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Zinc–Iron Couple Induced Conjugate Addition of Alkyl Halide Derived Radicals to Activated Olefins

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At present there are a number of examples of useful synthetic procedures which are based on the conjugate addition of radicals to electron-deficient olefins.[1] In this regard, it was suggested that the addition reaction which takes place when an alkyl iodide is activated by the zinc/copper couple in the presence of an electron-deficient olefin proceeds by a radical pathway.[2] This is in accord with the stereochemical course which was observed in the case of two epimeric 3-deoxy-3-iodohexofuranose derivatives.[3] Accordingly, the initial step of the reaction might be the transfer, by the reducing couple, of one electron into the carbon–halogen bond thereby producing a radical.[4] The latter would subsequently be trapped in the close vicinity of the metal surface[5] by an appropriate olefin to give, after further reduction of the intermediate radical adduct, the reaction product.

In recent work on the carbohydrate series, we were particularly interested in the reaction of the 5-deoxy-5-iodoribose derivative 1 which in the presence of Zn/CuI underwent addition to methyl acrylate to give the octose derivative 2 in 50% yield (Scheme I).[6] This particular example is illustrative of the potential advantages of using this type of chemistry for chain elongation of highly functionalized molecules such as carbohydrate compounds. Accordingly we were prompted to find improved reaction conditions for C–C bond formation by means of an addition of a halide to an olefin *via* electron donation. For this purpose we have undertaken a systematic study searching for a more efficient electron source to be employed under simple and mild experimental conditions to carry out the reaction above, which served as a standard for this particular study.[7]

Scheme I

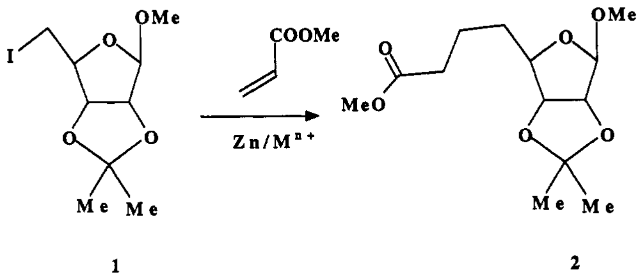

Table I

entry	MX$_n$	equiv	ligand	solvent	yield, %
1	$FeCl_3$	2	pyridine	pyridine	35
2	$FeCl_3$	0.5	pyridine	pyridine	35
3	$CoCl_2$	0.5	pyridine	pyridine	20
4	$NiCl_2$	0.5	pyridine	pyridine	0
5	$FeCl_3$	0.5	imidazole	methanol	25
6	$FeCl_3$ + NaI	0.5 + 2	pyridine	pyridine	60
7	$FeCl_3$ + NaI	0.5 + 4	pyridine	pyridine	60
8	$CoCl_2$ + NaI	0.5 + 2	pyridine	pyridine	45
9	$NiCl_2$ + NaI	0.5 + 2	pyridine	pyridine	<10
10	$FeCl_3$ + NaI	1 + 2	methanol	methanol	34
11	$FeCl_3$ + NaI	0.5 + 2	pyridine	methanol	47
12	$FeCl_3$ + NaI	0.5 + 2	2,2-bipyridine	acetonitrile	0
13	$FeCl_3$ + NaI	0.5 + 2	2,2-bipyridine	methanol	25
14	$FeCl_3$ + NaI	0.5 + 2	2,2-bipyridine	pyridine	47

In a preliminary series of experiments, electron sources Zn/$MCl_n \cdot 6H_2O$ with M = Ni (n = 2), Co (n = 2), and Fe (n = 3) were examined. Using the previously proposed conditions[6] nickel- and ferric chloride were found not to induce the reaction between 1 and methyl acrylate to give the desired chain-extended compound 2; whereas with cobalt chloride a modest yield was observed as reported.[6] Finally, a careful search for more favorable reaction conditions resulted in the observation of a beneficial effect due to the introduction of pyridine in the reaction medium. When the reaction was carried out in pyridine solution the chemical yields were 35, 20, and less than 10% for ferric-, cobalt-, and nickel chloride, respectively (Table I, entries 1–4). In the case of ferric chloride, the replacement of pyridine by imidazole (15 equiv), as a putative ligand of a presumably active low-valent iron species, in methanol solution resulted in a decreased yield (entry 5). Interestingly, the reaction conditions could be further optimized by adding sodium iodide to the reaction mixture.[8] As shown in Table I, the chemical yield of compound 2 was raised to 60% (entries 6, 7). This is very remarkable if one considers that the reaction presumably involves the addition of a primary radical (see below) to an olefin in moderate excess (5–7 equiv). The presence of sodium iodide was also beneficial when using cobalt- or nickel chloride in pyridine although giving lower yields (entries 8, 9).

To establish the role of pyridine, the reaction was carried in methanol to give a 34% yield which could be enhanced to 47% by addition of 5 equiv of pyridine (entries 10, 11). The use of 2,2-bipyridine (4 equiv) instead of pyridine resulted in a 25 and a 47% yield in methanol and pyridine, respectively. Surprisingly, the reaction did not work in acetonitrile solution thus underscoring an unexpected solvent effect (entries 12–14). In a pyrimidine solution a 20% yield was obtained whereas pyrazine and pyridazine solvents proved to be ineffective.

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(7) For the Zn/Ni^{2+} system see: (a) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani Bronchi, A. *J. Organomet. Chem.* **1986**, *301*, C62. (b) Sustman, R.; Hopp, P.; Holl, P. *Tetrahedron Lett.* **1989**, *30*, 689.

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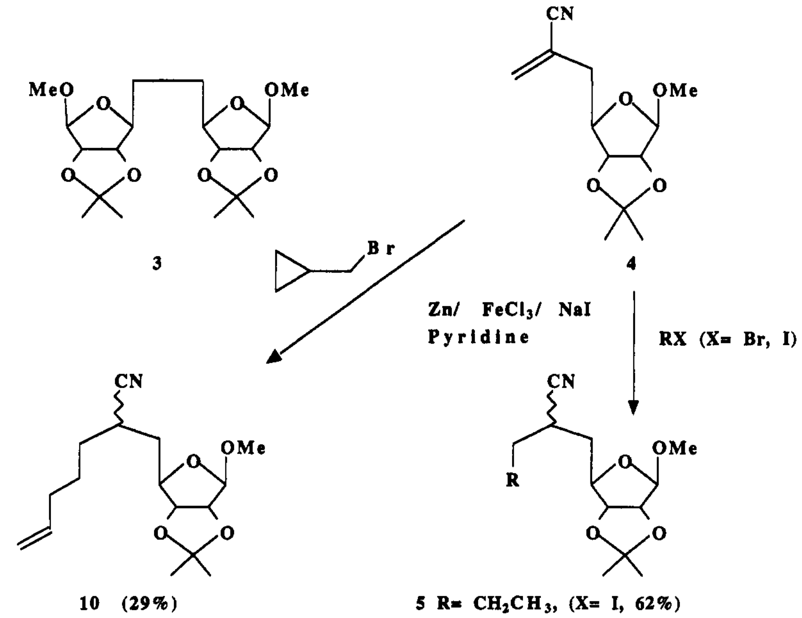
Scheme II



5 R= CH_2CH_3, (X= I, 62%)
6 R= $CH(CH_3)_2$, (X= I, 72%; X= Br, 62%)
7 R= $C(CH_3)_3$ (X= I, 75%; X= Br, 57%)
8 R= $CH_2CH(OEt)_2$ (X= Br, 36%)
9 R= $CH_2CH_2NHCOCF_3$ (X= I, 85%)

Finally, in an attempt to characterize the low-valent iron species which presumably participates in the electron transfer, an experiment was undertaken which showed that ferrous chloride was absolutely ineffective in the absence of zinc.

Another series of experiments was devised to elucidate the mechanism of this new zinc–iron couple induced reaction. Thus 1 gave, in the absence of methyl acrylate, a 32% yield of bis-adduct 3 favoring a radical pathway. Further evidence for such a mechanism was obtained after treatment of olefin 4,[9] as a model acceptor, in the presence of various halides. Iodoethane, 2-halopropane, 2-halo-2-methylpropane (halo being bromo and iodo), bromoacetaldehyde diethyl acetal, 1-iodo-2-(trifluoroacetyl)aminoethane, and (bromomethyl)cyclopropane (each 4 equiv/equiv of 4) gave rise to compounds 5, 6, 7, 8, 9, and 10, respectively, in moderate to good yields as indicated in Scheme II. In particular, the ready formation of such compounds as 8 and 10 is very illustrative of a radical mechanism. It is well known that bromoacetaldehyde diethyl acetal cannot be used in organometallic reactions of synthetic value.[10] Moreover ring opening in the case of (bromomethyl)cyclopropane to give the known compound 7[11] can be considered as a very convincing proof for the proposed reaction pathway. As anticipated for such a route, compared to the bromide derivatives, the corresponding iodides proved to be more effective.

In conclusion, the zinc–iron couple has been found to promote the efficient formation of radicals from various alkyl halides which are subsequently trapped by electron-deficient olefins. The first step of the reaction presumably involves the reductive formation of a radical by means of a not yet characterized low-valent iron species. More experimental work will be needed to determine the crucial roles played by iodide ions and pyridine in this reaction. In view of its simplicity (low-cost reagents are employed which do not need special care) and its high functional compatibility it is anticipated that such a procedure will certainly prove to be useful in many synthetic schemes.

Experimental Section

General Procedure. Zinc powder (3 mmol) was added, under nitrogen, to a vigorously stirred (vibromixer) solution which was prepared by mixing iron(III) chloride hexahydrate (0.25 mmol) and sodium iodide (0.5 mmol) in pyridine (500 μL). After 5 min a solution of derivative 1 (0.5 mmol) in methyl acrylate (300 μL) was added. Disappearance (TLC) of the starting material occurred at room temperature within 45 min. The reaction mixture was diluted with toluene and the solution filtered over Celite. After evaporation of the solvent, the residue was purified by column chromatography to give methyl 2,3-isopropylidene-7-(methoxycarbonyl)-5,6,7-trideoxy-β-D-heptaribofuranose 2 as a viscous oil: IR (neat) 1746 cm^{-1}; ^{1}H NMR ($CDCl_3$) 4.93 (s, 1H, H-1), 4.58 (d, 1H, H-2), 4.53 (d, 1H, H-3), 4.13 (m, 1H, H-4), 3.67 (s, 3H, COOMe), 3.34 (s, 3H, OMe), 2.36 (m, 2H, H-7), 1.65 (m, 4H, H-5 and H-6), 1.47 (s, 3H, Me), 1.3 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) 173.6, 112.2, 109.5, 86.7, 85.5, 84.1, 54.8, 51.3, 36.9, 34.3, 26.2, 24.7, 21.6; MS (EI) *m/z* 259 ($M^{\bullet+}$ − 15). Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.98; H, 8.03. Found: C, 57.15; H, 8.01.

Dimer 3. This compound was obtained using the same experimental conditions as above except that methyl acrylate was omitted: ^{1}H NMR ($CDCl_3$) 4.94 (s, 1H, H-1), 4.59 (d, 1H, H-2), 4.53 (d, 1H, H-3), 4.18 (m, 1H, H-4), 3.34 (s, 3H, OMe), 1.67 (m, 4H, H-5), 1.47 (s, 3H, Me), 1.31 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) 112.4, 109.7, 86.9, 85.7, 84.2, 55.2, 31.8, 26.6, 25.1; MS: (EI) *m/z* 359 ($M^{\bullet+}$ − 15). Anal. Calcd for $C_{18}H_{30}O_8$: C, 57.73; H, 8.08. Found: C, 57.55; H, 7.77.

Methyl 6-Cyano-2,3-isopropylidene-5,6,7,8,9-pentadeoxy-β-D-nonaribofuranose (5). The reaction conditions were the same as indicated in the general procedure, the only difference being the use of 1 equiv of nitrile 4 (0.5 mmol) in the presence of 2 mmol of halo derivative which served as solvent if liquid. In the case of solid reactants the reaction was run in pyridine solution: yield 62% (iodoethane); IR (neat) 2240 cm^{-1}; ^{1}H NMR ($CDCl_3$) 4.96 (s, 1H, H-1), 4.55 (m, 2H, H-2 and H-3), 4.4 and 4.3 (2m, 1H, H-4a and H-4b), 3.38 and 3.34 (2s, 3H, OMe), 2.75 (m, 1H, H-6), 1.8–1.4 (m, 6H, H-5, H-7 and H-8), 1.48 (s, 3H, Me),

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1.31 (s, 3H, Me), 0.97 (s, 9H, t-Bu); ^{13}C NMR ($CDCl_3$) 122 and 121.2 (1C), 112.6, 110, 85.3, 84.5, 84, 55.4, 37.9 and 37.3 (1C), 34.6 and 33.1 (1C), 28.5 and 28 (1C), 26.5, 25, 20.2, 13.5; MS (EI) *m/z* 254 ($M^{\bullet+}$ − 15). Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.75; H, 8.49; N, 4.88.

Methyl 6-cyano-8-methyl-2,3-isopropylidene-5,6,7,8,9-pentadeoxy-β-D-nonaribofuranose (6): yield 72% (2-iodopropane), 62% (2-bromopropane); IR (neat) 2238 cm^{-1}; ^{1}H NMR ($CDCl_3$) 4.96 (s, 1H, H-1), 4.55 (m, 2H, H-2 and H-3), 4.3 (m, 1H, H-4), 3.38 and 3.34 (2s, 3H, OMe), 2.8 (m, 1H, H-6), 1.8–1.4 (m, 5H, H-5, H-7 and H-8), 1.48 (s, 3H, Me), 1.31 (s, 3H, Me), 0.96 (s, 6H, Me); ^{13}C NMR ($CDCl_3$) 112.6, 110.2 and 110 (1C), 85.4, 84.4, 84, 55.4, 41.8 and 40.2 (1C), 38.3 and 37.8 (1C), 27 and 26.5 (1C), 26.3, 26, 25, 23.2 and 22.8 (1C), 21.5 and 21.2 (1C); MS (EI) *m/z* 268 ($M^{\bullet+}$ − 15). Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.65; H, 8.61; N, 5.20.

Methyl 6-cyano-8-dimethyl-2,3-isopropylidene-5,6,7,8,9-pentadeoxy-β-D-nonaribofuranose (7): yield 75% (2-iodo-2-methylpropane), 57% (2-bromo-2-methylpropane); IR (neat) 2238 cm^{-1}; ^{1}H NMR ($CDCl_3$) 4.9 (s, 1H, H-1), 4.52 (m, 2H, H-2 and H-3), 4.38 and 4.19 (2m, 1H, H-4a and H-4b), 3.32 and 3.28 (2s, 3H, OMe), 2.65 (m, 1H, H-6), 2–1.5 (m, 4H, H-5 and H-7), 1.41 (s, 3H, Me), 1.21 (s, 3H, Me), 0.94 (s, 9H, t-Bu); ^{13}C NMR ($CDCl_3$) 123.3 and 122.6 (1C), 112.7, 110, 85.5, 83.7, 82, 55.4, 46.4 and 45.1 (1C), 40.1 and 39.2 (1C), 29.4, 26.5, 24.5, 25.1 and 23.4 (1C); MS (EI) *m/z* 282 ($M^{\bullet+}$ − 15). Anal. Calcd for $C_{16}H_{27}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.65; H, 8.91; N, 4.87.

Methyl 6-cyano-8-(diethoxymethyl)-2,3-isopropylidene-5,6,7,8-tetradeoxy-β-D-octaribofuranose (8): IR (neat) 2239 cm^{-1}; ^{1}H NMR ($CDCl_3$) 4.96 (s, 1H, H-1), 4.5 (m, 3H, H-2, H-3 and H-9), 4.4 and 4.25 (2m, 1H, H-4a and H-4b), 3.64–3.49 (m, 4H, OCH_2), 3.37 and 3.33 (2s, 3H, OMe), 2.7 (m, 1H, H-6), 1.78 (m, 6H, H-5, H-7 and H-8), 1.47 (s, 3H, Me), 1.31 (s, 3H, Me), 1.22 (t, 6H, Me); ^{13}C NMR ($CDCl_3$) 112.8, 110.3, 102.2, 85.5, 84.6, 61.8 and 66.6 (1C), 55.5, 38.2 and 37.6 (1C), 31.2, 28.9 and 28.2 (1C), 28.2, 26.5, 25.2 and 15.4; MS (EI) *m/z* 342 ($M^{\bullet+}$ − 15), 312 ($M^{\bullet+}$ − 45). Anal. Calcd for $C_{18}H_{30}NO_6$: C, 60.48; H, 8.74; N, 3.91. Found: C, 60.25; H, 8.70; N, 3.85.

Methyl 6-cyano-2,3-isopropylidene-5,6,7,8,9-pentadeoxy-9-(trifluoroacetamido)-β-D-nonaribofuranose (9): yield 85%; IR (neat) 3327, 2242, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) 6.65 (s, 1H, NH), 4.96 (s, 1H, H-1), 4.56 (m, 2H, H-2 and H-3), 4.38 and 4.24 (2m, 1H, H-4a and H-4b), 3.42 (m, 2H, H-9), 3.38 and 3.33 (2s, 3H, OMe), 2.8 (m, 1H, H-6), 1.7 (m, 6H, H-5, H-7 and H-8), 1.47 (s, 3H, Me), 1.31 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) 121.4 and 121 (1C), 112.7, 110, 85.2, 84.3, 83.8, 55.5, 39.1, 37.7 and 37.1 (1C), 29.6 and 28.6 (1C), 28.2 and 28 (1C), 26.5, 25; MS (EI) *m/z* 365 ($M^{\bullet+}$ − 15). Anal. Calcd for $C_{16}F_3H_{23}N_2O_5$: C, 50.52; H, 6.09; N, 7.36. Found: C, 50.57; H, 6.02; N, 7.23.

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