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Alkylation of Aromatic Heterocycles with Oxalic Acid Monoalkyl Esters in the Presence of Trivalent Iodine Compounds

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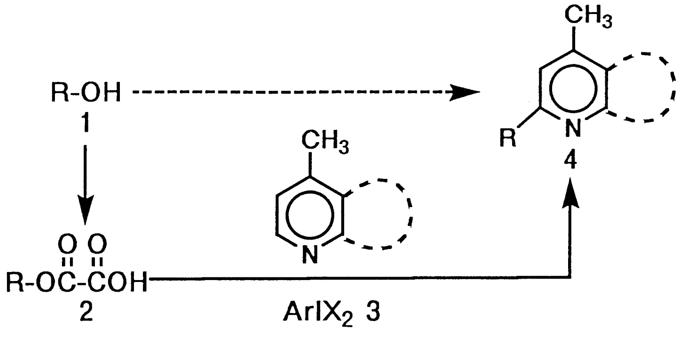
Aromatic heterocycles containing nitrogen atoms were easily alkylated with the half esters of oxalic acid, which were prepared from alcohols, in the presence of [bis(trifluoroacetoxy)iodo]benzene via radical decarboxylative pathways. This is the first method for the alkylation of aromatic heterocycles with alcohols via the formation of half esters of oxalic acid.

The radical alkylation onto aromatic heterocycles with carboxylic acids or halides has been well recognized.[1)] However, the deoxygenative alkylation of alcohols onto aromatic heterocycles has been never studied. While the uses of alkyl radical formed from alcohols via their xanthates and xanthate analogues with tributyltin hydride have been well studied,[2)] the alkylation onto aromatic heterocycles with these systems doesn't proceed because of the reductive systems.

Recently, much attention has been attracted in hypervalent iodine compounds for organic synthesis.[3)] Among them trivalent iodine compounds have become effective reagents, not only to oxidize various substrates but also to form the carbon-carbon bonds.[4)] As a part of our study directed toward the deoxygenative alkylation of alcohols onto heteroaromatic compounds, we present here the effective alkylation onto aromatic heterocycles with the half esters of oxalic acid, prepared from alcohols as a starting material, in the presence of trivalent iodine compound $ArIX_2$. This is the first report on the alkylation of the aromatic heterocycles starting from alcohols via half esters of oxalic acid.



3 a: Ar= C_6H_5, X= CF_3CO_2

b: Ar= C_6H_5, X= CH_3CO_2

c: Ar= C_6F_5, X= CF_3CO_2

Half esters **2** of oxalic acid were easily prepared by the reaction of alcohols with oxalyl chloride in CH_2Cl_2 at r.t., followed by hydrolysis. Using these half esters **2**, the alkylation of lepidine was carried out in the presence of **3a**, **3b**, or **3c**. The results and reaction conditions are shown in Table 1. The ratio of **2** / aromatic base / **3** of 3/3/1 was suitable for this reaction and [bis(trifluoroacetoxy)iodo]benzene (**3a**) was the most effective alkylating agent among the above trivalent iodine compounds (Entries 1, 3, and 4). Further, the heating

Table 1. Alkylation of Aromatic Heterocycles with **3**

	2	Aromatic			Products[5]/ %[a]		
Entry	R-	base	$ArIX_2$	Conditions [b]	**4**		$(COOR)_2$
1	1-Adamantyl	Lepidine	**3a**	A	2(1-Adamantyl)-4-methylquinoline	62	-
2	"	"	"	B	"	72 [c]	-
3	"	"	**3b**	A	"	31	-
4	"	"	**3c**	C	"	19	-
5	1-Methylcyclohexyl	"	**3a**	A	4-Methyl-2(1-methylcyclohexyl)quinoline	54	-
6	Cyclohexyl	"	"	A	2-Cyclohexyl-4-methylquinoline	43	20
7	"	"	"	B	"	52 [c]	6 [c]
8	2-Phenylethyl	"	"	A	4-Methyl-2(2-phenylethyl)quinoline	13	86
9	"	"	"	B	"	15 [c]	88 [c]
10	(-)-Menthyl	"	"	B	2-Menthyl-4-methylquinoline	41 [d]	trace
11	(-)-Bornyl	"	"	B	2-Bornyl-4-methylquinoline	23	40
12	1-Adamantyl	Methyl isonicotinate	"	A	Methyl 2(1-adamantyl)-isonicotinate	58	-
13	"	Phthalazine	"	A	1(1-Adamantyl)-phthalazine	33	-
14	"	Benzothiazole	"	A	2(1-Adamantyl)-benzothiazole	28	6
15	"	4-Cyanopyridine	"	A	2(1-Adamantyl)-4-cyanopyridine	47	12
16	Methylcyclohexyl	Methyl isonicotinate	"	A	Methyl 2(1-methylcyclohexyl)quinoline	36	-
17	Cyclohexyl	"	"	B	Methyl 2-cyclohexyl-isonicotinate	39	22
18	"	Phthalazine	"	B	1-Cyclohexyl-phthalazine	36	23

a) The yields were calculated based on $ArIX_2$. b) Conditions A : Refluxed in benzene, B : Refluxed in toluene, C : Irradiated with low pressure mercury lamp in CH_2Cl_2 at r.t. The ratio of **2** / aromatic base / **3** was 3/3/1. c) The yields were determined by G.C. d) $[\alpha]_D^{24}$ -63.31 (c 0.861, $CHCl_3$).

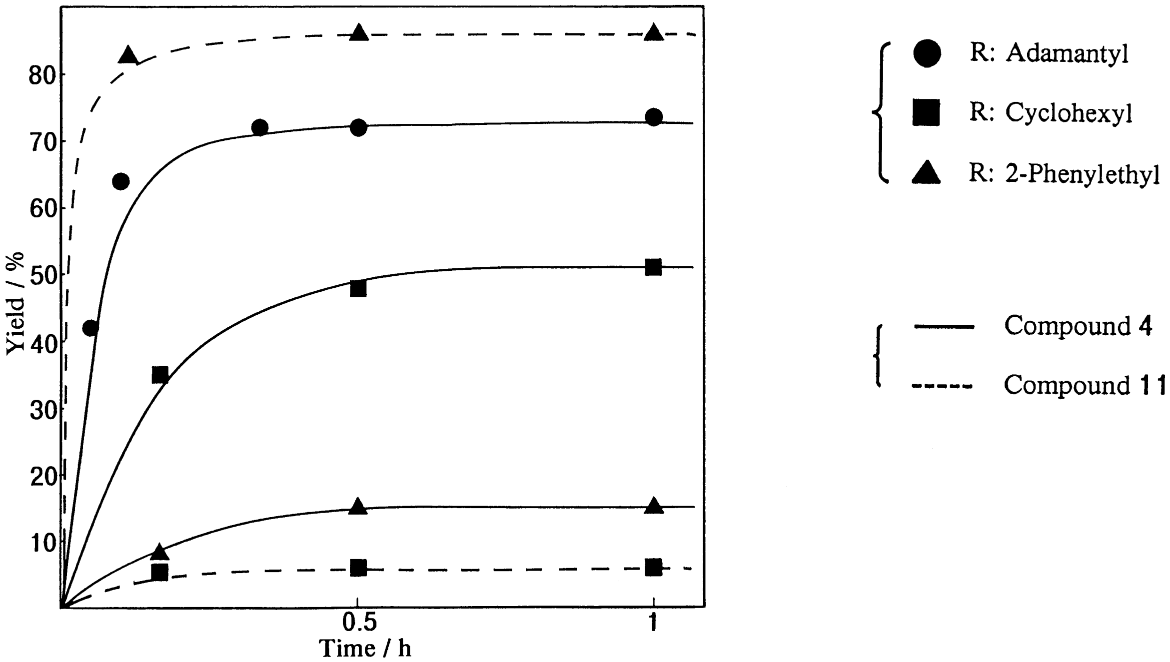
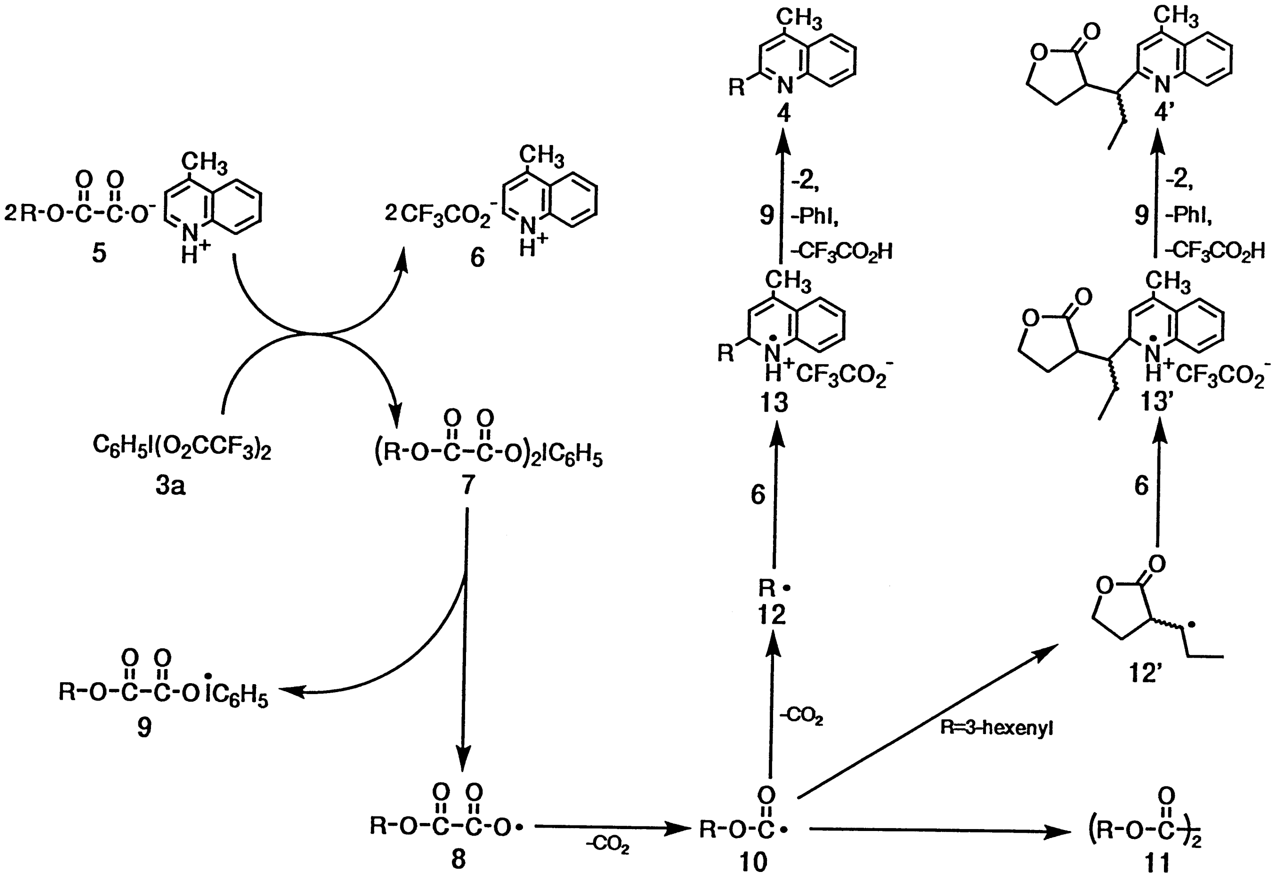


Fig. 1. Relative reactivity of 2 with 3a in the presence of lepidine.



Scheme 1.

conditions are required to give compound **4** in better yields (Entries 1 and 2). The reactivities of the half esters **2** prepared from primary, secondary, and tertiary alcohols are illustrated in Fig. 1. As shown in Fig. 1, these reactions are completed within one hour and the reactivities of **2** increase in the order of primary < secondary < tertiary esters. Oxalate diester was formed by radical coupling reaction of the alkoxy carbonyl radical formed together with the half ester of oxalic acid derived from primary alcohol, because the bond dissociation energy of its carbon-oxygen bond is higher than that of secondary and tertiary alcohol derivatives (Entries 8 and 9). These results indicate that the bond dissociation step of carbon-oxygen bond in alkoxycarbonyl radical formed seems to be the rate-determining step. When mono 3-hexenyl ester of oxalic acid was used in the presence of **3a** and lepidine, oxalate diester **11** and 2-alkylated lepidine **4'** via the cyclization from **10** to **12'** were obtained in 7% and 17% (diastereomeric mixture, 59:41) yields, respectively. This result suggests that the reaction proceeds via the reaction mechanism shown in Scheme 1. When the chiral compounds were used, the corresponding single isomer was obtained in moderate yields (Entries 10 and 11). The half esters of oxalic acid which have electron-withdrawing group such as ester or carbonyl group were less reactive because the generated radicals have low nucleophilicity. When half diisopropylamide of oxalic acid was used, 2-diisopropylaminocarbonyl-4-methylquinoline was obtained in 30% yield instead of 2-diisopropylamino-4-methylquinoline, and oxalyl bis(diisopropylamide) in 22% yield. While, other aromatic heterocycles like isonicotinate, phthalazine, and benzothiazole can be easily alkylated in the presence of **3a**.

Thus this method is very useful for the alkylation of aromatic heterocycles in view of using alcohols as starting materials. Further investigations are undergoing in this laboratory.

References

1) B. Giese, "C-C Bond Formation of Aromatic Systems (Chap. 5)," in "Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds," ed by J. E. Baldwin, Pergamon Press, Oxford (1986) ; F. Minisci, E. Vismara, and F. Fontana, *J. Org. Chem.*, **54**, 5224 (1989) and references cited therein.

2) D. H. R. Barton and J. Cs. Jaszberenji, *Tetrahedron Lett.*, **30**, 2619 (1989); S. C. Dolan and J. MacMillan, *J. Chem. Soc., Chem. Commun.*, **1985**, 1588.

3) M. Ochiai and Y. Nagao, *Yuki Gosei Kagaku Kyokai Shi*, **44**, 660 (1986); T. Umemoto, *ibid.*, **41**, 251 (1983); C. A. Varvoglis, *Synthesis*, **1984**, 709; R. M. Moriarty and R. K. Vaid, *ibid.*, **1990**, 431.

4) K. Furuta, T. Nagata, and H. Yamamoto, *Tetrahedron Lett.*, **31**, 2215 (1990); R. Hernandez, J. J. Marrero, and E. Suarez, *ibid.*, **30**, 5501 (1989); **29**, 5979 (1988); R. Freire, R. Hernandez, M. S. Rodriguez, and E. Suarez, *ibid.*, **28**, 981 (1987); C. G. Francisco, R. Freire, M. S. Rodriguez, and E. Suarez, *ibid.*, **28**, 3397 (1987); J. I. Concepcion, C. G. Francisco, R. Hernandez, J. A. Salazar, and E. Suarez, *ibid.*, **25**, 1953 (1984); R. Freire, J. J. Marrero, M. S. Rodriguez, and E. Suarez, *ibid.*, **27**, 383 (1986); M. A. Brimble and G. M. Williams, *ibid.*, **31**, 3043 (1990); J. I. Concepcion, C. G. Francisco, R. Freire, R. Hernandez, J. A. Salazar, and E. Suarez, *J. Org. Chem.*, **51**, 402 (1986); R. Singh and G. Just, *Synth. Commun.*, **18**, 1327 (1988); F. Minisci, E. Vismara, F. Fontana, and M. C. N. Barbosa, *Tetrahedron Lett.*, **30**, 4569 (1989); M. Karelsky and K. H. Pausacker, *Aust. J. Chem.*, **11**, 39 (1958); C. W. Ellwood and G. Pattenden, *Tetrahedron Lett.*, **32**, 1591 (1991).

5) All these compounds gave satisfactory spectroscopic and microanalytical data.

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