Asian Journal of Chemistry; Vol. 24, No. 2 (2012), 929-930

ASIAN JOURNAL OF CHEMISTRY

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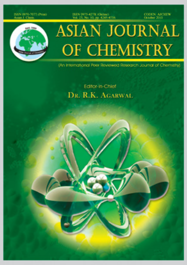

NOTE

Highly Selective Synthesis of α-Bromoesters Using Molecular Bromine Catalyzed by Phosphorus

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(*Received*: 7 February 2011; *Accepted*: 24 October 2011) AJC-10561

A series of α-bromoesters have been synthesized by applying Hell-Volhard-Zelinsky reaction catalyzed by phosphorus instead of usual phosphorus tribromide. An excellent regioselectivity to good yields are achieved at comparatively mild reaction conditions of an operational simplicity.

Key Words: α-Bromoester, Hell-Volhard-Zelinsky reaction, Phosphorus.

Bromo-derivatives have wide utility both as products and as intermediates, used in dyes, polymers and other chemical raw materials[1], particularly in pharmaceutical research, which has broad prospects for development. Substrates such as 1,3-dicarbonyl compounds have high reactivity making them prone to react with large number of nucleophiles to provide a variety of useful compounds. In recent years, several approaches of bromination have been introduced, including molecular bromine[2], copper(II) bromide with [hydroxy(tosyloxy)iodo] benzene[3], *N*-bromosuccinimide (NBS) in ionic liquids[4], *N*-bromosuccinimide in the presence of silica-supported sodium hydrogen sulfate[5] and various catalyzed bromination of tetrabutyl ammonium bromide[6] and organic ammonium tribromides such as tetrabutyl[7], benzyltrimethyl[8], pentylpyridinium[9], pyridinium[10], 1,2-dipyridiniumditribromideethane[11], Ethylbenzene (*N*-methylimidazolium) ditribromide (EBMIDTB)[12]. However, those reaction substrates which have comparatively stable α-C have not been involved.

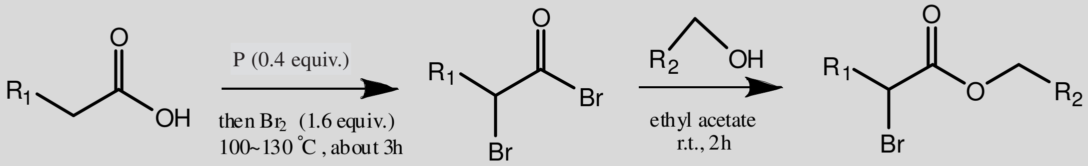
Vollhard' method preparing halogenated organic acids was first reported in the 1880's and become known as the Hell-Volhard-Zelinsky reaction[13] in which the acid is treated with bromine in the presence of phosphorus or phosphorus tribromide of poor regioselectivity. But the extension of this organic transformation to α-bromination has occurred only recently. In our previous work, a series of α-bromo esters were prepared from Hell-Volhard-Zelinsky reaction.

A mixture of propionic acid (3.72 g, 50 mmol) and phosphorus (0.65 g, 20 mmol) was stirred in a three-neck flask equipped with a dropping funnel and condenser connected to a hydrogen bromide gas absorption bottle containing aqueous sodium hydroxide solution. Liquid bromine (4.2 mL, 80 mmol) was added dropwise in 2 h when the mixture maintained at 100 - 130 ºC heated by oil bath, excess time was prolonged for reaction until the colour of the reaction mixture turned to light yellow, after that the oil bath was removed and ethyl acetate (20 mL) was introduced. After the mixture was cooled to room temperature, a solution of ethanol (4.6 g, 100 mmol) in ethyl acetate (20 mL) was added very slowly. After the reaction completed, the resulting mixture was washed by aqueous sodium bicarbonate solution, the aqueous layer was extracted with ethyl acetate (20 mL × 3) and the combined organic layer was dried over sodium sulfate, filtered and concentrated by vacuum distillation. The resulting compound was characterized by IR, ^{1}H NMR. IR (KBr, ν_{max}, cm^{-1}): 2982 s, 2892 s, 1741 s, 1443 m, 1372 m, 1336 s, 1225 s, 1158 s, 1063 s, 1021 m, 859 m, 766 w, 730 w, 674 w, 567 w. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, 3H), 1.83 (d, 3H), 4.23 (m, 2H), 4.36 (t, 1H).

The Hell-Volhard-Zelinsky reaction is synthetically useful, since it gives rise to α-brominated products which the bromine atom can be easily replaced to form other functional group substituted compounds. For the reaction catalyst appears rather important towards a high regioselection. To our experiment elementary phosphorus was selected and the amount required was employed in the transformation under similar conditions. Results with different acids and alcohols based the catalyst are summarized in Table-1.

In our work optimum conditions were examined, reaction of propionic acid and ethanol gave the excellent regioselectivity to a 79.8 % yield of α-bromoester by bromination stage at

TABLE-1
SYNTHESIS OF α-BROMOESTERS USING MOLECULAR BROMINE CATALYZED BY PHOSPHORUS WITH VARIOUS ACIDS AND ALCOHOLS AS SUBSTRATES



Entry	Acid	Alcohol	Time (h)	Temp (ºC)	Yield (%)[a]
1	$CH_3CH_2CO_2H$	CH_3CH_2OH	1	110	69.2
2	$CH_3CH_2CO_2H$	CH_3CH_2OH	2	110	79.5
3	$CH_3CH_2CO_2H$	CH_3CH_2OH	3	110	79.8
4	$CH_3CH_2CO_2H$	CH_3CH_2OH	4	110	78.4
5	$CH_3CH_2CO_2H$	CH_3CH_2OH	2	100	71.1
6	$CH_3CH_2CO_2H$	CH_3CH_2OH	2	115	77.3
7	$CH_3CH_2CO_2H$	CH_3CH_2OH	2	130	70.8
8	$CH_3CH_2CO_2H$	CH_3OH	2	110	81.6
9	$CH_3CH_2CO_2H$	$CH_3(CH_2)_2OH$	2	110	70.2
10	$CH_3CH_2CO_2H$	$(CH_3)_2CHOH$	2	110	71.4
11	CH_3CO_2H	CH_3CH_2OH	2	110	82.3
12	$CH_3(CH_2)_2CO_2H$	CH_3CH_2OH	2	110	72.6
13	$CH_3(CH_2)_5CO_2H$	CH_3CH_2OH	2	110	67.8
14	$CH_3(CH_2)_6CO_2H$	CH_3CH_2OH	2	110	66.4

[a] Yield was calculated by HPLC with nitrobenzene as internal standard

110 ºC followed by esterification step for 3 h at room temperature (Entry 3). The products did not show significant yields by increase reaction temperature as well as time. A wide range of acids and alcohols were applied to transform into the corresponding α-bromoesters without affording α,α-dibromo products. As showed in Table-1, methanol showed comparative high reactivity corresponding to same propionic acid (Entry 8), which is probably due to the higher polarity attacking the unstable α-bromoacyl bromide. Furthermore, the ease of an enolate formation of acetic acid in the precursors allowed us to achieve a higher yield of 82.3 % (Entry 11).

Conclusion

In summary, an efficient and useful synthetically methodology of α-bromoester was introduced, showing the chemical regioselectivity and excellent yields with a variety of substrates. This procedure offered several unique features including the enhanced yields, shorter reaction time, operational simplicity and ease of isolation of products. In comparison with phosphorus tribromide, phosphorus appear more convenient for its less hazard and easy to handle and facilitates maintaining the stoichiometric ratio while carrying out the reactions.

REFERENCES

1. (a) M. Kuroboshi, Y. Waki and H. Tanaka, *J. Org. Chem.*, **68**, 3938 (2003); (b) Y. Qingwei, P.K. Elizabeth and Y. Zhi, *J. Org. Chem.*, **68**, 7528 (2003); (c) A. Butler and J.V. Walker, *Chem. Rev.*, **93**, 1937 (1993).
2. (a) P. Dowd, C. Kaufman and P.J. Kaufman, *J. Org. Chem.*, **50**, 882 (1995); (b) K. Hakam, M. Thielmann, T. Thielmann and E. Winterfeldt, *Tetrahedron*, **43**, 2035 (1987); (c) A.D. Jordan, C. Luo and A.B. Reitz, *J. Org. Chem.*, **68**, 8693 (2003).
3. S.J. Coats and K.G. Wasserman, *J. Org. Chem.*, **60**, 554 (1995).
4. (a) H.M. Meshram, P.N. Reddy, P. Vishnu, K. Sadashiv and J.S. Yadav, *Tetrahedron Lett.*, **47**, 991 (2006); (b) S. Karimi and K.G. Grohmann, *J. Org. Chem.*, **60**, 554 (1995).
5. B. Das, K. Venkateswarlu, G. Mahender and I. Mahender, *Tetrahedron Lett.*, **46**, 3041 (2005).
6. U. Bora, G. Bose, M.K. Chaudhuri, S.S. Dhar, R. Gopinath, A.T. Khan and B.K. Patel, *Org. Lett.*, **2**, 247 (2000).
7. M.K. Ghaudhuri, A.T. Kan, B.K. Patel, D. Dey, W. Kharmawophlang, T.R. Lakshmiprabha and G.C. Mandal, *Tetrahedron Lett.*, **39**, 8163 (1998).
8. S. Kajigaeshi, T. Kakinami, H. Tokiyama, H. Yamasaki, T. Hirakawa and T.B. Okamoto, *J. Chem. Soc. (Japan)*, **60**, 2667 (1987).
9. K. Tanaka, R. Shiraishi and F. Toda, *J. Chem. Soc. Perkin Trans. I*, 3069 (1999).
10. (a) R. Markovic, M. Baranac and Z. Dzambaski, *Heterocycles*, **63**, 851 (2004); (b) W.P. Reeves, C.V. Lu, B. Schulmeier, L. Jonas and O. Hatlevik, *Synth. Commun.*, **28**, 499 (1998).
11. V. Kavala, S. Naik and B.K. Patel, *J. Org. Chem.*, **70**, 4267 (2005).
12. R. Hosseinzadeh, M. Tajbakhsh, M. Mohadjerani and Z. Lasemi, *Monatsh. Chem.*, **140**, 57 (2009).
13. (a) N.O.V. Sonntag, *Chem. Rev.*, **52**, 237 (1953); (b) H. Kwart and E.V. Scalzi, *J. Am. Chem. Soc.*, **86**, 5496 (1964); (c) A.R. Sexton, *J. Am. Chem. Soc.*, **91**, 7098 (1969); (d) G.L. Lange and J.A. Otulakowski, *J. Org. Chem.*, **47**, 5093 (1982); (e) R.J. Crawford, *J. Org. Chem.*, **48**, 1364 (1983); (f) H. Liu and W. Luo, *Synth. Commun.*, **21**, 2097 (1991).