Novel Intramolecular Michael Addition of Organomercury Halides Mediated by a Lewis Acid and Halide Anion

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Alkylmercury chloride bearing electron-deficient olefin **3** undergoes a Michael reaction intramolecularly *via* hypervalent intermediates **10** by the double activation method mediated by a Lewis acid and iodide anion to provide spirocyclic compounds **4** and **5**.

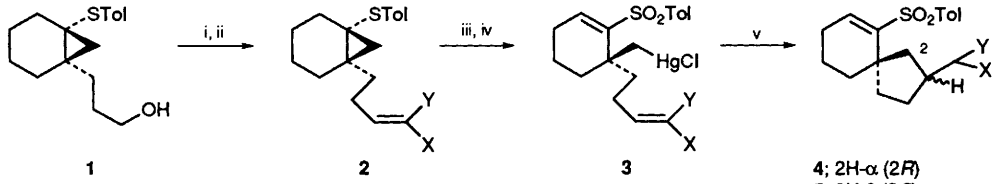
Organo-magnesium, -lithium and -copper reagents are classical and widely used carbanionic alkylating reagents, although they have some disadvantages for handling.[1] In order to overcome these difficulties, air-stable and storable reagents such as organo-silicon,[2] -stannane[3] and lead[4] reagents have been explored as alternative alkylating reagents, and utilized further for assembling carbon framework in natural product synthesis. However, organomercurials are also attractive synthetic intermediates in view of their easy preparation of functionalized reagents by solvomercurations,[5,6] but there are few applications of these reagents in Michael reactions except for radical induced carbon–carbon bond forming reactions[7] and metal exchange methodology employing transition metals (*e.g.* Pd and Cu).[8] As part of ongoing investigations into the use of organomercurials,[9,10] we have studied a new C–C bond forming reaction of these reagents to construct a spiro[4.5]decane skeleton. We report here a unique Lewis acid promotion of a C–Hg bond in the presence of *n*-tetrabutylammonium iodide (Bu^n_4NI) which effects the intramolecular Michael reactions of the alkylmercury chlorides bearing electron-deficient olefin **3a**, **3b** and **3c**.

Table 1 Intramolecular Michael addition of **3a** promoted by Lewis acids in the presence of halide anions

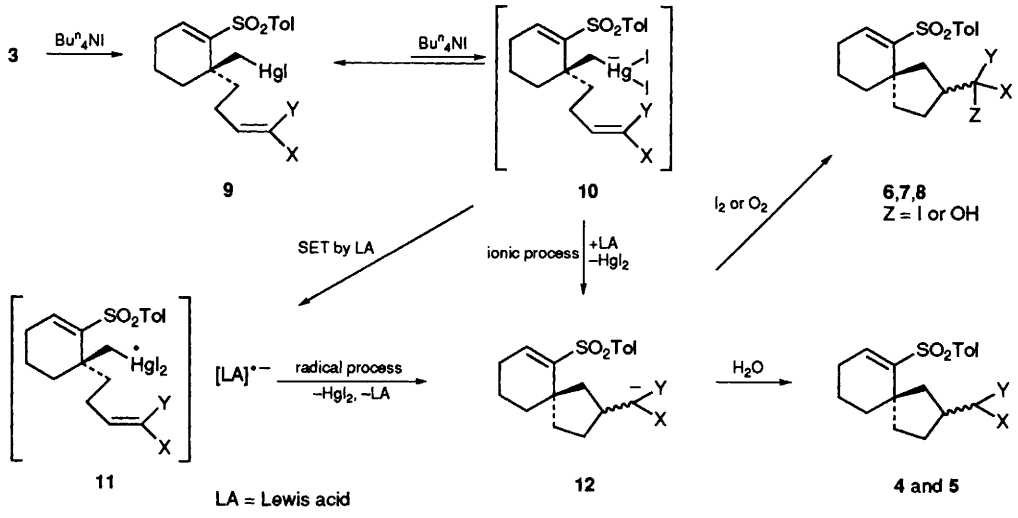
Run	Conditions[a] Ammonium halide	Lewis acid	Yield[b] (%)	Ratio[c] (**4a** : **5a**)
1	—	$TiCl_4$ (5 equiv.), 3 days	0	—
2	Bu^n_4NCl (2 equiv.)	$TiCl_4$ (5 equiv.), 3 days	0	—
3	Bu^n_4NBr (2 equiv.)	$TiCl_4$ (5 equiv.), 3 days	45	87 : 13
4	Bu^n_4NI (1 equiv.)	$TiCl_4$ (5 equiv.), 3 days	32	90 : 10
5	Bu^n_4NI (2 equiv.)	$TiCl_4$ (5 equiv.), 3 days	64	90 : 10
6	Bu^n_4NI (5 equiv.)	$TiCl_4$ (5 equiv.), 3 days	64	96 : 4
7	Bu^n_4NI (2 equiv.)	—	0	—
8	Bu^n_4NI (2 equiv.)	ZnI_2 (5 equiv.), 12 h	32	82 : 18
9	Bu^n_4NI (2 equiv.)	$SnCl_4$ (5 equiv.), 24 h	35	81 : 19
10	Bu^n_4NI (2 equiv.)	$AlCl_3$ (5 equiv.), 6 h	61	85 : 15

[a] All reactions were conducted in CH_2Cl_2 at room temp. [b] All values are isolated yields. [c] The ratio of **4a** to **5a** were determined by HPLC (Sumipax OA 2000A, ethyl acetate : hexane = 1 : 4).

We started with the preparation of **3a** from chiral cyclopropyl sulfide **1**[9] *via* **2a** by the following sequence (Scheme 1): (*i*) Swern oxidation (87%); (*ii*) Knoevenagel condensation with diethyl malonate (59%); (*iii*) ring-opening reaction of **2a** with mercury(II) trifluoroacetate [$Hg(OCOCF_3)_2$] (85%); (*iv*) oxidation using *m*-chloroperbenoic acid (MCPBA) (96%). The intramolecular cyclisation of **3a** was examined in the presence of various Lewis acids, and representative results were summarized in Table 1. Treatment of **3a** with Lewis acids such as titanium tetrachloride ($TiCl_4$) or aluminium chloride ($AlCl_3$) at room temp. unexpectedly did not induce the cleavage of the C–Hg bond and no cyclised product was obtained (run 1). Reinvestigation of another activator of the C–Hg bond revealed that the addition of halide anions was effective for a desired cyclisation of **3a** into the spiro[4.5]decanes (**4a** and **5a**).[11] Although both of the iodide and bromide anions similarly promoted the cyclisation to give **4a** as a major product,† the former anion is superior to the latter in terms of chemical yield (runs 2, 3 and 5). Furthermore, it is interesting to note that (i) the iodide anion does not promote the Michael reaction without $TiCl_4$ (run 7); (ii) the addition of more than two equivalents of Bu^n_4NI is essential to obtain the cyclised product in good yields (runs 4–6). These observations suggest that the iodide ion plays an important role not only for exchanging the counter anion of the mercury atom but also for weakening the C–Hg bond by hypervalent bonding to the mercury atom. Among the employed Lewis acids, the reaction with $TiCl_4$ or $AlCl_3$ furnished a preparative useful yield of a mixture of **4a** and **5a** (runs 5 and 8–10). Particularly, the use of $AlCl_3$ increased dramatically the reaction rate relative to that of $TiCl_4$. Encouraged by these results, we examined the Lewis acid–halide promoted cyclisation of another three analogues bearing lesser electron-deficient olefins **3b**, **3c** and **3d** in order to verify the generality. These were prepared in a similar manner as described for **3a** (Scheme 1). Subjection of **3b** and **3c** with the above conditions [2 equiv. Bu^n_4NI and then 5 equiv. $AlCl_3$ in methylene chloride (CH_2Cl_2) at room temp.] led to a clean cyclisation and gave the corresponding spiro[4.5]decanes **4b**/**5b** and **4c**/**5c** in 82 and 39% yields, respectively. The low yield of **4c** and **5c** in the latter case is attributed to the formation of over-reaction products such as **6** (11%) and **7** (25%). In contrast to the above cases, the α,β-unsaturated ketone **3d** failed to cyclise into **4d** and **5d**



Scheme 1 *Reagent and conditions*: i, $(COCl)_2$, Me_2SO, CH_2Cl_2, −50 °C; Et_3N, room temp. (87%); ii, diethyl malonate, piperidine, NaOAc, benzene, 80 °C (59% for **2a**); $(EtO)_2POCH_2CO_2Et$, NaH, THF, room temp. (82% for **2b**); $(EtO)_2POCH_2CN$, NaH, THF, room temp. (79% for **2c**); $Ph_3PCHCOMe$, THF, reflux (67% for **2d**); iii, $Hg(OCOCF_3)_2$, NaOAc, CH_2Cl_2, room temp.; saturated NaCl, CH_2Cl_2, room temp.; iv, MCPBA, CH_2Cl_2, 0 °C (82% from **2a**, 85% from **2b**, 57% from **2c**, 60% from **2d**); v, Bu^n_4NI, CH_2Cl_2, room temp. then $AlCl_3$ (61% from **3a**, 82% from **3b**, 39% from **3c**)



Scheme 2 Proposed mechanism of the intramolecular Michael reaction promoted by a Lewis acid in the presence of an iodide anion

under the same conditions, while use of tris(4-bromophenyl)-aminium hexachloroantimonate in place of $AlCl_3$ resulted in a smooth formation of the cyclised product **8** in 74% yield. These results suggest that a combination of Michael acceptors and Lewis acids hold the key for the success of the cyclisation and also to determine the product ratio of the final electrophilic reaction; *e.g.* iodination *vs.* protonation.

We speculate that the intramolecular Michael reaction proceeds as shown in Scheme 2. Namely, the hypervalent alkylmercury diiodide anion **10**[11] would be formed as an equilibrium mixture with the alkylmercury iodide **9** which has been produced initially by the halide-exchange reaction with Bu^n_4NI. The intramolecular Michael addition of **10** occurs through an anionic or radical process with the aid of a Lewis acid to give the stabilized anions **12**, which are subsequently exposed to competitive electrophilic reaction with water and iodine (or oxygen), that is, either of the desired products **4/5** or the over-reaction products **6/8** (or **7**) are produced whether **12** was trapped by water or iodide (or oxygen). On the basis on the fact that $AlCl_3$ and tris(4-bromophenyl)aminium hexachloroantimonate, which are known to be strong one-electron oxidants,[12] accelerated the cyclisation into the spiro[4,5]decane skeleton, the latter radical process *via* the radical intermediate **11** which was produced by single-electron transfer (SET), might be more promising than the former ionic one.‡ Further investigations will be required to fully understand a more detailed mechanism and the different results depending on the Michael acceptor moiety.

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Footnotes

† To confirm the stereochemistry at C-2 of **4a** and **5a**, a mixture of ethyl {(2*R*, 5*R*) and (2*S*, 5*R*)-6-(*p*-tolylthio)spiro[4.5]dec-6-en-2-yl}-acetate in a ratio of 89 : 11[9] was converted to **4a** and **5a** in a ratio of 83 : 17 by the following sequence: (*i*) ethoxycarbonylation, (LDA, $CNCO_2Et$, THF, −78 °C); (*ii*) oxidation (MCPBA, CH_2Cl_2, 0 °C). We also examined the cyclisation of **3a** by a radical reaction with *n*-butyltin hydride in CH_2Cl_2 at −40 °C → room temp. to give a mixture of **4a** and **5a** (**4a** : **5a** = 82 : 18) in 68% yield.

‡ Addition of Lewis acids such as $TiCl_4$ and $AlCl_3$ to a solution of **3** and Bu^n_4NI in dry CH_2Cl_2 caused a rapid colour change of the resulting mixture to reddish-purple, which disappeared gradually as the reaction proceeded.