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FACILE RADICAL DECARBOXYLATIVE ALKYLATION OF HETEROAROMATIC BASES USING CARBOXYLIC ACIDS AND TRIVALENT IODINE COMPOUNDS

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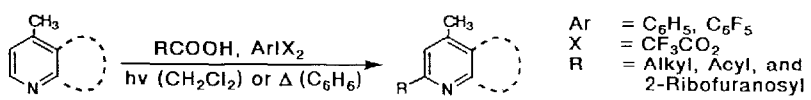
Summary: Many kinds of heteroaromatic bases were easily alkylated by the reaction of carboxylic acids with [bis(trifluoroacetoxy)iodo]benzene or [bis(trifluoroacetoxy)iodo]pentafluorobenzene via radical decarboxylative pathways. This system was further applied to the reaction with tetrahydrofurylcarboxylic acid, 1-(2,3,5-tri-O-benzyl)-D-ribofuranosylacetic acid, and 1-(2,3,5-tri-O-benzyl)-D-ribofuranosylcarboxylic acid for the model synthesis of C-nucleosides.

The hypervalent organoiodine compounds have been well recognized as versatile reagents in organic synthesis.[1] One of the important reactions with these iodine compounds is a carbon-carbon bond forming reaction. Among the trivalent organoiodine compounds, (diacetoxyiodo)benzene (DAIB) is an attractive reagent because it has a moderate oxidizing ability and is commercially available.[2] The decarboxylative iodonation of carboxylic acids with DAIB in the presence of iodine,[3a] the phenylation of dichlorobenzene with (dibenzoyloxyiodo)benzene,[3b] and the alkylation of heteroaromatic bases with DAIB[3c] have hitherto been reported. However, DAIB has limitations for the alkylation of heteroaromatic bases because of its low reactivity. Here we present an effective decarboxylative alkylation with various carboxylic acids onto heteroaromatic bases using [bis(trifluoroacetoxy)iodo]benzene (BFAIB) or [bis(trifluoroacetoxy)-iodo]pentafluorobenzene (BFAIFB),[4] which is a more powerful oxidant than DAIB.



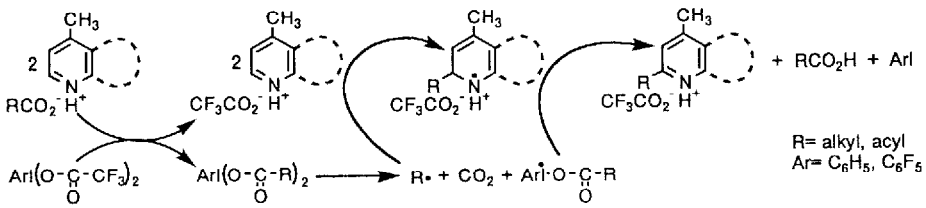
The reactions were carried out as follows. Method A: To the solution of $ArIX_2$ (1 mmol) in dry methylene chloride (8 ml) in quartz cell was added a carboxylic acid (3 mmol) and a heteroaromatic base (3 mmol) under argon atmosphere and the mixture was irradiated with low pressure mercury lamp at 0°C-r.t. for 2.5 h. Method B: To the solution of $ArIX_2$ (1 mmol) in dry benzene (8 ml) was added a carboxylic acid (3 mmol) and a heteroaromatic base (3 mmol) under argon atmosphere and the mixture was heated under reflux for 2.5 h. After the reaction in each method, the product was isolated by standard procedure including silica gel chromatography. The results are shown in Table 1. While the cyclohexylation of lepidine with DAIB did not proceed effectively under irradiation or thermal conditions (entries 1 and 2), the reactions with BFAIB gave 2-cyclohexyl-4-methylquinoline in moderate yield under irradiation or thermal conditions (entries 6 and 7). 2-Cyclohexyl-4-methylquinoline was obtained in the best yield (among entries 3, 4, 5, and 6), when the ratio of cyclohexanecarboxylic acid / heteroaromatic base / $ArIX_2$ was 3/3/1. When

Table 1 Alkylation of Heteroaromatic Bases

entry	RCOOH (I) R-	Base (II)	ArIX2 (III)	ratio and method (I)/(II)/(III) (mmol)		Product (%)[a]	
1	c-C_6H_{11}-	lepidine	X=CH_3CO_2- Ar=C_6H_5-	3/3/1	A	2-cyclohexyl-4-methylquinoline	4
2	〃	〃	〃	〃	B	〃	3
3	〃	〃	X=CF_3CO_2- Ar=C_6H_5-	1/1/1	B	〃	1
4	〃	〃	〃	3/1/1	B	〃	1
5	〃	〃	〃	1/3/1	B	〃	26
6	〃	〃	〃	3/3/1	B	〃	50
7	〃	〃	〃	〃	A	〃	52
8	1-adamantyl-	〃	〃	3/3/1	B	2(1-adamantyl)-4-methylquinoline	91[b]
9	$C_6H_5CH_2CH_2$-	〃	〃	〃	B	2(2-phenylethyl)-4-methylquinoline	19
10	CF_3-	〃	X=$C_6H_5CH_2CH_2CO_2$- Ar=C_6H_5-	3/3/0.5	B	〃	29
11	CF_3-	〃	X=c-$C_6H_{11}CO_2$- Ar=C_6H_5-	〃	B	2-cyclohexyl-4-methylquinoline	46
12	CF_3-	〃	X=1-adamantyl-CO_2- Ar=C_6H_5-	〃	B	2(1-adamantyl)-4-methylquinoline	81[c]
13	CF_3-	〃	d)	3/3/1	B	〃	41[e]
14	1-adamantyl-	4-cyanopyridine	〃	〃	B	2(1-adamantyl)-4-cyanopyridine	88
15	〃	benzothiazole	〃	〃	B	2(1-adamantyl)-benzothiazole	54[f]
16	〃	methyl isonicotinate	〃	〃	B	methyl 2(1-adamantyl)isonicotinate	68
17	〃	phthalazine	〃	〃	B	1(1-adamantyl)-phthalazine	57
18	〃	5-bromo-pyrimidine	〃	〃	B	2(1-adamantyl)-5-bromopyrimidine	27
19	$C_6H_5OCH_2$-	lepidine	〃	〃	B	2-phenoxymethyl-4-methylquinoline	61
20	$C_6H_5CH_2CH_2O_2C$-	〃	〃	〃	B	2(2-phenylethyl)-4-methylquinoline	139[g]
21	(L)-$CH_3CH(OAc)$-[h]	〃	〃	〃	B	2[(1-acetoxy)ethyl]-4-methylquinoline	20[i]
22	CH_2=$CHCH_2OCH_2CH_2$-	〃	〃	〃	B	2[(3-tetrahydrofuryl)methyl)-4-methylquinoline	13
23	$C_6H_5CH_2CH_2CO$-	〃	〃	2.8/2.8/1	B	2(2-phenylpropionyl)-4-methylquinoline	56
24	C_6H_5CO-	〃	〃	3/3/1	B	2-benzoyl-4-methylquinoline	46
25	1-adamantyl	〃	X=CF_3CO_2- Ar=C_6F_5-	〃	A	2(1-adamantyl)-4-methylquinoline	85
26	c-C_6H_{11}-	〃	〃	〃	A	2-cyclohexyl-4-methylquinoline	78
27	$C_6H_5CH_2CH_2$-	〃	〃	〃	A	2(2-phenylethyl)-4-methylquinoline	24

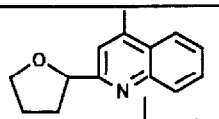
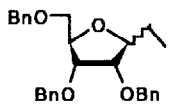
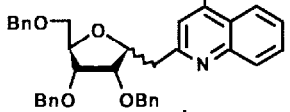
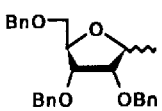
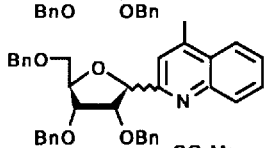
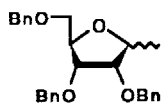
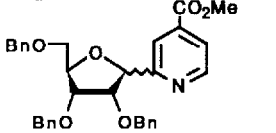
a) The yields were calculated based on $ArIX_2$. b) The recovered (I) and (II) were 1.31 and 2.10 mmols. c) The recovered (I) and (II) were 0.47 and 2.60 mmols. d) $PhI(O_2CCF_3)(O_2CR)$ [R=1-adamantyl] was used. e) The recovered (I) and (II) were 0.28 and 2.59 mmols. f) The recovered (I) and (II) were 2.44 and 2.40 mmols. g) Di(2-phenylethyl) oxalate was obtained in 86% yield. h) $[\alpha]_D^{24}$ -49.8° (optical purity 100%, c 0.49, $CHCl_3$). i) $[\alpha]_D^{24}$ -10.5° (c 0.40, $CHCl_3$). It was converted to the ester (ratio of two diastereomers, 54:47) with (R)-(+)-2-methoxy-2-phenyl-3,3,3-trifluoropropionyl chloride (Mosher's method).

quinoline was used instead of lepidine, it was alkylated at 2- and 4- positions. The excess of carboxylic acid and base used can be recovered. The reactivity of carboxylic acids increased in the order of primary < secondary < tertiary (entries 6, 8 and 9). Since the similar yields were achieved in entries 10~12 as in entries 6, 8, and 9, and the use of [acyloxy(trifluoroacetoxy)iodo]benzene decreased the yield of the product (entry 12 vs. entry 13), the reaction intermediate is concluded to be (diacyloxyiodo)benzenes, not [acyloxy(trifluoroacetoxy)iodo]benzenes, though (diacyloxyiodo)benzenes, [acyloxy(trifluoroacetoxy)-iodo]benzenes, and BFAIB may exist in equilibrium state in reaction media.[6] Thus the origin of the alkyl group in the product came from an acyloxy group in (diacyloxyiodo)benzene and the remaining acyloxy group was recovered as a carboxylic acid. 1-Adamantanecarboxylic acid reacted with other heteroaromatic bases in the presence of BFAIB to give the corresponding adamantylated heteroaromatic bases (enties 14~18) and phenoxyacetic acid also reacted with lepidine under the same conditions to give 2-phenoxymethyl-4-methylquinoline (entry 19). When 2-phenylethyl hydrogen oxalate was used, di(2-phenylethyl) oxalate was obtained in good yield as a major product (entry 20), suggesting that the alkylation proceeded via radical mechanism. This is further supported both by racemization and by cyclization (5-exo-trig). Thus the almost completely racemized 2[(1-acetoxy)ethyl]-4-methylquinoline (6% ee) was obtained when (L)-O-acetyllactic acid was used (entry 21) and 2[(3-tetrahydrofuryl)methyl]-4-methylquinoline was obtained when 2-allyloxypropionic acid was used (entry 22). The reaction may proceed via the following pathway



Scheme 1

Table 2 Preparation of C-Nucleoside Skeletons[a]

entry	RCOOH R-	RCOOH / Base / $C_6F_5I(O_2CCF_3)_2$ (mmol)	Time (h)	Products (%)[b]
1		3/3/1 Base = lepidine	5	 29
2		5/5/1 Base = lepidine	10	 10 (α:β=3:7)
3		3/3/1 Base = lepidine	10	 34[5a] (α:β=4:6)
4		5/5/1 Base = methyl isonicotinate	10	 19[5b] (α:β=7:3)

a) Method A was used and the reaction time is shown in Table. b) All the compounds gave satisfactory spectroscopic and microanalytical data.

Scheme 1). However, the detailed reaction mechanism is still not clear because only trace of iodobenzene was recovered (<5%). The reaction can successfully be applied for acylation of lepidine with α-ketocarboxylic acid (entries 23 and 24). Entries 25, 26, and 27 show that BFAIFB is also reactive under photochemical conditions, though it is not effective under thermal conditions because of its thermal instability. Advantage of BFAIFB is that it can be used for C-glycosidation of heteroaromatic bases (Table 2), in which DAIB and BFAIB are not effective. Recently, many natural and unnatural C-nucleosides have been synthesized in multistep sequences because of their marked antiviral and antitumor activities.[7] The present method may be useful for the preparation of these bioactive compounds.

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5) Selected data; a) (β): ^{1}H-NMR: δ=8.08(1H, bd, J=8.3 Hz, base-H^8), 7.94(1H, dd, J=8.4, 0.9 Hz, base-H^5), 7.70(1H, ddd, J=8.3, 7.0, 0.9 Hz, base-H^7), 7.40(1H, bs, base-H^3), 7.53(1H, ddd, J=8.3, 7.0, 1.1 Hz, base-H^6), 5.38(1H, d, J=3.3 Hz, H$^{1'}$), 4.45-4.49(1H, m, H$^{4'}$), 4.28(1H, dd, J=5.1, 3.3 Hz, H$^{2'}$), 4.05(1H, dd, J=7.1, 5.1 Hz, H$^{3'}$), 3.90(1H, dd, J=10.8, 2.9 Hz, H$^{5'}$), 3.73(1H, dd, J=10.8, 3.8 Hz, H$^{5'}$), 2.48(3H, d, J=0.7 Hz, CH$_3$), MS(FAB): M+1=546. (α): ^{1}H-NMR: δ=8.02-7.99(2H, m, base-H^5, H^8), 7.71(1H, ddd, J=8.2, 7.0, 1.3 Hz, base-H^7), 7.68(1H, bs, base-H^3), 7.55(1H, ddd, J=8.2, 7.0, 1.3 Hz, base-H^6), 5.36(1H, d, J=2.8 Hz, H$^{1'}$), 4.57-4.54(1H, m, H$^{4'}$), 4.44(1H, m, H$^{2'}$), 4.28(1H, dd, J=8.6, 4.0 Hz, H$^{3'}$), 3.84(1H, dd, J=10.8, 2.6 Hz, H$^{5'}$), 3.67(1H, dd, J=10.8, 4.2 Hz, H$^{5'}$), 2.68(3H, d, J=0.6 Hz, CH$_3$), MS(FAB): M+1=546. b)(α): ^{1}H-NMR: δ=8.64(1H, d, J=5.0 Hz, base-H^6), 8.18(1H, d, J=1.4 Hz, base-H^3), 7.75(1H, dd, J=5.0, 1.4 Hz, base-H^5), 5.31(1H, d, J=2.8 Hz, H$^{1'}$), 4.43(1H, d, J=11.8 Hz, OCH$_2$Ph), 4.50(1H, dd, J=4.1, 2.8 Hz, H$^{2'}$), 4.38(1H, bs, H$^{4'}$), 4.29(1H, dd, J=8.5, 4.1 Hz, H$^{3'}$), 3.93(3H, s, CH$_3$), 3.82(1H, dd, J=10.7, 2.5 Hz, H$^{5'}$), 3.65(1H, dd, J=10.7, 3.9 Hz, H$^{5'}$), MS(FAB): M+1=540. b)(β): ^{1}H-NMR: δ=8.73(1H, d, J=5.0 Hz, base-H^6), 8.18(1H, d, J=1.4 Hz, base-H^3), 7.73(1H, dd, J=5.0, 1.4 Hz, base-H^5), 5.28(1H, d, J=3.3 Hz, H$^{1'}$), 4.43-4.45(1H, m, H$^{4'}$), 4.18(1H, dd, J=5.0, 3.3 Hz, H$^{2'}$), 4.00 (1H, dd, J=7.2, 5.0 Hz, H$^{3'}$), 3.83(3H, s, CH$_3$), 3.83(1H, dd, J=10.7, 3.0 Hz, H$^{5'}$), 3.68(1H, dd, J=10.7, 4.1 Hz, H$^{5'}$), MS(FAB): M+1=540.

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