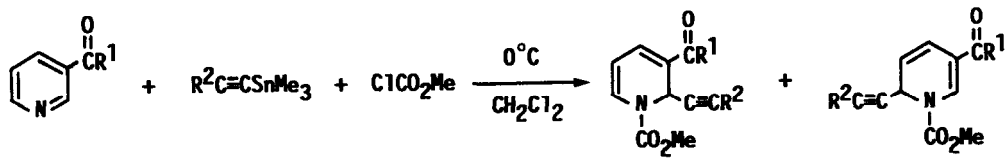
Abstract: Alkynyltin reagents add to the 2-position of 3-acylpyridines activated by methyl chloroformate regio- and chemoselectively to give 2,3-disubstituted 1,2-dihydropyridines, whereas alkynyl Grignard reagents suffer from a lack of regio- or chemoselectivity.

Nucleophilic addition of organometallic reagents to pyridinium salts has provided the valuable and convenient methods for the synthesis of 2-and 4-substituted 1,2- and 1,4-dihydropyridines, which turn to be useful synthetic intermediates for a variety of nitrogen heterocycles.[1] The regioselectivity of these reactions has been of prime importance in synthetic and mechanistic points of view and several regioselective methods have been developed so far.[2,3] In the cases of 3-substituted pyridines, it must be highly desirable and inevitable to control the regioselectivity in the 1,2- or 1,6-addition manner.[4-6] While we have reported that alkynyl Grignard reagents add to the α-position of pyridinium salts exclusively,[2a] it has been found that alkynyl Grignard reagents suffer from poor regio- and chemoselectivity in the reaction with 3-acylpyridinium salts (vide infra). In the course of our continuing interest in the chemo- and regioselective reactions of organotin reagents with nitrogen heteroaromatics activated by acyl chlorides,[2b,3g] we wish to report here that alkynyltin reagents add regio- and chemoselectively to the 2-position of 3-acylpyridines activated by methyl chloroformate to give 2,3-disubstituted 1,2-dihydropyridines predominantly.[7]



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When 1-hexynyltrimethyltin was subjected to the reaction with 3-formylpyridine activated by methyl chloroformate in dry dichloromethane under ice-cooling, the 1,2-addition took place chemo- and regioselectively to give 3-formyl-2-(1-hexynyl)-1-methoxycarbonyl-1,2-dihydropyridine (**2**, R^1=H, R^2=n-Bu) predominantly. Several alkynyltin reagents also reacted with 3-formyl-, 3-acetyl- and 3-methoxycarbonylpyridines activated by methyl chloroformate in high selectivity, as shown in Table 1. It should be mentioned here that, since alkynyltin reagents do not react with 3-acylpyridines or methyl chloroformate, the pyridinium slats do not necessarily prepared in advance and, there-

fore, 3-acylpyridines are conveniently added to a mixture of alkynyltin reagents and methyl chloroformate in dichloromethane.

Table 1. Reactions of Alkynyltin Reagents with 3-Acylpyridines (1) Activated by Methyl Chloroformate

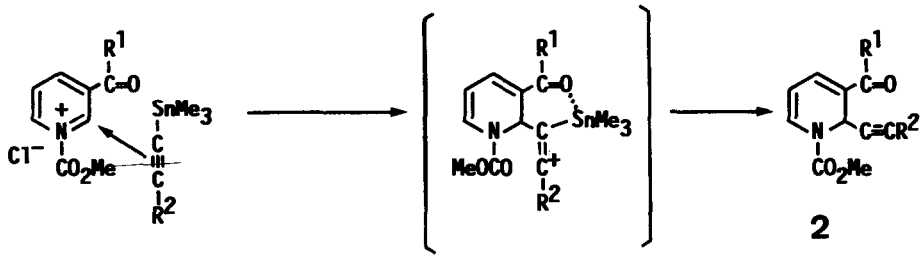
Entry	R^1	R^2	Products, 2+3 Yield(%)[a]	Ratio, 2/3[b]
1	H	n-Bu	60	93/ 7
2	Me	n-Bu	63	95/ 5
3	OMe	n-Bu	51[c]	86/14
4	H	n-Hex	63	93/ 7
5	Me	n-Hex	75	93/ 7
6	OMe	n-Hex	66	80/20
7	H	$-CH_2OBn$	--[d]	
8	H	$-(CH_2)_2OBn$	55	90/10
9	Me	$-(CH_2)_2OBn$	63	86/14
10	H	$-(CH_2)_3OBn$	68	92/ 8
11	Me	$-(CH_2)_3OBn$	68	89/11

a) Isolated yield. b) Determined by GLC and/or ^1H NMR. c) Methyl chloroformate was added to a mixture of two other reactants. d) No reaction occurred. The reason is not clear.

A typical experimental procedure is as follows: To a solution of 1-hexynyltrimethyltin (490 mg, 2.0 mmol) and methyl chloroformate (0.23 mL, 3.0 mmol) in dry CH_2Cl_2 (5 mL) was added a solution of 3-acetylpyridine (246 mg, 2.0 mmol) in CH_2Cl_2 (6 mL) under ice-cooling. The reaction mixture was stirred for 10 h at that temp., washed with water and 5% aq. HCl, and dried (Na_2SO_4). Flash chromatography on silica gel eluted by CH_2Cl_2 gave a mixture of **2** and **3** (R^1=Me, R^2=n-Bu)(331 mg, 63%) in a ratio of 95:5 by GLC analysis. **2** (R^1=Me, R^2=n-Bu): MS m/e 261 (M^+, 15), 202 (100); IR (neat) 1740, 1660, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (d, 1H, J=7.5 H), 7.00 (d, 1H, J=6 Hz), 6.15 (s, 1H), 5.57 (d.d, 1H, J=6 and 7.5 Hz), 3.86 (s, 3H), 2.33 (s, 3H), 2.00-2.20 (m, 2H), 1.10-1.60 (m, 4H), 0.70-1.10 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 194.2 (s), 153.3 (s), 132.4 (d), 131.4 (d), 128.7 (s), 104.7 (d), 83.4 (s), 77.4 (s), 53.9 (q), 41.9 (d), 30.6 (t), 25.0 (q), 21.9 (t), 18.4 (t), 13.6 (q). **3** (R^1=Me, R^2=n-Bu): MS m/e 261 (M^+, 100), 202 (90); IR (neat) 1740, 1660, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (s, 1H), 6.55 (d, 1H, J=9 Hz), 5.40-5.73 (m, 2H), 3.93 (s, 3H), 2.30 (s, 3H), 1.97-2.23 (m, 2H), 1.17-1.60 (m, 2H), 0.77-1.03 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 193.8 (s), 153.5 (s), 134.8 (d), 119.1 (d), 118.8 (d), 117.8 (s), 85.4 (s), 83.7 (s), 54.3 (q), 44.8 (d), 30.5 (t), 24.8 (q), 21.9 (t), 18.4 (t), 13.5 (q).

Very recently, Sundberg et al. reported[5] the substituent effects on the regioselectivity of hydride reduction of 3-substituted 1-alkoxycarbonylpyridinium chloride and concluded that electron donating groups at the 3-position cause the selective addition of hydride to the 2-position ("ortho" directing effect[3c,4]), whereas electron withdrawing groups, exhibit the poor regioselectivity.[8]

In contrast with the latter, alkynyltin reagents add to the 2-positions of 3-acylpyridines regioselectively. This predominant 1,2-addition over the 1,6-addition is most likely rationalized by the coordination of tin to acyl groups,[9] as shown below.[10]



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The reactions of alkynyl Grignard reagents with a few 3-substituted 1-methoxycarbonylpyridinium salts (**5**) deserve to be mentioned here. The results are summarized in Table 2. The reaction of 3-methylpyridinium salt with 1-hexynyl Grignard gave the 2,3-substituted 1,2-dihydropyridine (**6**) selectively (entry 1), in accordance with the "ortho" directing effect of 3-methyl group.[3c,4,5] However, reactions of 3-formyl and 3-acetylpyridinium salts showed poor selectivity (entries 2 and 3); the former resulted in the attack on the formyl group, the latter gave almost 1:1 mixture of 1,2- and 1,6-addition products (**6** and **7**).[11] Thus, alkynyl Grignard reagents suffer from a lack of the chemo- and regioselectivity toward 3-acylpyridinium salts.

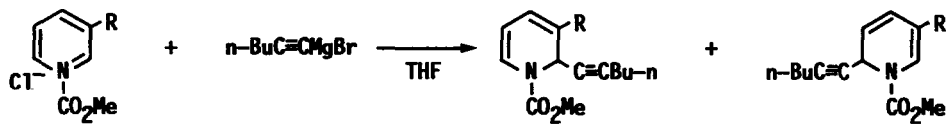

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Table 2. Reactions of Alkynyl Grignard Reagent with 3-Substituted 1-Methoxycarbonylpyridinium Chlorides (**5**).

Entry	R	Products, 6+7 Yield(%)[a]	Ratio, 6/7[b]
1	CH_3	78[c]	91/ 9
2	CHO	--[d,e]	
3	$COCH_3$	76[d]	47/53

a) Isolated yield. b) Determined by GLC and/or ^1H NMR. c) Pyridinium salt was formed in situ. d) Pyridinium salts were prepared in advance. e) Addition to formyl group took place exclusively.

Further studies on organotin methodology for selective introduction of carbon substituents into nitrogen heterocycles are under way.

We thank professor Sinpei Kozima (College of Liberal Arts and Science, Kyoto University) for helpful discussions.

References and Notes

1) For reviews on dihydropyridine chemistry: U. Eisner and J. Kuthan, Chem. Rev., 1972, 72, 1; D. M. Stout and A. I. Meyers, ibid., 1982, 82, 223.

2) For the selective α-addition: (a) R. Yamaguchi, Y. Nakazono, T. Matsuki, E. Hata, and M. Kawanisi, Bull. Chem. Soc. Jpn., 1987, 60, 215 and references cited therein; (b) R. Yamaguchi, M. Moriyasu, M. Yoshioka, and M. Kawanisi, J. Org. Chem., 1985, 50, 287; (c) R. Yamaguchi, E. Hata, T. Matsuki, and M. Kawanisi, ibid., 1987, 52, 2094; (d) M. Natsume and M. Ogawa, Heterocycles, 1983, 20, 601.

3) For the selective γ-addition: (a) E. Piers and M. Soucy, Can. J. Chem., 1974, 52, 3563; (b) K. Akiba, Y. Iseki, and M. Wada, Bull. Chem. Soc. Jpn., 1984, 57, 1994; (c) D. L. Comins and A. H. Abdullah, J. Org. Chem., 1982, 47, 4315; (d) K. Akiba, Y. Nishihara, and M. Wada, Tetrahedron Lett., 1983, 24, 5269; (e) D. L. Comins and J. D. Brown, ibid., 1984, 25, 3297; (f) A. Pelter and K. J. Gould, J. Chem. Soc. Chem. Commun., 1974, 347; (g) R. Yamaguchi, M. Moriyasu, and M. Kawanisi, Tetrahedron Lett., 1986, 27, 211.

4) Very recently, Comins and Mantlo reported the regioselective 1,6-addition of Grignard and hydride reagents to 3-trialkylstannylpyridinium salts, in which the steric bulkiness of the 3-stannyl group is supposed to control the regioselectivity: D. L. Comins and N. B. Mantlo, Tetrahedron Lett., 1987, 28, 759.

5) Sundberg et al. also recently reported the substituent effects on the regioselectivity of hydride reduction of 3-substituted 1-alkoxycarbonylpyridinium chlorides: R. J. Sundberg, G. Hamilton, and C. Trindle, J. Org. Chem., 1986, 51, 3672 and references cited therein.

6) On the other hand, the γ(1,4)-addition apparently is not affected by a variety of 3-substituents: (a) D. L. Comins, E. D. Stroud, and J. J. Herrick, Heterocycles, 1984, 22, 151; (b) D. L. Comins, R. K. Smith, and E. D. Stroud, ibid., 1984, 22, 339; (c) M. Wada, Y. Nishihara, and K. Akiba, Tetrahedron Lett., 1985, 26, 3267; (d) K. Akiba, A. Ohtani, and Y. Yamamoto, J. Org. Chem., 1986, 51, 5328. See also refs 3c and 3g.

7) To the best of our knowledge, this is the first example of the regioselective 1,2-addition of nucleophile to 3-acylpyridinium salts.[5]

8) It has been reported that electron withdrawing groups at the 3-position show the poor directing effect in the reactions with other nucleophiles. See references cited ref 5.

9) During our research, the intramolecular coordination of trialkyltin to acyl groups has been documented in the literatures: B. Jousseaume and P. Villeneuve, J. Chem. Soc. Chem. Commun., 1987, 513 and references cited therein.

10) The β-stannyl cation intermediate such as **4** has been postulated in reactions of alkynyltin reagents with electrophiles; E. Negishi, "Organometallics in Organic Synthesis", John Wiley & Sons, NY, 1980, p 417.

11) These results indicate that alkynyl Grignard reagents share the similar property with other nucleophiles which has been reported so far.[5]

(Received in Japan 20 June 1987)