## A NEW SYNTHESIS OF 3-AMINO-2-ALKENOATES

Tamejiro Hiyama\* and Kazuhiro Kobayashi

Sagami Chemical Research Center, 4-4-1 Nishiohnuma, Sagamihara, Kanagawa 229, Japan

Dedicated to Professor Hitosi Nozaki on the occasion of his 60th birthday.

Magnesium enolates of t-butyl (or ethyl) acetate and t-butyl propionate are found to react with nitriles to give 3-amino-2-alkenoates having Z configuration.

The title compounds are versatile intermediates for the synthesis of heterocycles such as pyridines,<sup>1</sup> pyrimidines,<sup>2</sup> indoles,<sup>3</sup> and isothiazoles.<sup>4</sup> In particular, some N-aroyl derivatives of 3-amino-2butenoic acid exhibit anti-inflammatory activity.<sup>5</sup> Limited approaches<sup>4,6</sup> to this class of compounds prompted us to explore a new general synthetic method.

It is logical to contemplate that the desired 3-amino-2-alkenoates (I) should be derived from nitriles and ester enolates.<sup>7</sup> Thus, we first applied lithium enolate of t-butyl acetate to the reaction,<sup>8</sup> hereby obtaining no trace of the product. This failure may be ascribed to the incapability of the lithium ion to take nitrile group in its ligand sphere and to the instability of the primary adduct as well. We have found the magnesium enolate<sup>9</sup> of t-butyl acetate fulfils the task to give t-butyl 3-amino-2-alkenoates (I,  $R^1 = H$ ,  $R^2 = t-C_AH_o$ ) efficiently.

Magnesium enolate of t-butyl acetate was prepared by treatment of the ester with the reagent derived from disopropylamine (2 mol) and ethylmagnesium bromide (1 mol) at 0°C in ether,  $^{10}$  and then allowed to react with a nitrile at 0°C. Work-up with aqueous ammonium chloride solution followed by distillation afforded I.  $^{11}$  Results are summarized in Table 1.



	R	R <sup>1</sup>	R <sup>2</sup>	Temp (°C)	Yield (%) of I	Bp (°C/Torr) or Mp (°C)
a	Сн <sub>3</sub>	н	t-C4H9	0	66	73/0.3 <sup>b</sup>
ь	<sup>n-C</sup> 3 <sup>H</sup> 7	н	t-C4H9	0	57	78/0.3
c	i-C <sub>3</sub> H <sub>7</sub>	Н	t-C4H9	0	74	95/0.7
d	t-C <sub>4</sub> H <sub>9</sub>	н	t-C <sub>4</sub> H <sub>9</sub>	0	43	104/0.4
е	С <sub>6</sub> Н <sub>5</sub> СН <sub>2</sub>	H	t-C4H9	0	25	116/0.3 <sup><u>c</u></sup>
f	р-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	Н	t-C <sub>4</sub> H <sub>9</sub>	0	30	138/0.3
g	C <sub>6</sub> H <sub>5</sub> CH=CH	H	t-C4H9	0	44	<u>d</u>
h	С <sub>6</sub> н <sub>5</sub>	Н	t-C <sub>4</sub> H <sub>9</sub>	0	83	(93)
i	3-pyridyl	Н	t-C4H9	0	65	144/0.3 (50-50.5)
j	$CH_3CH[OSI(CH_3)_3]$	н	t-C <sub>4</sub> H <sub>9</sub>	0	65	72/0.3
k	CH <sub>3</sub> CH(OTHP) <sup>€</sup>	H	t-C4H9	0	86	160/0.3
1	Сн <sup>3</sup> сн(оее) <sub>б</sub>	н	t-C <sub>4</sub> H <sub>9</sub>	0	76	102/0.3
m	с <sub>6</sub> н <sub>5</sub>	н	$C_2^{H_5}$	-78—0	57	$112/0.3^{f}$
n	$C_6^{H_5}$	сн <sub>3</sub>	t-C <sub>4</sub> H <sub>9</sub>	-780	30 <sup>g</sup>	112/0.3

Table 1 Synthesis of 3-Amino-2-alkenoates  $(I)^{\underline{a}}$ 

<sup>a</sup> The reaction was carried out in 1 to 2 mmol scale. <sup>b</sup> Lit (ref 5)  $60^{\circ}C/0.4$  Torr. <sup>c</sup> Lit (ref 6a) 120°C/0.01 Torr. <sup>d</sup> Viscous oil,  $R_f 0.70$  (silica gel TLC, hexane-AcOEt 3:1). <sup>e</sup> THP: tetrahydropyran-2-yl, EE: 1-ethoxyethyl. <sup>f</sup> Lit (ref 4) 110-112°C/0.2 Torr. <sup>g</sup> E/Z ratio not determined. Although the procedure is applicable to various nitriles, those having relatively acidic  $\alpha$ -hydrogen gave comparatively low yields of the adducts (Ie and If). The reaction was applicable to protected acetaldehyde cyanohydrins to give adducts Ij-II in good yields. Ethyl acetate and t-butyl propionate can be used in place of t-butyl acetate only under milder conditions: both generation of magnesium enolates and reaction with benzonitrile were carried out at -78°C and the reaction mixture was allowed to warm up gradually to give Im and In in 57% and 30% yields respectively.

The products Ia-Im are all uniform by GLC assay and assigned to Z isomers on the basis of <sup>1</sup>H-NMR spectra. For example, Ia and Ic gave olefinic absorptions at  $\delta$  (CDCl<sub>3</sub>) 4.42 and 4.47 respectively, consistent with the literature values,  $\delta$  4.49 and 4.56, for the ethyl esters of Z configuration corresponding to Ia and Ic respectively. <sup>12</sup> Acetylation of I with acetic anhydride in pyridine gave N-acetyl derivatives of Z configuration. <sup>12</sup>

Typical experimental procedure is illustrated for the preparation of Ia. Diisopropylamine (0.61 g, 6.0 mmol) was added to an ethereal solution (4.3 ml) of ethylmagnesium bromide (3.0 mmol) at 0°C, and the reaction mixture was stirred for 1 hr. To the resulting turbid solution<sup>10</sup> was added t-butyl acetate (0.35 g, 3.0 mmol) at 0°C. After 0.5 h acetonitrile (62 mg, 1.5 mmol) was injected with the aid of microsyringe to the reaction mixture, and allowed to react for 3 h at 0°C. Quenching with aqueous ammonium chloride solution, extraction with ether, and purification by distillation gave t-butyl 3-amino-2-butenoate (Ia) (0.156 g, 66% yield).

Bivalent magnesium ion is entirely responsible for the success of the present reaction. We extended the concept to zinc enolates and applied the Reformatsky reaction in vain to preparing Im from ethyl bromoacetate and benzonitrile under various conditions.<sup>13</sup> However, the zinc enolate derived from zinc iodide<sup>14</sup> and the lithium enolate of t-butyl acetate<sup>8</sup> was found competent to give Ia (24%), Ib (47%), and Ih (38%) upon the reaction with acetonitrile, butyronitrile, and benzonitrile respectively. Tin(IV) chloride and titanium(IV) chloride turned out futile.

## References and Notes

- (a) T. Kato, H. Yamanaka, and T. Hozumi, <u>Yakugaku Zasshi</u>, <u>91</u>, 740 (1971). (b) G. Hörlein, B. Kübel, A. Studeneer, and G. Salbeck, <u>Liebigs Ann. Chem.</u>, 371 (1979).
- 2. K. Grohe and H. Heitzer, Liebigs Ann. Chem., 1025 (1973).
- 3. D. Răileaunu, M. Palagbită, and C. D. Nenitzescu, Tetrabedron, 27, 5031 (1971).
- R. K. Howe, T. A. Grumer, L. G. Carter, and J. E. Frans, <u>J. Heterocyclic Chem.</u>, <u>15</u>, 1001 (1978).
- 5. R T. Buckler, H. E. Hartzler, and B. M. Phillips, J. Med. Chem., 18, 509 (1975).
- 6. (a) H. G. O. Becker, <u>J. Prakt. Chem.</u>, <u>4</u>, 294 (1961). (b) T. Iwasaki, H. Horikawa, K. Matsumoto, and M. Miyoshi, <u>J. Org. Chem.</u>, <u>42</u>, 2419 (1977). (c) F. Risitano, G. Grassi, F. Foti, F. Caruso, and G. L. Vecchio, <u>J. Chem. Soc.</u>, Perkin Trans. 1, 1522 (1979).

(d) A. Krantz and B. Hoppe, <u>J. Am. Cnem. Soc.</u>, <u>97</u>, 6590 (1975). (e) US Patent 3,908,012 (<u>Chem.</u> Abstr., <u>84</u>, P59528r), 3,950,525 (<u>Chem. Abstr.</u>, <u>85</u>, P78153b). (f) M. A. Mavrodin, <u>C. R. Acad.</u>
<u>Sci.</u>, <u>188</u>, 1504 (1929). (g) J. Kovarand and F. Petru, <u>Collect. Czech. Cnem. Commun.</u>, <u>25</u>, 607 (1960). (h) R. Lukes, J. Kovar, K. Blaha, and J. Kloubek, <u>Cnem. Listy</u>, <u>50</u>, 278 (1956).

4

7. M. W. Rathke, Organic Reactions, 22, 423 (1975).

1. 20 34

- 8. M. W. Rathke and D. F. Sullivan, J. Am. Chem. Soc., 95, 3050 (1973).
- 9. The magnesium enolate of t-butyl acetate was used for aldol-type reaction with aldehydes or ketones about 30 years ago by Professors Sisido and Nozaki. (a) K. Sisido, K. Kumazawa, and H. Nozaki, J. Am. Chem. Soc., <u>82</u>, 125 (1960). (b) K. Sisido, H. Nozaki, and O. Kurihara, <u>ibid.</u>, <u>74</u>, 6254 (1952).
- 10. Magnesium base derived from equimolar amounts of disopropylamine and ethylmagnesium bromide also give Ia albeit somewhat lower yields. In this case a complex of type Mg(Ni-Pr<sub>2</sub>)<sub>2</sub>·MgBr<sub>2</sub> is assumed to be responsible. Cf. H. Kuckertz and U. Wannagat, <u>Angew. Chem. Int. Ed.</u>, <u>2</u>, 47 (1963). Use of 2 mol of disopropylamine improved the yield and suppressed the self-condensation of the ester.
- 11. The products gave correct analytical and/or spectral data. Characteristic IR (neat or KBr) and  ${}^{1}$ H-NMR (CDCl<sub>3</sub>) properties of the products follow. Ib: 3460, 3345, 1655, 1560 cm<sup>-1</sup>,  $\delta$  4.43 (s, 1H), 5.3-6.6 (br, NH<sub>2</sub>); Ic: 3460, 3345, 1660, 1615, 1545 cm<sup>-1</sup>,  $\delta$  4.47 (s), 5.8-6.8 (br); Id: 3500, 3455, 3345, 1675, 1615, 1540 cm<sup>-1</sup>,  $\delta$  4.52 (s), 5.9-7.0 (br); If: 3450, 3340, 1660, 1610, 1555 cm<sup>-1</sup>;  $\delta$  4.49 (s), 5.4-6.4 (br); Ig: 3460, 3340, 1655, 1635, 1605, 1540 cm<sup>-1</sup>,  $\delta$  4.76 (s), 5.9-6.3 (br); Ih: 3460, 3425, 3345, 1665, 1645, 1615, 1550 cm<sup>-1</sup>,  $\delta$  4.86 (s), 5.8-6.8 (br); Ii: 3400, 3310, 3275, 3235, 3190, 1665, 1625, 1595, 1555 cm<sup>-1</sup>,  $\delta$  4.86 (s), 6.0-7.0 (br); Ij: 3400, 3345, 1665, 1615, 1540 cm<sup>-1</sup>,  $\delta$  4.25 (q), 4.30 (s), 5.9-7.4 (br); Ik: 3500, 3440, 1665, 1615, 1540 cm<sup>-1</sup>,  $\delta$  3.2-4.7 (m), 5.8-6.6 (br); II: 3455, 3345, 1670, 1620, 1560 cm<sup>-1</sup>,  $\delta$  4.51 (s), 5.7-7.0 (br).
- (a) T. Kato, H. Yamanaka, and T. Shibata, <u>Yakugaku Zasshi</u>, <u>89</u>, 1637 (1969).
   (b) D. J. Aberhart and H.-J. Lin, J. Org. Chem., <u>46</u>, 3749 (1981).
- (a) K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, and H. Nozaki, <u>J. Am. Chem. Soc.</u>, <u>99</u>, 7705 (1977).
   (b) J. Cason, K. L. Rinehart, Jr., and S. D. Thornton, Jr., <u>J. Org. Chem</u>., <u>18</u>, 1594 (1953).
   (c) H. B. Kagan and Y.-Heng Suen, <u>Bull. Soc. Chim. Fr</u>., 1819 (1966).
- 14. U. Krüerke, Chem. Ber., 95, 174 (1962).

(Received in Japan 4 January 1982)