Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Selective Bromination of Ketones. A Convenient Synthesis of 5-Aminolevulinic Acid

Hyun-Joon Ha [a] , Sung-Koo Lee [a] , Young-Jin Ha [a] & Jun-Weon Park [a]

[a] Department of Chemistry, Hankuk University of Foreign Studies Yongin-Gun, Kyunggi-Do, 449-791, Korea

Version of record first published: 23 Sep 2006.

To cite this article: Hyun-Joon Ha , Sung-Koo Lee , Young-Jin Ha & Jun-Weon Park (1994): Selective Bromination of Ketones. A Convenient Synthesis of 5-Aminolevulinic Acid, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:18, 2557-2562

To link to this article: http://dx.doi.org/10.1080/00397919408010567

SYNTHETIC COMMUNICATIONS, 24(18), 2557-2562 (1994)

SELECTIVE BROMINATION OF KETONES. A CONVENIENT SYNTHESIS OF 5-AMINOLEVULINIC ACID

Hyun-Joon Ha*, Sung-Koo Lee, Young-Jin Ha, and Jun-Weon Park

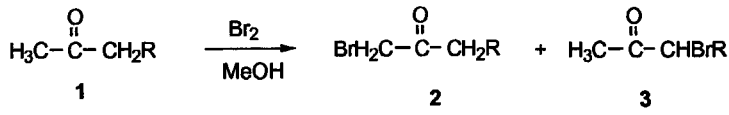
Department of Chemistry, Hankuk University of Foreign Studies
Yongin-Gun, Kyunggi-Do, 449-791 Korea

Abstract: Bromination of unsymmetrical ketones with Br_2 in methanol proceeded regioselectively in good yield at the less substituted methyl carbon. The bromination of levulinic acid using this method was followed by azidation and amination to lead to an efficient three-step synthesis of 5-aminolevulinic acid in 36% overall yield.

Regioselective bromination of unsymmetrical ketones has long attracted attention as a method to introduce functionality at the α-position. The preferred position of bromination with most brominating agents is usually at the more substituted carbon rather than at a methyl carbon.[1] Sometimes complex mixtures including polybrominated products are obtained. One of the most well-known procedures for the bromination of less substituted carbons such as methyl involves use of a silyl enol ether generated from the kinetic enolate with LDA.[2] In addition to the limitation of generating kinetic enolates on a large scale, this method can give difficulties with compounds containing carboxylate, nitrate, and phosphonate groups. We are interested in selective bromination of the methyl groups of

*To whom correspondence should be addressed

compounds **1** to make a natural substrate and several putative inhibitors of 5-aminolevulinic acid dehydratase (E.C.4.2.1.24), the first enzyme responsible for the biosynthesis of tetrapyrroles such as hemes, phycobilins, and cobalamines.[3] In this communication we describe the regioselective introduction of bromine at the methyl groups of compounds **1** such as 2-pentanone (**1a**), n-butyl levulinate (**1b**), levulinic acid (**1c**), 4-nitro-2-butanone (**1d**), and dimethyl (3-oxobutyl)phosphonate (**1e**).



1 **2** **3**

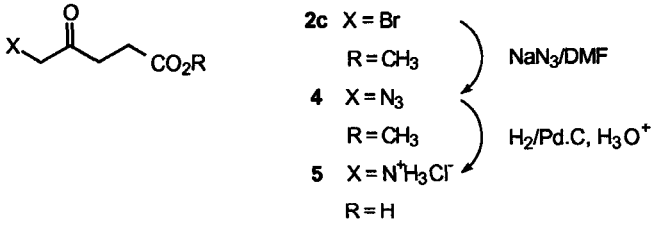
2-Pentanone (**1a**) was brominated by addition of Br_2 to yield a mixture of **2** and **3** in the ratio 5:1 in 61% yield. However, the reverse addition, i.e. addition of 2-pentanone to Br_2 in methanol, gives only **3** as product in 75% yield. For n-butyl levulinate (**1b**) the best result was obtained as 4:1 ratio in 86% yield by running the reaction at reflux while 3:1 ratio of selectivity was observed in the reaction at room temperature. Levulinic acid (**1c**) gave the product as brominated methyl ester under the typical reaction condition of reflux.[5] At room temperature only methyl levulinate was obtained as the reaction product. In the course of the reaction we observed that levulinic acid was methylated as methyl ester first, then brominated with the similar selectivity of 3:1 to n-butyl levulinate. Bromination was successful with good selectivities of 2.5:1 and 4:1 in 45 and 60% yield on 4-nitro-2-butanone (**1d**) and dimethyl (3-oxobutyl)phosphonate (**1e**) respectively in due course for the formation of nitrate and phosphonate isosteres[6] of 5-aminolevulinate.

The brominated methyl ester of levulinic acid was used for the preparation of 5-aminolevulinic acid[7], a precusor in the tetrahydropyrrolic biosynthetic pathway with herbicidal[8,9] and insecticidal activity.[10]

Table. Selective Bromination of Ketones **1** in Methanol[4]

Compound	R	Temp	Time(h)	Yield[a](%)	Ratio[b](2:3)
1a	CH_2CH_3	reflux	1.3	61	5:1
1a[c]	CH_2CH_3	reflux	1.3	75	**3** only
1b	CH_2CO_2n-Bu	reflux	1.5	86	4:1
1b	CH_2CO_2n-Bu	r.t.	21	65	3:1
1c[d]	CH_2CO_2H	reflux	3.5	64	3:1
1d	CH_2NO_2	reflux	0.7	45	2.5:1
1e	$CH_2P(=O)(OCH_3)_2$	reflux	2.5	60	4:1

a. Isolated yield b. Determined by GC and/or NMR. c. Ketone was added to Br_2 as reverse addition. d. Product was obtained as methyl ester. see, reference 5.



Scheme

Methyl 5-bromolevulinate (**2c**) was converted to azide (**4**) in quantitative yield by the reaction with NaN_3 in DMF at -10°C. Reduction of the azide and hydrolysis of the methyl ester was accomplished by one-pot catalytic hydrogenation in methanol with hydrochloric acid in 75% yield. This procedure affords 5-aminolevulinic acid

(5) as the hydrochloride in 36% overall yield, starting from readily available levulinic acid.

Experimental

General Procedure for Bromination. Bromine (25 mmol) was added to a solution of ketone **1** (25 mmol) in methanol (60 ml) at room temperature for 15 min under N_2 atmosphere. After the addition was completed the reaction mixture was stirred for 30 min at room temperature after which time the reaction proceeded further under the condition specified on the table. After the reaction was completed methanol was removed from the reaction mixture under reduced pressure. The residue was partitioned between ether and water. The pH of the resulting solution was adjusted to 8.0 by adding $NaHCO_3$. The ether layer was washed successively with aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to yield crude product. This material was purified by either fractional distillation or flash chromatography over silica gel.

Methyl 5-azidolevulinate (4). Methyl 5-bromolevulinate (**2c**, 0.50 g, 2.4 mmol) was added to the sodium azide (0.47 g, 7.2 mmol) solution dissolved in dry DMF under N_2 atmosphere at -10°C. The resultant reaction mixture was stirred for 1 hr keeping the temperature -10°C. After the reaction was completed ether (50ml) was added and DMF was washed out with brine (3 x 100ml). The organic layer was washed successively with 5% $NaHCO_3$ solution and water, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give product in quantitative yield. ^1H NMR ($CDCl_3$): δ 2.63-2.80 (m, 4H, -CH_2CH_2-), 3.65 (s, 3H, OCH3), 4.07 (s, 2H, -CH_2N_3); ^{13}C NMR ($CDCl_3$): δ 27.6, 43.5,

52.0, 57.4 173.1, 203.4; Anal calcd. for $C_6H_9N_3O_3$: C, 42.1; H, 5.30; N, 24.5; Found: C, 40.8; H, 5.11; N, 25.5%.

5-Aminolevulinic acid hydrochloride (5). The foregoing methyl 5-azidolevulinate (**4**, 0.36 g, 2.1 mmol) in 10 ml of methanol was stirred with 2 ml of c-HCl and 30% Pd/C catalyst (130 mg) under an atmospheric H_2 gas at room temperature. After 2 hr the reaction mixture was filtered through Celite to remove catalyst and concentrated under reduced pressure. The crude product was purified by recrystallization with butanol/acetic acid to give crystalline solid product in 75% yield. ^1H NMR (D_2O): δ 2.79 (t, J = 6.1 Hz, 2H, $-CH_2CO_2$), 2.99 (t, J = 6.1 Hz, 2H, $-CH_2C(=O)C$), 4.22 (s, 2H, $-CH_2N^+H_3Cl^-$); ^{13}C NMR (D_2O): δ 30.0, 36.6, 49.7 179.3, 206.6; Anal calcd. for $C_5H_{10}NO_3Cl$: C, 35.8; H, 6.01; N, 8.36; Found: C, 35.5; H, 6.21; N, 8.39%.

Acknowledgment: This work was supported by funds from Korea Science & Engineering Foundation whom we would like to thank.

References and Notes

1. March, J., "Advanced Organic Chemistry (4th ed.)," John Wiley & Sons, New York, 1992, pp. 587-590
2. (a) Blanco, L., Amice, P. and Conia, J. M., Synthesis, 1976, 194 (b) Reuss, R. H. and Hassner, A., J. Org. Chem., 1974, 39, 1785
3. Ha, H.-J., Park, J.-W., Oh, S.-J., Lee, J.-C and Song, C. E., Bull. Kor. Chem. Soc., 1993, 14, 652: and references cited therein.
4. For chlorination, it was reported that the preferred position was the less substituted carbon when the solvent was methanol. Gallucci, R. R. and Going, R., J. Org. Chem., 1981, 46, 2532

5. MacDonald, S. F., Cad. J. Chem. 1974, 52, 3257

6. (a) Thornber, C. W., Chem. Soc. Rev., 1979, 8, 563 (b) Schloss, J. V., in the book "Target Sites of Herbicide Action" Ed. by Boger, P. and Sandmann, G., CRC Press, Boca Raton, 1989, pp. 165-245 (c) Silverman, R. B., "The Organic Chemistry of Drug Design and Drug Action", Academic Press, San Diego, 1992, pp. 19-23

7. Several reports have appeared of the synthesis of 5-aminolevulinic acid. (a) Neuberger, A. and Scott, J. J., J. Chem. Soc., 1954, 1820 (b) Awruch, J. and Frydman, B., Tetrahedron Lett., 1976, 46, 4121 (c) Evans, D. A., Sidebottom, P. J., J. Chem. Soc., Chem. Commun., 1978, 753 (d) Beale, S. I., Gold, M. H. and Granick, S., Phytochemistry, 1979, 18, 441 (e) Herdeis, C. and Dimmerling, A., Arch. Pharm., 1984, 317, 304 (f) Pfaltz, A. and Anwar, S., Tetrahedron Lett., 1984, 25, 2977 (g) Benedikt, E. and Kost, H. P., Z. Naturforsch., 1986, 41b, 1593 (h) Kawakami, H., Ebata, T. and Matsushita, H., Agric. Biol. Chem., 1991, 55, 1687

8. Rebeiz, C. A., Montazer-Zouhoor A., Hopen, H. J. and Wu, S. M., Enzyme Microb. Technol., 1984, 6, 390

9. Herbicidal activity was also observed in alkylesters of 5-aminolevulinate. see, Takeya, H., Jpn. Kokai Tokyo Koho JP 04 09 360 (1992) (Chem. Abstract., 116, 19755 (1992))

10. Rebeiz, C. A., Juvik, J. A. and Rebeiz, C. C., Pestic. Biochem. Physiol., 1988, 30, 11

(Received in the UK 06 January 1994)