Tetrahedron Letters,Vol.22,No.49,pp 4961-4964,1981 0040-4039/81/494961-04$02.00/
Printed in Great Britain

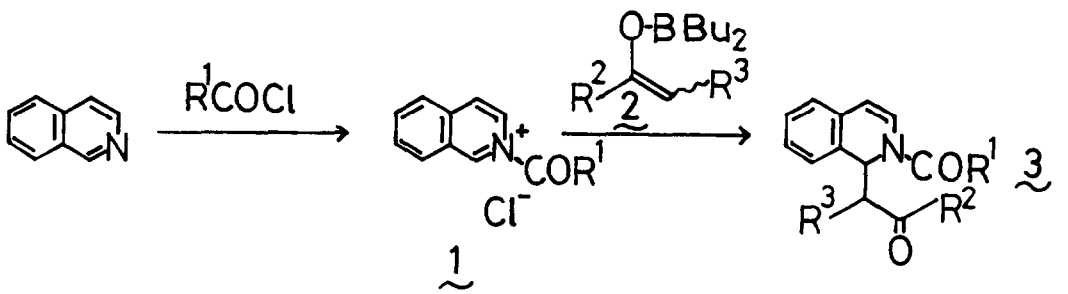
ADDITION OF BORON ENOLATES TO ISOQUINOLINIUM SALTS : A FACILE SYNTHESIS OF 1-β-KETO SUBSTITUTED 2-ETHOXYCARBONYL-1, 2-DIHYDROISOQUINOLINES AND THEIR CYCLIZATION

Kin-ya Akiba*, Kei-ichi Araki, Masayuki Nakatani, and Makoto Wada
Department of Chemistry, Faculty of Science, Hiroshima University
Higashisenda-machi, Hiroshima 730, Japan

Abstract : An efficient method to synthesize 1-β-keto substituted 2-ethoxycarbonyl (or 2-acetyl)-1, 2-dihydroisoquinolines (3) is described, utilizing boron enolates and isoquinolinium salts. The products were treated with sodium ethoxide to afford the corresponding cyclic compounds (6).

Boron enolates have been recognized as versatile reagents in organic synthesis. For example, boron enolates react with various carbonyl compounds to afford the corresponding β-hydroxycarbonyl derivatives,[1] and reaction of such boron enolates with N-bromosuccinimide or dimethyl (methylene) ammonium iodide results in a highly useful regiospecific synthesis of α-haloketones[2] or Mannich bases.[3] However, to our knowledge, the reaction of boron enolates with heteroaromatic cations[4] is hitherto unknown.

We tried to introduce a β-keto group into 1-position of isoquinoline and found that the reaction of isoquinolinium salts (1) and boron enolates (2) is the best choice to give 1-β-keto substituted 2-ethoxycarbonyl (or 2-acetyl)-1, 2-dihydroisoquinolines (3) in good yields as shown in the schme.



In order to compare the reactivity among enolates, we examined the reaction of 1a with trimethylsilyl enol ether (4)[5], lithium enolate (5)[6], and dibutylboron enolate (2a)[7] of acetophenone in ether at room temperature for 3h under nitrogen. Treatment of 1a with 4 afforded 3a in 40% yield, and when 5 was used 3a was obtained in 54% yield accompanied with unidentified products. However, the corresponding boron enolate (2a) reacted

smoothly with 1a to give 3a in an excellent yield (98%). Thus, it was found that the boron enolate is a superior nucleophilic reagent to an isoquinolinium salt (1a). Although no optimization of the yields was attempted, ether was found to be the best solvent for C-C bond formation, and dimethylsulfoxide or acetonitrile was found to be a poorer solvent. Moreover, it was found that ethyl chloroformate was a superior quarternization reagent to acetyl chloride and some of the results are summarized in the Table.

Table. Syntheses of 1-β-Keto Substituted 1, 2-Dihydroisoquinolines (3)

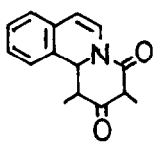
Compound 3[a]	R^1	R^2	R^3	Yield (%)[b]	mp (°C)
3a	C_2H_5O	C_6H_5	H	98	89 - 91
3b[c]	C_2H_5O	C_6H_5	CH_3	70[d]	oil
3c	C_2H_5O	- (CH_2)$_4$ -		71[d]	oil
3d	C_2H_5O	$CH_3CH_2CH_2$	H	68	oil
3e	C_2H_5O	CH_3CH_2	CH_3	66[d]	oil
3f	C_2H_5O	$C_6H_5CH_2CH_2$	H	64	oil
3g	CH_3	C_6H_5	H	64	112 - 113

a) Satisfactory IR, NMR, MS, and elemental analyses data were obtained for these compounds.
b) Isolated yield by flash column chromatography.
c) Reaction conditions for preparation of boron enolate ; room temperature, 1h.[1c)]
d) A mixture of erythro and threo isomers.

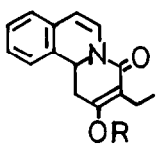
A typical procedure of the reaction is as follows : Boron enolate (2a : R^2=C_6H_5, R^3= H) of acetophenone was prepared in situ following the procedure of Mukaiyama, et al[7)] [dibutylboron triflate (0.658 g, 2.4 mmol), tributylamine (0.445 g, 2.4 mmol), acetophenone (0.264 g, 2.2 mmol), 6 ml Et_2O, -78 °C] . Isoquinolinium salt (1a : R^1= C_2H_5O) was prepared from isoquinoline (0.258 g, 2 mmol) and ethyl chloroformate (0.217 g, 2 mmol) in 5 ml Et_2O at 0 °C. To the suspension of 1a at room temperature was transferred the boron enolate through a double-ended needle under the atmosphere of nitrogen and the reaction mixture was stirred for 3h at room temperature. The resulting reaction mixture was treated with 3N NaOH (2 ml), then H_2O (20 ml) was added and the product was extracted with Et_2O (10 ml × 3). After removal of the ether under reduced pressure, the residue was dissolved in tetrahydrofuran (15 ml), cooled to 0 °C and treated with 30% H_2O_2 (1 ml) and 3N NaOH (0.5 ml). The mixture was allowed to stand for 1h at 0 °C and for 1h at room temperature, then brine (30 ml) was added. The product was extracted with ether (15 ml × 3) and after drying the ether layer over anhydrous $MgSO_4$, the

solvent was evaporated in vacuo. The crude product was purified on flash column chromatography with hexane : CH_3COOEt= 9 : 1 as eluent to afford 3a (0.629 g) in 98% yield.[8] m.p. 89 - 91 °C. ^{1}H NMR ($CDCl_3$) ; δ 1.20 (t, 3H, J=7 Hz), 3.27 (d, 2H, J=7 Hz), 4.13 (q, 2H, J=7 Hz), 5.67 - 6.15 (m, 2H), 6.67 - 7.55 (m, 8H), 7.67 - 8.18 (m, 2H). IR (nujol) ; 1710, 1680, 1630 cm^{-1}. MS (m / e) ; 321 (M^+, 5%), 202 (M^+-$PhCOCH_2$, 100), 158 (202 - EtO + H, 66).

In the next, the adduct (3e) was tested for cyclization to form the third ring to isoquinoline in order to use the present adduct (3) for synthesis of isoquinoline alkaloids. Treatment of 3e with two equivalents of EtONa in refluxing ether for 4h gave the expected product (6e) in 56% yield. Satisfactory IR, NMR, and MS data were obtained for 6e.[8] m.p. 122 -123 °C (recrystallized from ether). ^{1}H NMR ($CDCl_3$) ; δ 1.22 (d, 3H, J=8 Hz), 1.35 (d, 3H, J=6 Hz), 2.67 (dq, 1H, J=10, 8 Hz), 3.73 (q, 1H, J=6 Hz), 5.32 (d, 1H, J=10 Hz), 5.70 (d, 1H, J=8 Hz), 6.81 - 7.42 (m, 5H). IR (nujol) ; 1725, 1690, 1640 cm^{-1}. MS (m / e) ; 241 (M^+, 67%), 157 (47), 130 (100). On the other hand, when the adducts 3d and 3f were cyclized under the same conditions, enol compounds 6d and 6f were obtained in 78% and 73% yields, respectively.[9] 6d : m.p. 182 - 183 °C (recrystallized from petroleum ether and ethanol). ^{1}H NMR (pyridine - d_5) ; δ 1.25 (t, 3H, J=7 Hz), 2.81 (q, 2H, J=7 Hz), 3.18 (dd, 1H, J=13, 0.3 Hz), 3.27 (dd, 1H, J=6, 0.3 Hz), 5.12 (dd, 1H, J=13, 6 Hz), 5.80 (d, 1H, J=8 Hz), 7.13 (s, 4H), 7.80 (d, 1H, J=8 Hz), 10.6 (bs, 1H). IR (KBr) ; 3600 - 2500, 1675, 1640, 1600 cm^{-1}. MS (m / e) ; 241 (M^+, 43%), 130 (100). 6f : m.p. 183 - 184 °C (recrystallized from petroleum ether and ethanol). ^{1}H NMR (pyridine - d_5) ; δ 3.14 (dd, 1H, J=12, 0.2 Hz), 3.27 (dd, 1H, J=6, 0.2 Hz), 4.05 (s, 2H), 5.05 (dd, 1H, J=12, 6 Hz), 5.70 (d, 1H, J=8 Hz), 7.60 - 6.80 (m, 9H), 7.65 (d, 1H, J=8 Hz), 9.23 (bs, 1H). IR (KBr) ; 3600 - 2500, 1665, 1640, 1595 cm^{-1}. MS (m / e) ; 303 (M^+).

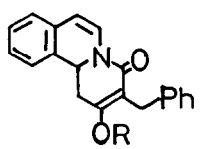


6e



6d (R=H)

7d (R=C-CH$_3$, O)



6f (R=H)

7f (R=C-CH$_3$, O)

Acetylation of 6d and 6f (Ac_2O / pyridine) produced the acetate 7d and 7f in 91% and 98% yields, respectively. Satisfactory IR, NMR, and MS data were obtained for 7d and 7f.

In summary, we have described in this communication an efficient method for the synthesis of 1-β-keto substituted-2-ethoxycarbonyl-1, 2-dihydroisoquinolines (3), which were cyclized to afford 6, by the reaction of boron enolates with isoquinolinium salts. We are continuing to explore the potential use of this system to the synthesis of isoquinoline and related heterocycles.

Acknowledgment : We are grateful for partial support of this research to Grant-in-Aid for Scientific Research (No. 554139) administered by The Ministry of Education, Science and Culture.

References and Notes.

1. a) T. Mukaiyama, K. Inomata, and M. Muraki, J. Am. Chem. Soc., 95, 968 (1973). b) K. Inomata, M. Muraki, and T. Mukaiyama, Bull. Chem. Soc. Jpn., 46, 1807 (1973). c) M. Muraki, K. Inomata, and T. Mukaiyama, ibid., 48, 3200 (1975). d) M. Hirama, D. S. Garvery, L. D. L. Lu, and S. Masamune, Tetrahedron Lett., 1979, 3937. e) D. A. Evans, E. Vogel, and J. V. Nelson, J. Am. Chem. Soc., 101, 6120 (1979).
2. J. Hooz and J. N. Bridson, Can. J. Chem., 50, 2387 (1972).
3. J. Hooz and J. N. Bridson, J. Am. Chem. Soc., 95, 602 (1972).
4. In the recent papers, we have reported several successful examples utilizing easily available heteroaromatic cations in order to develop a generally applicable method to introduce substituents into heteroaromatics. a) K. Ishikawa, K. Akiba, and N. Inamoto, Tetrahedron Lett., 1976, 3695. b) K. Akiba, K. Ishikawa, and N. Inamoto, Bull. Chem. Soc. Jpn., 51, 2674 (1978). c) K. Ishikawa, K. Akiba, and N. Inamoto, ibid., 51, 2684 (1978). d) K. Akiba, Y. Negishi, and N. Inamoto, Synthesis, 1979, 55.
5. a) J. K. Rasmussen, Synthesis, 1977, 91. b) E. W. Colvin, Chem. Soc. Rev., 7, 15 (1978).
6. J. d'Angelo, Tetrahedron, 32, 2979 (1976).
7. a) T. Mukaiyama and T. Inoue, Chem. Lett., 1976, 559. b) T. Inoue, T. Uchimaru, and T. Mukaiyama, Chem. Lett., 1977, 153. c) T. Inoue and T. Mukaiyama, Bull. Chem. Soc. Jpn., 53, 174 (1980).
8. Correct elemental analyses were obtained for 3 and 6 described here.
9. 6e exists as a keto form, whereas 6d and 6f are almost entirely enolic. Exact reason for this difference is not yet clear.

((Received in Japan 18 August 1981)