NUCLEOPHILIC RADICAL SUBSTITUTION OF POLYCHLOROAZINES

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Abstract - Polychloroazines (1-6) are susceptible to homolytic chlorine substitution by alkyl radicals. In general, the chlorine at the ortho-position to the ring nitrogen is readily replaced by an alkyl radical like adamantyl and *tert*-butyl. However, the chlorine at the C_2-position of pyrimidine did not show any sign of the radical substitution. The reactivity decreases in the order of adamantyl, *tert*-butyl, and isopropyl radicals.

Pyridine and quinoline derivatives react with an alkyl or acyl radical to give the corresponding substitutuion products under acidic conditions.[1-3] In line with our effort to modify *N*-heterocyclic coenzyme models, we have reported radical alkylations of pyridine and pyrazine derivatives having an amide or a cyano group.[4-6]

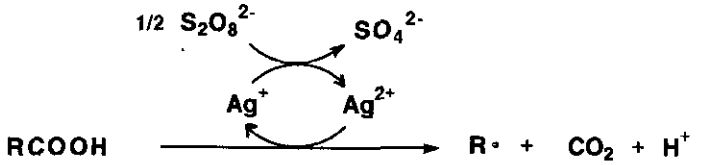
Pyridine derivatives having an electron withdrawing substituent such as carbamoyl or cyano group are important as the analogs of nicotinamide, the reaction center of NAD(P) coenzyme. Pyrazinedicarbonitrile can be transformed into a pteridine derivative, a folic acid model, by a simple procedure.[7] Polychloropyridines and polychlorodiazines are dehalogenated by catalytic hydrogenolysis in the presence of base, and they are important

synthetic intermediates of *N*-heterocycle in many cases.[8]

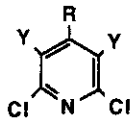
In π-deficient *N*-heterocycles, the radical substitution begins by a nucleophilic attack of an alkyl radicasl on the heterocycles.[4-6] This feature suggests us the possibility of the homolytic dechloro-alkylation of chloro-*N*-heterocycles, which has not been reported to the best of our knowledge. Based on this back ground, we investigated the homolytic alkylation of polychloroazines to get a scope of the reaction as a means for the preparation of alkylazines and also to chracterize this new type of homolytic chlorine-alkyl displacement.

Alkyl radicals were generated by the silver(II) mediated oxidation of alkanoic acids by peroxodisulfate (Scheme I):[9] *N*-heterocycle (0.3 mmol), silver(I) nitrate (0.6 mmol), alkanoic acid (0.9 mmol), and ammonium peroxodisulfate (0.6 mmol) in water-acetonitrile (1:1) at 80°C for 22 h under argon. All the reactions were carried out under the identical conditions to compare the reactivities and the reactions were quenched prior to completion.

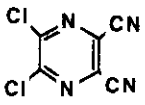
The reaction of 2,6-dichloro-4-methylpyridine-3,5-dicarbonitrile (1a) with adamantyl radical, which was generated under the conditions described above, gave 2-adamantyl-6-chloro-4-methylpyridine-3,5-dicarbonitrile (7a) along with 2,6-diadamantylpyridine-3,5-dicarbonitrile (8a).[11] Structure (7a) was determined by elemental analyses and mass spectrum, 313 (M^++2, 34%), 311 (M^+, 100%). Similar products were obtained with *tert*-butyl radical as well as with isopropyl radical and the results are listed in Table 1. The



Scheme I



1a: R=Me, Y=CN
1b: R=H, Y=H



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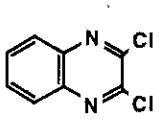

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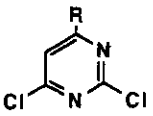

5a: R=Cl
5b: R=H

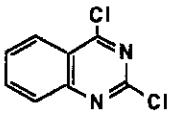

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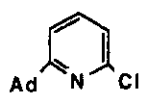
Table 1. Alkyl radical substitution of pyridine and diazine derivatives.

Starting material	Alkyl radical (R·)	Product	Yield (%)
1a	Ad	7a	57
		8a[11]	1
1a	*t*-Bu	7b	37
		8b[11]	1
1a	i-Pr	7c	37
		8c[11]	1
1b	Ad	9	3
2	Ad	10a	35
		11	6
2	*t*-Bu	10b	31
2	i-Pr	10c	12
3	Ad	12	47
4	Ad	13a	38
4	*t*-Bu	13b	2
5a	Ad	14a	16
5b	Ad	14a	47
		14b	13
6	Ad	15	65

7a: R=Ad, R'=Cl
7b: R=*t*-Bu, R'=Cl
7c: R=i-Pr, R'=Cl
8a: R=R'=Ad
8b: R=R'=*t*-Bu
8c: R=R'=i-Pr



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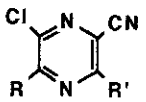
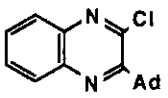


10a: R=Ad, R'=CN
10b: R=*t*-Bu, R'=CN
10c: R=i-Pr, R'=CN
11: R=Cl, R'=Ad



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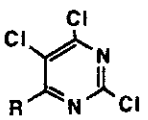
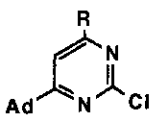
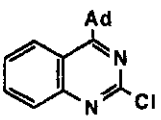


13a: R=Ad
13b: R=*t*-Bu



14a: R=Cl
14b: R=H



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reaction of 2,6-dichloropyridine (1b) with adamantyl radical gave a chlorine-substituted product (9) in poor yield but no hydrogen-substituted product. Dichloropyridine (1b) does not react with *tert*-butyl and isopropyl radicals. Structure (9) was deduced from the molecular isotope peaks in the mass spectrum, which showed 9 to be a monochloro-derivative; m/z=249 (M^++2, 33%) and 247 (M^+, 100%), and a triplet (δ 7.56) for C_4-H and two doublets (δ 7.10 and 7.15) for C_3- and C_5-H in ^{1}H-nmr spectrum.

The reaction of 5,6-dichloropyrazine-2,3-dicarbonitrile (2) with adamantyl radical gave a chlorine-substituted product (10a) along with a cyano group substituted product (11). Structures for 10a and 11 were unequivocally deduced from the mass spectra, which showed typical molecular isotope peaks for a monochloro and dichloro derivative: m/z=300 (M^++2, 33%) and 298 (M^+, 100%) for 10a; 311 (M^++4, 11%), 309 (M^++2, 66%), and 307 (M^+, 100%) for 11. The reaction of 2 with *tert*-butyl and isopropyl radicals gave only monochlorine-substituted products (10b) and (10c) respectively (Table 1).

The reaction of 2,3-dichloroquinoxaline (3) with adamantyl radical gave only monochlorine-substituted product (12).

2,4,5,6-Tetrachloropyrimidine (4) reacted with adamantyl and *tert*-butyl radicals to give monochlorine-substituted products (13a) and (13b) respectively, but did not react with isopropyl radical. There are three possible sites of substitution for 4. Four peaks due to the ring carbons in ^{13}C-nmr spectrum clearly deduced the unsymmetrical structures (13).

2,4,6-Trichloropyrimidine (5a) reacted with adamantyl radical to give a dichloro-derivative (14a). The four ^{13}C-nmr signals due to the ring carbons showed the unsymmetrical structure (14a).

2,4-Dichloropyrimidine (5b) reacted with adamantyl radical to give a hydrogen-substituted product (14a) and a C_4-chlorine substituted product (14b). The structure assignment of 14b was made by the comparison of the ^{13}C-nmr data with those of 5b; C_2 (δ 162.6), C_4 (159.9), C_5 (120.2), and C_6

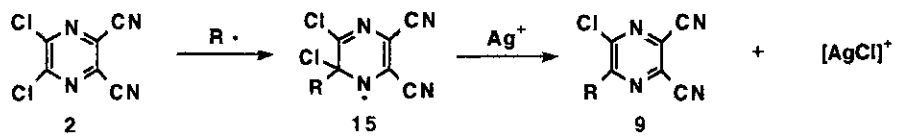
(161.0) and the observation of NOE between the adamantyl and *ortho*-hydrogen. Diazines 3, 5a, 5b, and 6 gave no substitution product with *tert*-butyl and isopropyl radical.

2,4-Dichloroquinazoline (6) reacted with adamantyl radical to give the substitution product (15) of C_4-chlorine. Structure assignment was made by the comparison of ^{13}C-nmr signals with those of dichloroquinazoline (6) and the observation of NOE between the adamantyl and *peri*-hydrogen.

DISCUSSION

A proposed reaction mechanism for the present radical substitution is shown in Scheme II. Alkyl radicals attack the chlorine-bearing carbon adjacent to a ring nitrogen rather than the cyano group bearing carbon, and the silver-assisted chlorine rupture gave an alkylated product. The last process gives silver(I) chloride and the oxidant silver (II) ion (Equation 1). Contrary to hydrogen-alkyl radical substitutions,[1-6] a silver ion was consumed stoichiometrically to give precipitates of silver(I) chloride. All the reactions were carried out under the same reaction conditions and the yields listed in Table 1 can be regarded as a reasonable reflection of the relative reactivity of chloro-derivatives of pyridine and diazine, and also the relative reactivity of alkyl radicals.

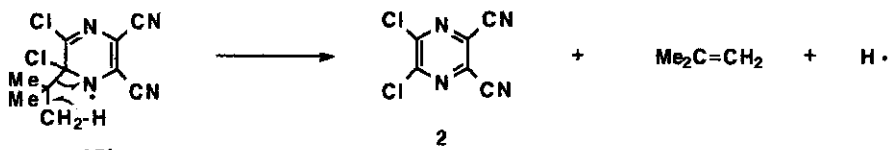
These radical substitutions must proceed in a nucleophilic manner as reported for the related π-deficient nitrogen-heterocycles.[1-6] Adamantyl



Scheme II

$$[AgCl]^+ + Ag^+ \rightleftharpoons AgCl + Ag^{2+} \qquad \text{(Eq. 1)}$$

radical is superb in these radical substitutions as expected from its high SOMO energy level.[10] Isopropyl radical showed a modest reactivity to give the product (7c), (8c), and (10c) from 1 and 2, but did not react with other tested diazines. *tert*-Butyl radical is expected to have as high reactivity as adamantyl radical,[11] but there is an escaping route to generate the starting material and isobutene from the intermediate radical (15') (Scheme III). This dissipation route suppresses the substitution process. The intermediate from adamantyl radical is considered to lack this dissipation route since this envisaged process is highly prohibited by the formation a bridge-head double bond.



Scheme III

2,6-Dichloro-4-methylpyridine-3,5-dicarbonitrile (1a) is reactive to the radical substitution, but 2,6-dichloropyridine (1b) hardly reacts with alkyl radicals. This result suggests that the chloro-substituent does not activate a pyridine ring as alkoxycarbonyl, carbamoyl, and cyano groups.[4,11] The reaction of 2 with alkyl radicals gave the chlorine-substituted products, preferentially with adamantyl radical or exclusively with *tert*-butyl and isopropyl radical. Thus in the present type of reaction, the chlorine-substitution takes place more easily than the cyano group substitution. In the reaction of tetrachloropyrimidine (4), there are three kinds of chlorine-bearing sites but only the $C_4(=C_6)$ was the active site for the reaction. Thus the C_2 and C_5-sites of 4 are nonreactive. The site selectivity in those chlorine-alkyl radical substitutions of pyrimidine derivatives has similar trend as the selectivity of ionic nucleophilic

aminolysis and alcoholysis of chloropyrimidine derivatives.[8] In these nucleophilic aminolyses and alcoholyses, the C_4-site is more reactive but the C_2-site retains its reactivity. Present alkyl radical substitution, on the other hand, showed no reactivity on the C_2-chlorine. This feature can be accounted for by the less nucleophilicity of alkyl radical than those of amine and alcohol.

In the reaction of **5b**, C_6-H is more susceptible to the radical substitution than C_4-Cl group. This result indicates that hydrogen is more reactive than chlorine when those are under the same electronic circumstance. The relative reactivity of hydrogen, chlorine, and cyano group on *N*-heterocycles for the alkyl radical substitution decreases in that order. The above mentioned reactions are new types of radical substitution on *N*-heterocycles and the yields can be improved by adopting appropriate reaction conditions.

Chloropyridines and dichloropyrazines are conventionally prepared from the corresponding pyridinones and diazinediones respectively, and the chloro-derivatives can be dehalogenated as mentioned earlier.[8] The present study, therefore, opens a new aspect for the syntheses of alkylated *N*-heterocycles.

EXPERIMENTAL

Ir spectra were measured by a Perkin-Elmer 1640 FT-IR spectrophotometer in chloroform solution. ^{1}H-nmr spectra (90 MHz) and ^{13}C-nmr spectra (100 MHz) were measured by a Hitachi R-90 spectrometer and a JEOL GSX-400 spectrometer, respectively, in deuteriochloroform. Chemical shifts and coupling constants were recorded in δ-value (TMS standard) and Hz respectively. Mass spectra were made by a JEOL JMS-DX306 spectrometer by electron impact ionization at 70 eV.

Starting materials (**1b**, **3**, **4**, **5a**, and **5b**) were commercially available from

Aldrich Co. and used without purification. Starting materials (1a, 2, and 6) were prepared by the reported procedures.[12-14]

Alkylation of polychloroazines.

A mixture of one of the polychloroazines (0.3 mmol), an alkanoic acid (0.9 mmol), $AgNO_3$ (100 mg, 0.6 mmol) in 1 ml of acetonitrile-water (1:1) was deaerated by bubbling argon, and treated with ammonium peroxodisulfate (80 mg, 0.6 mmol) in 0.5 ml of water at 80°C. The reaction mixture was kept at the same temperature for 2.2 h under argon. After cooling, the mixture was added with aqueous ammonia to make alkaline and extracted with chloroform. The extract was washed with saturated sodium hydrogen carbonate, dried over sodium sulfate, and concentrated *in vacuo*. The reaction products along with the starting material were separated from the residue by tlc on silica gel plate (20X20 cm, 2 mm thickness) using the solvent system recorded in the following description. All the products were recrystallized from ethanol unless otherwise mentioned.

The reaction of dichloropyridine derivative (1a) with adamantyl, *tert*-butyl, and isopropyl radical and tlc separation gave 7a, 7b, and 7c, respectively, along with 8a, 8b, and 8c which were reported in our previous paper[11] (tlc solvent: hexane-ether 1:1 for 7a, 7b, 8a, and 8b; hexane-ether 2:1 for 7c and 8c). The reaction of dichloropyridine (1b) with adamantyl radical under the same conditions gave 9 (tlc solvent: chloroform).

7a, mp 212.8-213.5°C, ir 2904, 2854, 2229, 1556, 1531 cm^{-1}; ^{1}H-nmr 1.63-1.89 (6H, m), 1.95-2.32 (9H, m), 2.79 (3H, s); ms (m/z) 313 (M^++2, 34%), 311 (M^+, 100%), 310 (14%). *Anal.* Calcd for $C_{18}H_{18}N_3Cl$: C, 69.34; H, 5.82; N, 13.48. Found: C, 69.29; H, 5.85; N, 13.33.

7b, mp 152.5-153.0°C; ir 2937, 2908, 2874, 2230, 1560, 1526 cm^{-1}; ^{1}H-nmr 1.55 (9H, s), 2.79 (3H, s); ms (m/z) 235 (M^++2, 5%), 233 (M^+, 16%), 220

(32%), 218 (100%). *Anal.* Calcd for $C_{12}H_{12}N_3Cl$: C, 61.69; H, 5.18; N, 17.98. Found: C, 61.41; H, 4.94; N, 17.95.

7c, mp 106.0-106.7°C; ir 2935, 2876, 2234, 1564, 1541 cm^{-1}; ^{1}H-nmr 1.35 (6H, d, J=6.8), 2.78 (3H, s), 3.35 (1H, sept, J=6.8); ms (m/z) 221 (M^++2, 8%), 219 (M^+, 23%), 206 (29%), 204 (100%). *Anal.* Calcd for $C_{11}H_{10}N_3Cl$: C, 60.14; H, 4.59; N, 19.13. Found: C, 60.17; H, 4.64; N, 19.20.

9, mp 109.0-112.0°C; ir 2908, 2851, 1583, 1557 cm^{-1}; ^{1}H-nmr 1.45-1.85 (6H, m), 1.90-2.30 (9H, m), 7.10 (1H, d, J=7.7), 7.15 (1H, d, J=7.7), 7.56 (1H, t, J=7.7); ms (m/z) 249 (M^++2, 33%), 247 (M^+, 100%). High resolution ms Calcd for $C_{15}H_{18}NCl$: (m/z) 247.1128. Found: 247.1109.

The reaction of dichloropyrazine derivative (2) with adamantyl radical gave 10a and 11 (tlc solvent: chloroform). The reaction with *tert*-butyl and isopropyl radicals gave 10b and 10c respectively (tlc solvent: chloroform).

10a, mp 118.5-120.3°C; ir 2911, 2855, 2234, 1453 cm^{-1}; ^{1}H-nmr 1.61-1.92 (6H, m), 1.92-2.35 (9H, m); ^{13}C-nmr 28.1, 36.2, 38.2, 42.5, 112.0, 112.5, 128.8, 129.8, 150.7, 166.1; ms (m/z) 300 (M^++2, 33%), 298 (M^+, 100%), 263 (32%). High resolution ms Calcd for $C_{10}H_{15}N_4Cl$: (m/z) 298.0985. Found: 298.0965.

11, mp 90.2-91.8°C; ir 2911, 2854, 2237, 1453 cm^{-1}; ^{1}H-nmr 1.45-1.94 (6H, m), 1.94-2.52 (9H, m); ^{13}C-nmr 28.5, 36.3, 40.0, 40.2, 115.4, 124.4, 144.4, 149.1, 165.4; ms (m/z) 311 (M^++4, 11%), 309 (M^++2, 66%), 307 (M^+, 100%). High resolution ms Calcd for $C_{15}H_{15}N_3Cl_2$: (m/z) 307.0643. Found: 307.0611.

10b, mp 106.4-107.6°C; ir 2938, 2874, 2384, 1523, 1480 cm^{-1}; ^{1}H-nmr 1.55 (9H, m); ^{13}C-nmr 27.8, 40.1, 111.9, 112.5, 129.3, 129.5, 151.0, 166.8; ms (m/z) 222 (M^++2, 5%), 220 (M^+, 15%), 207 (32%), 205 (100%). High resolution ms Calcd for $C_{10}H_9N_4Cl$: (m/z) 220.0516. Found: 220.0528.

10c, mp 66.8-68.1°C; ir 2936, 2876, 2243, 1526, 1470 cm^{-1}; ^{1}H-nmr 1.35 (6H, d, J=6.6), 3.63 (1H, sept, J=6.6); ^{13}C-nmr 20.5, 33.1, 112.0, 112.5, 129.6, 130.9, 151.3, 166.2; ms (m/z) 208 (M^++2, 8%), 206 (M^+, 24%), 193 (33%), 191

(100%). High resolution ms Calcd for $C_9H_7N_4Cl$: (m/z) 206.0359. Found: 206.0369.

The reaction of dichloroquinoxaline (3) with adamantyl radical gave 12 (tlc solvent: hexane-chloroform, 1:1).
12, mp 98.5-99.6°C; ir 3014, 2908, 2852, 1565, 1478, 1454 cm^{-1}; ^{1}H-nmr 1.56-1.80 (6H, m), 1.80-2.46 (9H, m), 7.36-8.05 (4H, m); ^{13}C-nmr 28.6, 36.7, 39.0, 41.4, 127.7, 129.0, 129.9, 130.0, 140.0, 140.1, 146.2, 159.8; ms (m/z) 300 (M^++2, 34%), 298 (M^+,100%), 263 (39%). High resolution ms Calcd for $C_{18}H_{19}N_2Cl$: (m/z) 298.1236. Found: 298.1222.

The reaction of tetrachloropyrimidine (4) with adamantyl and *tert*-butyl radical gave 13a and 13b respectively (tlc solvent: hexane-benzene, 2:1).
13a, mp 147.1-148.0°C; ir 2908, 2854, 1530, 1485, 1455 cm^{-1}; ^{1}H-nmr 1.56-1.88 (6H, m), 1.88-2.35 (9H, m); ^{13}C-nmr 28.3, 36.4, 38.0, 42.7, 127.4, 156.2, 161.5, 176.2; ms (m/z) 322 (M^++6, 4%), 320 (M^++4, 34%), 318 (M^++2, 99%), 316 (M^+, 100%). *Anal.* Calcd for $C_{14}H_{15}N_2Cl_3$: C, 52.94; H, 4.76; N, 8.82. Found: C, 52.66; H, 4.85; N, 8.58.
13b, mp 60.0-61.2°C; ir 2936, 2908, 2873, 1526, 1486 cm^{-1}; ^{1}H-nmr 1.49 (9H, s); ^{13}C-nmr 27.8, 40.4, 127.3, 155.9, 161.0, 177.1; ms (m/z) 244 (M^++6, 1%), 242 (M^++4, 4%), 240 (M^++2, 10%), 238 (M^+, 11%), 229 (4%), 227 (32%), 225 (97%), 223 (100%). *Anal.* Calcd for $C_8H_9N_2Cl_3$: C, 40.12; H, 3.79; N, 11.69. Found: C, 40.09; H, 3.79; N, 11.70.

The reaction of trichloropyrimidine (5a) and dichloropyrimidine (5b) with adamantyl radical gave 14a and 14b (tlc solvent: carbon tetrachloride).
14a, mp 158.0-158.6°C; ir 3012, 2910, 2854 cm^{-1}; ^{1}H-nmr 1.65-1.87 (6H, m), 1.78-2.26 (9H, m), 7.20 (1H, s); ^{13}C-nmr 28.2, 36.3, 39.8, 40.8, 115.6, 160.3, 162.6, 182.5; ms (m/z) 286 (M^++4, 11%), 284 (M^++2, 68%), 282 (M^+,

100%). *Anal.* Calcd for $C_{14}H_{16}N_2Cl_2$: C, 59.38; H, 5.69; N, 9.89. Found: C, 59.12; H, 5.74; N,9.80.

14b, mp 45.5-46.1°C (ethanol-hexane, 1:1); ir 2910, 2853, 1572, 1527, 1452 cm^{-1}; ^{1}H-nmr 1.55-1.87 (6H, m), 1.87-2.26 (9H, m), 7.18 (1H, d, J=5.3), 8.51 (1H, d, J=5.3); ^{13}C-nmr 28.4, 36.4, 39.6, 41.0, 115.0, 159.2, 162.2, 181.0; ms (m/z) 250 (M^++2, 35%), 248 (M^+, 100%). High resolution ms Calcd for $C_{14}H_{17}N_2Cl$: (m/z) 248.1080. Found: 248.1088.

The reaction of dichloroquinazoline (**6**) with adamantyl radical gave **15** (tlc solvent: hexane-chloroform, 1:1).

15, mp 175.8-176.4°C; ir 2909, 2854, 1567, 1526, 1495, 1455 cm^{-1}; ^{1}H-nmr 1.53-1.95 (6H, m), 1.95-2.45 (9H, m), 7.35-8.21 (3H, m), 8.55-8.82 (1H, m); ^{13}C-nmr 28.8, 36.8, 41.6, 43.3, 121.7, 126.3, 126.6, 129.4, 133.5, 153.0, 156.7, 180.2; ms (m/z) 300 (M^++2, 34%), 298 (M^+, 100%), 297 (48%). *Anal.* Calcd for $C_{18}H_{19}N_2Cl$: C, 72.11; H, 6.39; N, 9.34. Found: C, 72.21; H, 6.27; N, 9.34.

REFERENCES

1. F. Minisci, E. Vismara, and F. Fontana, *Heterocycles, 1989,* **28**, 489.
2. F. Minisci, F. Fontana, and E. Vismara, *J. Heterocycl. Chem., 1990,* **27**, 79.
3. R. Baur, E. Kleiner, and W. Pfleiderer, *Liebigs Ann. Chem., 1984,* 1798.
4. M. Tada and Y. Yokoi, *J. Heterocycl. Chem., 1989,* **26**, 45.
5. M. Tada, T. Ito, and K. Ohshima, *J. Heterocycl. Chem., 1986,* **23**, 1893.
6. M. Tada and S. Totoki, *J. Heterocycl. Chem., 1988,* **25**, 1295.
7. K. Tsuzuki and M. Tada, *J. Heterocycl. Chem., 1986,* **23**, 1299.
8. "*Comprehensive Heterocyclic Chemistry" Vol. 3,* ed. by A. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1979, pp. 98-104.

9. F. Minisci, A. Citterio, and C. Giordano, *Acc. Chem. Res., 1983,* 16, 27.

10. G. H. Kruppa and J. L. Beauchamp, *J. Amer. Chem. Soc., 1986,* 108, 2162.

11. N. Kanomata, H. Nagahara, and M. Tada, *J. Heterocycl. Chem., 1992,* 29, 1567.

12. M. Lounasmaa, *Acta Chem. Scand., 1971,* 25, 1151.

13. T. Suzuki, Y. Nagase, and K. Mitsuhashi, *J. Heterocycl. Chem., 1986,* 23, 1419.

14. K. Butler and M. W. Partridge, *J. Chem. Soc., 1959,* 1512.

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