HETEROCYCLES, Vol 28, No. 1, 1989

ALKYLATIONS OF HETEROCYCLES BY ALKYLMERCURIALS[1]

Glen A. Russell,* Deliang Guo, Woonphil Baik, and S. J. Herron

Department of Chemistry, Iowa State University, Ames, Iowa 50011, U.S.A.

Abstract - Alkylmercurials can participate in free radical chain reactions in which the alkyl group substitutes for hydrogen or halogen at a heterocyclic vinyl or aromatic carbon atom, adds in a conjugate manner to α,β-unsaturated lactones or lactams, or undergoes addition-elimination (cyclization) reactions leading to a new heterocyclic ring.

Alkylmercurials (RHgX, R_2Hg) are an excellent source of alkyl radicals upon photolysis or thermolysis. Electron transfer to an alkylmercury halide,[2,3] or attack of an electrophilic radical upon the mercury atom,[4,5] also generates the alkyl radical (Reactions 1 and 2). These

$$\mathrm{RHgX} + \mathrm{D}^{\bullet} \longrightarrow \mathrm{D}^{+} + \mathrm{R}^{\bullet} + \mathrm{Hg}^{\circ} + \mathrm{X}^{-} \qquad (1)$$

$$\mathrm{RHgX} + \mathrm{A}^{\bullet} \longrightarrow \mathrm{AHgX} + \mathrm{R}^{\bullet} \qquad (2)$$

reactions appear to be concerted processes whose rates increase with the stability of the incipient R• (*t*-Bu > *i*-Pr > *n*-Bu).[5,6] Chain reactions can be achieved if a donor (D•) or acceptor (A•) radical can be formed by further reactions of an alkyl radical which is itself not a strong donor or acceptor species. Some examples of D• and A• radicals which have been observed to participate in Reactions 1 or 2 are:[1-7]

Donor Species: $RNO_2^{\bullet -}$; $RCMe_2\dot{C}(O^-)Ph$; $RP(Ph)_2^{\bullet -}$; $R\dot{P}(OMe)_3$; $RCH_2\dot{C}H(C_6H_4OMe\text{-}p)_2$; pyridinyl•

Acceptor Species: $PhSO_2^{\bullet}$; RS•, PhSe•; PhTe•; halogen atoms; *t*-BuO•; $SO_4^{\bullet -}$; $RCH_2\dot{C}H(EWG)$, EWG = $(EtO)_2PO$, $PhSO_2$, $p\text{-}O_2NC_6H_4$, Ph_3Si, $CH_2OP(O)(OEt)_2$, CH_2O_2CR, CH_2OSiMe_3, $CH_2OSMe_2^+$; $RCH{=}\dot{C}Y$, Y = Ph, CO_2Et, COPh, CH_2OTs, $CH_2OP(O)(OEt)_2$

Evidence for Reaction 2 is the observation of strong CIDNP signals in the A/E multiplet mode for RH, R(-H) and R-R when a solution of RHgCl (R = 1°, 2°, 3°-alkyl) and $(NH_4)_2S_2O_8$ is heated in $d_6\text{-}Me_2SO$ at 80°C (Scheme 1). Reaction of Me_3CCO_2H with $S_2O_8^{-2}$ gives a CIDNP signal for $Me_2C{=}CH_2$, but completely in the emission mode from the diffusive encounter of *t*-Bu• and $SO_4^{\bullet -}$.

---

† Dedicated to Sir Derek Barton on the occasion of his 70th birthday.

Scheme 1

$S_2O_8^{-2} \rightleftharpoons 2\ SO_4^{\cdot -}$

$SO_4^{\cdot -} + RHgCl \longrightarrow {}^{-}O_3SOHgCl + R^{\cdot}$

$2\ R^{\cdot} \rightleftharpoons [R^{\cdot}\ R^{\cdot}] \longrightarrow RH,\ R(-H),\ R-R$

Trapping of alkyl radicals by an added radicaphile can lead to chain reactions if the radicaphile derived species will regenerate R· from the alkylmercurial via Reactions 1 or 2. Some examples of reactions which provide such radicals or radical ions are listed according to reaction type in A-C ($Q^{\cdot} = D^{\cdot}$ or $A^{\cdot}$):

(A) S_H2 reactions of R· ($R^{\cdot} = Y\text{-}Q \longrightarrow R\text{-}Y + Q^{\cdot}$)[5-7]

$Y\text{-}Q$ = dichalcogenides, H-SPh, $H\text{-}SnBu_3$, $PhSe\text{-}SO_2Ph$, $Cl\text{-}SO_2Ph$, N-alkyl-1,4-dihydropyridines

(B) Addition ($R^{\cdot} + \pi \longrightarrow R\text{-}\pi^{\cdot}$)

$R\text{-}\pi^{\cdot}$ is an acceptor ($R\text{-}\pi^{\cdot} + RHgX \longrightarrow R\text{-}\pi\text{-}HgX + R^{\cdot}$)[6]

$\pi = CH_2{=}CHP(O)(OEt)_2$, $CH_2{=}CHSO_2Ph$, $CH_2{=}C(C_6H_4NO_2\text{-}\underline{p})_2$, $CH_2{=}CHCH_2OTs$, $CH_2{=}CHCH_2OP(O)(OEt)_2$, $HC{\equiv}CPh$, $HC{\equiv}CCO_2Et$, $HC{\equiv}CCOPh$, $HC{\equiv}CCH_2OTs$, $HC{\equiv}CCH_2OP(O)(OEt)_2$

$R\text{-}\pi^{\cdot}$ is a donor ($R\text{-}\pi^{\cdot} + RHgX \longrightarrow R\text{-}\pi^{+} + R^{\cdot} + Hg^{\circ} + X^{-}$)[2,3,8]

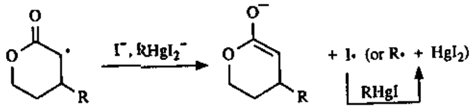
π = pyridine, $CH_2{=}C(C_6H_4OMe\text{-}\underline{p})_2$, $R^1R^2C{=}NO_2^{-}$, $R^1R^2C{=}C(O^{-})Ph$, Ph_2P^{-}, $(MeO)_3P$

(C) Addition-elimination ($R^{\cdot} + \pi\text{-}Q \longrightarrow R\text{-}\dot{\pi}\text{-}Q \longrightarrow R\text{-}\pi + Q^{\cdot}$)[5,9,10]

$\pi\text{-}Q = PhCH{=}CHQ$ or $PHC{\equiv}CQ$ with Q = Cl, Br, I, $PhSO_2$, PhSO, PhS, HgCl, $SnBu_3$; $PhCOCH{=}CHCl$; $PhSO_2CH{=}CHSnBu_3$; $MeO_2CCH{=}CHI$; $CH_2{=}CHCH_2Cl(Br, I)$; $HC{\equiv}CCH_2Cl$

Figure 1 illustrates reactions involving heterocyclic products. These reactions involve (a) substitution of alkyl for hydrogen at a sp^2-center, (b) substitution of alkyl for halogen at a sp^2-center, (c) addition of the elements of R and H to an α,β-unsaturated system and (d) cyclization of an adduct radical yielding a heterocyclic ring.

Reactions of α,β-unsaturated ketones, esters, amides or anhydrides with 2° or 3°-alkyl radicals occur readily to form enolyl radicals. However, enolyl radicals often react inefficiently with RHgCl *although they are trapped in good yields* by hydrogen atom transfer from RHgH or Bu_3SnH.[11] However, in the presence of iodide ion, enolyl radicals can be reduced to the enolate anion (I^- or $RHgI_2^-$ may be the reducing agent) and the chain reaction propagated (Reaction 3). 5,6-Dihydro-2H-pyran-2-one gives only a low yield of tert-butylated product with t-BuHgCl/hν in the absence of I^-



(3)

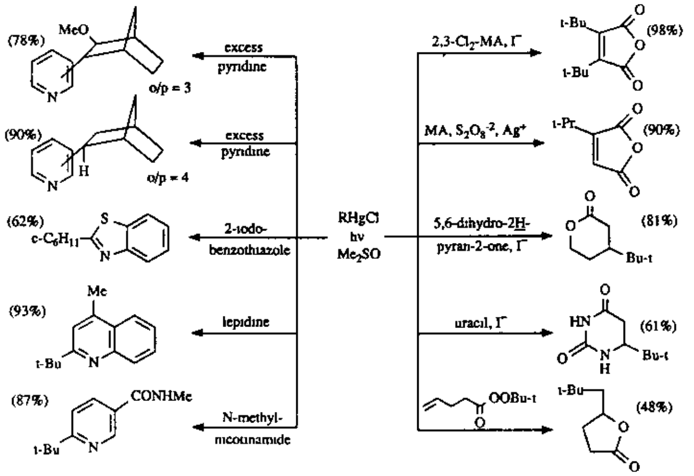
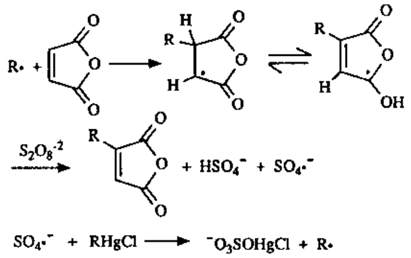


Figure 1. Photostimulated reaction (sunlamp or 350 nm Rayonet Photoreactor) of 2-5 equivalents of RHgX with various substrates in Me_2SO at 40-45 °C for 3-10 h.

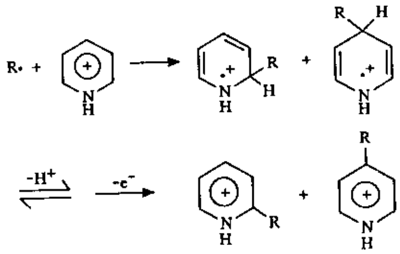
and is a substrate not easily alkylated by conventional cuprate reagents. However, with t-BuHgCl/NaI/hν in Me_2SO, an excellent yield of the 4-tert-butyl derivative is formed (Figure 1). In a similar fashion uracil reacts to form the conjugate addition product.

Another ploy which converts an enolyl radical into a substitution product is β-hydrogen atom abstraction. Thus, photolysis of t-BuHgCl in the presence of maleic anhydride gives a low yield of the mono tert-butylated product. Even in the presence of I^- the reaction is not clean. However, in the presence of $S_2O_8^{-2}$ the intermediate adduct radical is converted to tert-butylmaleic anhydride by electron or hydrogen atom transfer to $S_2O_8^{-2}$. Tautomerization of the initial adduct radical may be involved (Scheme 2). Yields of the substitution product with a 2-fold excess of RHgX of 63% and 90% are observed with R = t-Bu and i-Pr by the use of 2 equiv. of $S_2O_8^{-2}$ with t-BuHgCl or 2 equiv. of $S_2O_8^{-2}$ and 1 equiv. of Ag^+ with i-$PrHgNO_3$.

Scheme 2



Scheme 3



Attack of alkyl radicals upon pyridine or pyridinium ions occurs ortho and para to the nitrogen atom; loss of a proton, or tautomerization in case of the uncharged adduct radical, leads to an easily oxidized pyridinyl radical which can be oxidized to the pyridinium ion by electron transfer either to RHgCl (Reaction 1)[3,7] or to an added oxidant such as $S_2O_8^{-2}$.[12] Photostimulated reaction of pyridium salts with RHgCl thus follows Scheme 3. Faster reactions are observed with the RHgCl/$S_2O_8^{-2}$/Ag^{+1} system where Ag^{+2} ($Ag^{+} + S_2O_8^{-2} \longrightarrow Ag^{+2} + SO_4^{\cdot -} + SO_4^{-2}$) and/or $S_2O_8^{-2}$ oxidize the pyridinyl radical and the chain reaction continues by attack of $SO_4^{\cdot -}$ upon RHgCl.

The utility of alkylation processes with alkylmercurials is not restricted by weakly acidic (e.g., uracil in Figure 1) or basic groups. Furthermore, a wide variety of solvomercuration products can be employed, often without isolation of the mercurial (e.g., the alkylated pyridine in Figure 1).[3] In most cases better yields of alkylation products and faster rates of reaction are observed with 2° or 3°-alkylmercurials than with 1°-alkylmercurials.

REFERENCES AND NOTES

1. Electron Transfer Processes. Part 44. Work supported by grants from the National Science Foundation (CHE-8717871) and the Petroleum Research Fund (18911-AC4-C).
2. G. A. Russell, J. Hershberger, and K. Owens, J. Am. Chem. Soc., 1979, **101**, 1312.
3. G. A. Russell, D. Guo, and R. K. Khanna, J. Org. Chem., 1985, **50**, 3423.
4. G. A. Russell and H. Tashtoush, J. Am. Chem. Soc., 1983, **105**, 1398.
5. G. A. Russell, P. Ngoviwatchai, H. I. Tashtoush, A. Pla-Dalmau, and R. K. Khanna, J. Am. Chem. Soc., 1988, **110**, 3530.
6. G. A. Russell, W. Jiang, S. S. Hu, and R. K. Khanna, J. Org. Chem., 1986, **51**, 5498.
7. H. Kurosawa, H. Okada, and T. Hattori, Tetrahedron Lett., 1981, **22**, 4495.
8. G. A. Russell and R. K. Khanna, J. Am. Chem. Soc., 1985, **107**, 1450.
9. G. A. Russell, H. Tashtoush, and P. Ngoviwatchai, J. Am. Chem. Soc., 1984, **106**, 4622.
10. G. A. Russell and P. Ngoviwatchai, Tetrahedron Lett., 1985, **26**, 4975; 1986, **27**, 3479; 1987, **28**, 6113.
11. B. Giese, 'Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds,' Pergamon Press, Oxford, 1986.
12. F. Minisci, C. Giordano, E. Vismara, S. Levi, and V. Tortelli, J. Am. Chem. Soc., 1984, **106**, 7146.

Received, 27th August, 1988