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

Improved Synthesis of N-Alkoxyphthalimdes

Jae Nyoung Kim [a], Kyoung Man Kim [a] & Eung K. Ryu [a]

[a] Division of Organic Chemistry, Korea Research Institute of Chemical Technology, P. O. Box 9 Daedeog-Danji, Daejeon, 305-606, Korea

Version of record first published: 23 Sep 2006.

To cite this article: Jae Nyoung Kim, Kyoung Man Kim & Eung K. Ryu (1992): Improved Synthesis of N-Alkoxyphthalimdes, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:10, 1427-1432

To link to this article: http://dx.doi.org/10.1080/00397919208021609

SYNTHETIC COMMUNICATIONS, 22(10), 1427-1432 (1992)

IMPROVED SYNTHESIS OF N-ALKOXYPHTHALIMIDES

Jae Nyoung Kim, Kyoung Man Kim, and Eung K. Ryu*

Division of Organic Chemistry,
Korea Research Institute of Chemical Technology, P. O. Box 9
Daedeog-Danji, Daejeon 305-606, Korea

Abstract: Synthetically useful N-alkoxyphthalimide derivatives can be conveniently prepared in high yields from the reactions of N-hydroxyphthalimide with alkyl halides by using DBU in DMF.

N-Alkoxyphthalimide derivatives are important synthetic intermediates to prepare *O*-substituted hydroxylamines.[1] In general, there are two methods to prepare N-alkoxyphthalimides. First, the reaction of N-hydroxyphthalimide with alkyl halide in the presence of base such as triethylamine or potassium carbonate was reported.[2] This method could be generally applied, however, there are some restrictions such as relatively long reaction time, excess use of alkyl halide in most cases, and variable yields. And the second, the reaction of N-hydroxyph-

*To whom correspondence should be addressed.

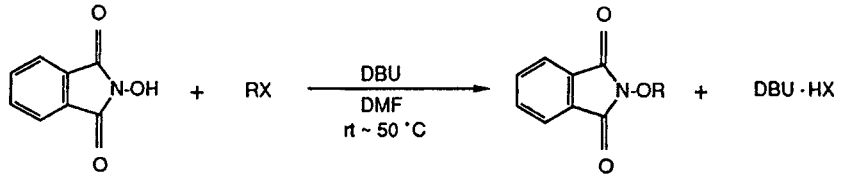
thalimide with various alcohols by DEAD-Ph_3P system was reported.[3] The second method gives relatively high yield of products, but the use of expensive DEAD and the tedious purification procedure render to limit the use in the case of scale-up preparation of N-alkoxyphthalimides.

In our research program to prepare herbicidal cyclohexanedione derivatives,[4] we need various kinds of *O*-substituted hydroxylamines, and thus preparation method of N-alkoxyphthalimides in high yields and by simple procedure is needed. Thus, we reinvestigate the reaction of N-hydroxyphthalimide and alkyl halide with various kinds of bases and solvents. Consequently, we found that the use of DBU in DMF shows marked rate-increase, clean reaction, simple work-up procedure, and high yields. Thus, we prepare some N-alkoxyphthalimide derivatives, and wish to report herein.

In general, to a stirred solution of N-hydroxyphthalimide (1) and alkyl halide (1.1 equiv) in DMF was added DBU at room temperature, and stirred for 0.5~2 h. The reaction mixture was then poured into cold 1 N HCl solution, the precipitated solid was collected by filtration, and purified by crystallization from ethanol or by column chromatography. The results were summarized in Table I and II.

The reaction is clean and fast (within 1 h) at room temperature with reactive alkyl halide, allylic halide, propargylic halide, and benzyl halide. With less reactive alkyl halides, somewhat long reaction time (2 h, rt, entry 2 and 5) or gentle warming (40-50 °C, 1 h, entry 3 and 4) was needed to improve yields. DBN could also be used instead of DBU without decrease in yields. Benzene may be used as solvent, but the reaction is somewhat slower than in DMF. In large scale preparations of N-alkoxyphthalimides, DBU could be recovered from the reaction mixtures by appropriate work-up procedure.[9]

Table I. Preparation of Some N-Alkoxyphthalimides



1 2

Entry	RX	Time (h)	Yield (%)	mp[b] (Lit, mp)
1	CH_3-I	1	86	134-135 (133)[5]
2	CH_3CH_2-Br	2	82	98-99 (97-98)[5]
3	$(CH_3)_2CH$-Br	1	71[a]	57-59[6]
4	$(CH_3CH_2)_2CH$-Br	1	74[a]	39-40
5	CH_3SCH_2-Cl	2	78	96-98 (96-97)[2c]
6	CH_2=CH-CH_2-Br	0.5	83	60-61 (59-60)[3]
7	CH≡ C-CH_2-Br	0.5	96	150-152 (149-150)[2a]
8	CH_2=C(Cl)-CH_2-Cl	1	80	115-117[7]
9	CH_3-CH=CH-CH_2-Br	0.5	96	117-118 (115-116)[8]
10	$PhCH_2$-Br	0.5	94	144-145 (143-144)[3]

a. Gentle warming (40-50 °C).

b. Melting points were measured with a Thomas-Hoover melting point apparatus, and not corrected. All products were recrystallized from 95% ethanol except for entry 3, 4, and 6, which were purified by column chromatography.

Table II. ^1H NMR and MS Data of N-Alkoxyphthalimide Derivatives (2)

R	^1H NMR ($CDCl_3$/TMS)[a] δ (ppm)	MS (70 eV)[b] m/z (%)
$-CH_3$	4.07 (s, 3H), 7.60-8.00 (m, 4H)	105 (100), 177 (M^+, 11)
$-CH_2CH_3$	1.43 (t, 3H), 4.30 (q, 2H), 7.65-8.00 (m, 4H)	105 (32), 192 (M^++1, 100)
$-CH(CH_3)_2$	1.35 (s, 3H), 1.40 (s, 3H), 4.55 (heptet, 1H), 7.60-8.00 (m, 4H)	45 (61), 163 (100), 206 (M^++1, 74)
$-CH(CH_2CH_3)_2$	1.03 (t, 6H), 1.70 (m, 4H), 4.12 (quintet, 1H), 7.60-7.95 (m, 4H)	45 (38), 164 (100), 234 (M^++1, 29)
$-CH_2SCH_3$	2.40 (s, 3H), 5.30 (s, 2H), 7.60-8.00 (m, 4H)	61 (88), 62 (100), 223 (M^+, 2)
$-CH_2CH=CH_2$	4.72 (d, 2H), 5.25-5.50 (m, 2H), 6.00-6.30 (m, 1H), 7.65-8.00 (m, 4H)	43 (91), 76 (47), 105 (100), 204 (M^++1, 33)
$-CH_2C\equiv CH$	2.60 (t, 1H), 4.89 (d, 2H), 7.70-7.95 (m, 4H)	41 (68), 76 (48), 105 (100), 130 (58), 202 (M^++1, 24)
$-CH_2C(Cl)=CH_2$	4.80 (s, 2H), 5.56 (d, 1H), 5.72 (d, 1H), 7.70-7.95 (m, 4H)	41 (37), 105 (100), 202 (39), 238 (M^++1, 6)
$-CH_2CH=CH-CH_3$	1.70 (d, 3H), 4.58-4.70 (m, 2H), 5.70-5.95 (m, 2H), 7.70-7.95 (m, 4H)	56 (59), 164 (100), 218 (M^++1, 80)
$-CH_2Ph$	5.22 (s, 2H), 7.35-7.90 (m, 9H)	91 (100), 181 (24), 254 (M^++1, 7)

a. Recorded on a Varian Gemini-200 NMR Spectrometer.

b. Obtained on a Shimadzu QP 1000 Spectrometer.

Experimental

Synthesis of N-(Propargyloxy)phthalimide; Typical Procedure:

To a stirred solution of N-hydroxyphthalimide (3.3 g, 20 mmol) and propargyl bromide (80 wt. % solution in toluene, 3.3 g, 22 mmol) in DMF (50 ml) was added dropwise DBU (3.1 g, 20 mmol) at room temperature over 5 min. After futher stirred for 25 min, the reaction mixture was poured into cold 1 N HCl solution (500 ml). The precipitated solid was filtered, washed with water to afford nearly pure product. Crystallization from 95% EtOH gave analytically pure N-(propargyloxy)phthalimide, 3.86 g (96%).

Acknowledgement: We wish to thank the Korea Science and Engineering Foundation for financial support of this work.

References

1. Sandler, S. R. and Karo, W., *"Organic Functional Group Preparations,"* Academic Press, New York, 1972, Vol III, p 344.
2. a) Biel, J. H. and Jaeger, E. R., U. S. Patent 3337560; *Chem. Abstr.*, 1968, **68**, 87028r.
   b) Annie, R. and Marc, D., *Bull. Soc. Chim. Fr.*, 1976, 833.
   c) Takasugi, H., Kochi, H., Masugi, T., Nakano, H., and Takaya, T., *J. Antibiotics*, 1983, **36**, 846.
3. Grochowski, E. and Jurczak, J., *Synthesis*, 1976, 682.
4. For example, see Ishikawa, H., Iwataki, I., and Sawaki, M., *J. Pesticide Sci.*, 1985, 10, 301.
5. Major, R. T. and Hedrich, R. J., *J. Org. Chem.*, 1965, **30**, 1270.

6. Yoshio, U., Tsutomu, K., Michinori, T., and Mikio, S., Japan Patent 144571 ; *Chem. Abstr.*, 1979, **90**, 203691g.

7. Tatao, L., U. S. Patent 4440566; *Chem. Abstr.*, 1984, **101**, 23036j.

8. Amlaiky, N., Leclerc, G., and Carpy, A., *J. Org. Chem.*, 1982, **47**, 517.

9. Ono, N., Yamada, T., Saito, T., Tanaka, K., and Kaji, A., *Bull. Chem. Soc. Jpn.*, 1978, **51**, 2401.

(Received in UK 31 December, 1991)