Pergamon

Tetrahedron 54 (1998) 2107–2112

TETRAHEDRON

Synthesis of 5-(2′-Pyridyl)-Indolizines by the Reaction of 2-(2′-Pyridyl)-Pyridinium-Ylides with Activated Alkynes

Ioan I. Druta*, Mioara A. Andrei, Pompiliu S. Aburel

"Al. I. Cuza" University, Organic Chemistry Departament, B-dul Copou, Nr. 11, Iasi-6600, Romania.

Received 9 October 1997; revised 10 December 1997; accepted 11 December 1997

Abstract : New heterocyclic compounds, indolizine derivatives, were prepared by 3+2 dipolar cycloaddition reactions. These compounds were synthesized by the reaction of 2–(2′–pyridyl)–pyridinium–ylides **5–8** with dimethyl acetylenedicarboxylate or ethyl propiolate. The structure of the new compounds was established by elemental analysis (C,H,N) and IR and ^{1}HNMR spectral methods.

Introduction

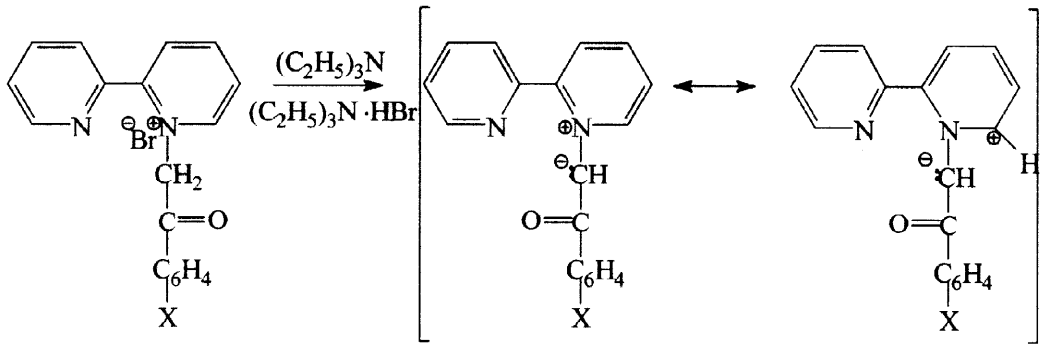
There are many references in the literature [1-9] related to the cycloaddition reactions of cycloimmonium ylides to activated symmetrical or non-symmetrical olefins and alkynes. These reactions are very interesting due to the possibility of preparing new heterocycles which are difficult to obtain otherwise.

This is the reason for which we decided to carryout, for the first time, in the class of 2,2′–bipyridyl, some reactions of 2–(2′–pyridyl)–pyridinium–ylides with dimethyl acetylenedicarboxylate and ethyl propiolate to yield indolizine derivatives.

Results and Discussion

Heterocyclic compounds, namely indolizine derivatives, were synthesized by the 3+2 dipolar cycloadditions of 2–(2′–pyridyl)–pyridinium–ylides **5–8** to dimethyl acetylenedicarboxylate or ethyl propiolate. 2–(2′–Pyridyl)–pyridinium salts **1–4** were synthesized by reaction of 2,2′–bipyridyl with reactive halide derivatives, as previously reported.[10] Ylides **5–8** were obtained *in situ* by the reaction between salts **1–4** and triethylamine in benzene. Ylides **5–8** have an amphionic structure and can react in the 3+2 dipolar cycloaddition reactions like dipole 1,3, according to the structures **5–8b** (figure 1).

PII: S0040-4020(97)10419-7

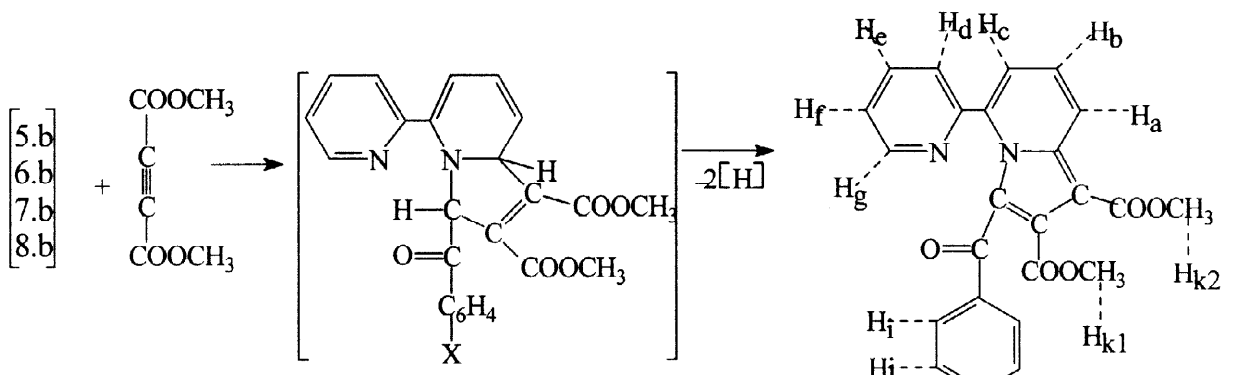


1.X=H
2.X=NO_2
3.X=OCH_3
4.X=Br

5.X=H
6.X=NO_2
7.X=OCH_3
8.X=Br

Fig. 1.Amphionic structure of 2–(2′–pyridyl)–pyridinium–ylides

2–(2′–Pyridyl)–pyridinium–ylides **5–8b** react with dimethyl acetylenedicarboxylate to give cycloadducts **13–16**. As figure 2 shows, ylides obtained *in situ*, very likely form unisolable intermediate cycloadducts of type **9–12,** which due to the tendency of stabilization suffer a dehydrogenation process. As we worked in ambient conditions, it is possible an oxidative dehydrogenation process occurred, too. Finally, isolable cycloadducts **13–16** were obtained. These products contain a system of conjugated double bonds.



9.X=H
10.X=NO_2
11.X=OCH_3
12.X=Br

13.X=H - - - - H_m
14.X=NO_2
15.X=OCH_3 - -H_n
16.X=Br

Fig. 2. Reaction between cycloimmonium ylides and dimethyl acetylenedicarboxylate.

According with the orbital, steric and electronic factors, the cycloaddition reactions of cycloimmonium ylides to activated and non-symmetrical alkynes could follow, theoretically, two pathways with formation of regioisomers **A** or **B**.[8,11] (figure 3). The spectral analyses put in evidence the obtaining of the regioisomer **A**.This is in agreement with the electronic effects from ethyl propiolate molecule. In conclusion we suppose

that the reaction between 2-(2′-pyridyl)-pyridinium-ylides **5–8b** with ethyl propiolate follows route I to give cycloadducts **17_19**.

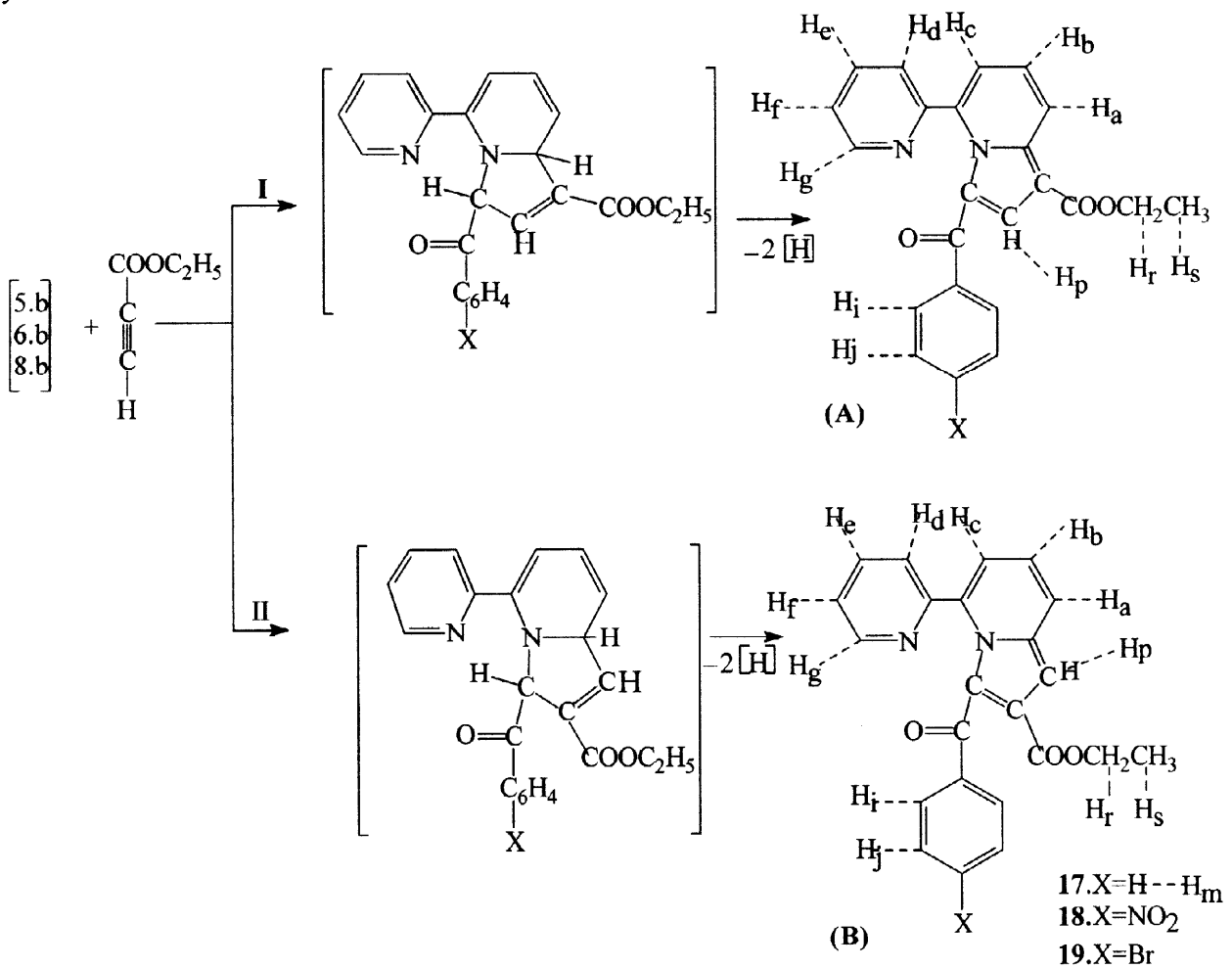


Fig. 3. Reaction between cycloimmonium ylides and ethyl propiolate

The structures of **13–16** and **17–19** compounds were proved by elemental and spectral methods. The IR spectra for compounds **13–16** show absorption bands between 1635 cm^{-1} and 1680 cm^{-1} which are characteristic for the ketonic carbonylic groups. The esteric carbonyl groups absorb at different frequencies. The appearance of two absorption bands shows that the two esteric groups are not in the same plan. The group which absorbs at higher wave numbers (C=O esther k_2), between 1730–1756 cm^{-1}, is unconjugated with the double bonds of the indolizinic cycle due to steric reasons. The band which appears at lower wave numbers, 1695–1705 cm^{-1}, was ascribed to an esteric carbonyl group (C=O esther k_1). This band appears at lower wave numbers due to the conjugation with double bonds in the indolizinic cycle. The conjugation is extended to the pyridinic cycle, too. The IR spectra of the compounds **17–19** sustain the structure of type A of these products. The esteric carbonyl group absorbs at 1695–1700 cm^{-1} like k_1 esteric carbonyl group in

compounds **13–16**. If the compound structures had been of type **B**, the esteric carbonyl group should have absorbed at higher wave numbers. The ketone bands are present at wave numbers between 1645 - 1655cm^{-1}.

The structure of the compounds **13–16** and **17–19** were also investigated by ^{1}HNMR spectroscopy. For the compounds **13–16** two singlets corresponding to methylic protons appear: δ=3,88– 3,83 ppm for the H_{k2} protons and δ=3,37 – 3,3 ppm for the H_{k1} protons. We have established that the doublet of doublets which appears at δ=8,49– 8,42 ppm is assigned to H_a proton. This signal appeared at weak field due to the carboxymethyl group nearby. For compounds **20–22** there is a clear singlet of the H_p proton in the aromatic region: δ=7,59–7,57ppm. The H_r and H_s protons gave a quartet at δ=4,38 ppm, and a triplet at δ=1,39ppm. . Each signal for pyridinic protons was attributed taking into account the literature data available.[12-14]

Experimental

The ^{1}HNMR spectra were obtained on VARIAN-GEMIMI–200 spectrometer and were recorded in ppm downfield from an internal standard, TMS in $CDCl_3$. The coupling constants are given in Hertz.

The IR spectra were recorded with a SPECORD–71 spectrometer in KBr.

General procedure. 1 Mmol cycloimmonium salt was suspended in 10ml anhydrous benzene. Then 1 mmol dimethyl acetylenedicarboxylate or ethyl propiolate and 1mmol triethylamine (dissolved in 5 ml benzen) was added with vigorous stirring. The solution was slowly heated and the solvent evaporated on a steam bath. The residue was washed with methanol and the resulting precipitate was picked up by filtration. The crude product was recrystallized from an appropriate solvent.

Dimethyl 3–benzoyl–5–(2′–pyridyl)–indolizine–1,2–dicarboxylate (13). The product was recrystallized from methanol and yellow crystals were obtained.Yield 45%, mp 195–196°C. Anal.$C_{24}H_{18}N_2O_5$ .Calcd. C 67,70; H 4,69;N 6,57. Found C67,52; H 4,61; N 6,48. IR (KBr,cm^{-1}): 1735(C=O ester k_2) , 1700 (C=Oester k_1), 1635 (C=O ketone). ^{1}HNMR ($CDCl_3$): δ : 8,42 (d of d ,H_a, J_{ab}=9.J_{ac}=1,2); 8,01 (d of d, H_g, J_{gf} = 4,02, J_{ge} = 1,8); 7,75 (t of d, H_e, J_{ed} = 7,8, J_{ef} = 7,6); 7,68 (d, 2H_i, J_{ij} = 8,9); 7,55 (d of d, H_d, J_{de} =7,8, J_{df} = 1,1); 7,5-7,2 (m, H_m, 2H_i, H_b); 7,05 (q of d, H_f, J_{fe} = 7,6, J_{fg}= 4,02, J_{fd} = 1,1); 7,02 (d of d, H_c, J_{cb} = 7,1, J_{ca} = 1,2) ; 3,85 (s, 3Hk_2) ; 3,3 (s, 3Hk_1).

Dimethyl 3–(p–nitro–benzoyl)– 5–(2′–pyridyl)–indolizine–1,2–dicarboxylate (14). Recrystallized from methanol and yellow crystals were obtained.Yield 40%, mp 189°C. Anal. $C_{24}H_{19}N_3O_7$ .Calcd. C 62,47; H

4,12; N 9,11.Found C 62,35; H 4,03; N 9,2.IR (KBr, cm^{-1}):1745(C=O ester k_2), 1705(C=O ester k_1),1675 (C=O ketone). ^{1}HNMR ($CDCl_3$): δ : 8,45 (d of d, H_a, J_{ab} = 9, J_{ac} = 1,18); 8,22 (d , $2H_j$, J_{ji} = 8,9); 7,98 (d of d, H_g, J_{gf} =4,02 , J_{ge} = 1,76) ;7,91 (d , $2H_i$, J_{ij} = 8,9); 7,81 (t of d , H_e, J_{ef} = 7,8, J_{ed} = 7,6); 7,61 (d of d, H_d , J_{de} = 7,8, J_{df} = 1,1); 7,47 (d of d , H_b, J_{ba} = 9, J_{bc} = 7,1) ; 7,1 (q of d , H_f, J_{fe} = 7,6, J_{fg} = 4,1, J_{fd} = 1,1); 7,09 (d of d, H_c, J_{cb} = 7,1, J_{ca} = 1,18); 3,88 (s , $3Hk_2$); 3,3 (s, $3Hk_1$) .

Dimethyl 3–(p–methoxy –benzoyl) – 5–(2′–pyridyl) –indolizine–1,2 –dicarboxylate (15) Recrystallized from methanol and a yellow powder was isolated. Yield 35 %, mp 196–197°C. Anal. $C_{25}H_{22}N_2O_6$.Calcd. C 67,26 ; H 4,93 ; N 6,27. Found C 67,5; H 4,70 ; N 6,11. IR (KBr, cm^{-1}): 1730(C=O ester k_2), 1700(C=O ester k_1), 1680 (C=O ketone). ^{1}HNMR ($CDCl_3$): δ : 8,42 (d of d, H_a , J_{ab} = 8,9, J_{ac} = 1,1); 7,97 (d of d , H_g, J_{gf} = 4,1 , J_{ge} = 1,85); 7,75 (t of d, H_e, J_{ef} = 7,9, J_{ed} = 7,7); 7,61 (d, $2H_i$, J_{ij} = 8,57); 7,55 (d of d, H_d, J_{de} = 7,7, J_{df} =1,1); 7,35 (d of d, H_b , J_{ba} = 8,9 , J_{bc} =7) ; 7,05 (q of d, H_f , J_{fe} = 7,9, J_{fg} = 4,1, J_{fd} = 1,1); 7 (d of d, H_c, J_{cb} = 7, J_{ca} = 1,1) ; 6,8 (d , $2H_j$, J_{ji} = 8,57) ; 3,83 (s , $3Hk_2$) ; 3,78 (s, $3H_n$), 3,31 (s, $3Hk_1$).

Dimethyl 3–(p –bromo –benzoyl) –5–(2′–pyridyl) –indolizine–1,2–dicarboxylate (16). Recrystallized from methanol and yellow dark crystals were obtained. Yield 35 %, mp 240°C. Anal. $C_{24}H_{19}N_2O_5$ Br. Calcd. C 58,18; H 3,83 ; N 5,65 . Found C 58,34; H 3,8 ; N 5,55 . IR (KBr, cm^{-1}): 1756 (C=O ester k_2), 1695 (C=O ester k_1), 1655 (C=O ketone). ^{1}HNMR ($CDCl_3$).: δ : 8,44 (d of d, H_a , J_{ab} = 9, J_{ac} = 1,2); 8,02 (d of d, H_g, J_{gf} =4, J_{ge} =1,8); 7,79 (t of d , H_e, J_{ef} = 7,9, J_{ed} = 7,6); 7,6 (d, $2H_i$, J_{ij} = 8,8) ; 7,52(d , $2H_j$, J_{ji} = 8,8) ; 7,5 (d of d, H_d, J_{de} = 7,6, J_{df} = 1,1); 7,43 (d of d, H_b, J_{ba} = 9, J_{bc} = 7); 7,08 (q of d, H_f , J_{fe} = 7,9, J_{fg} = 4, J_{fd} = 1,1); 7,05 (d of d, H_c, J_{cb} = 7 , J_{ca}= 1,2); 3,87 (s, $3Hk_2$); 3,37 (s , $3Hk_1$).

Ethyl 3–benzoyl–5–(2′–pyridyl) –indolizine –1–carboxylate (17). Recrystallized from ethanol and water; A yellow powder was obtained .Yield 65%, mp 155°C. Anal.$C_{23}H_{18}N_2O_3$.Calcd. C 74,59; H 4,86 ;N 7,56 . Found C 74,45; H 4,76 ; N 7,5 . IR (KBr,cm^{-1}): 1700 (C=Oester), 1655 (C=O ketone). ^{1}HNMR ($CDCl_3$): δ : 8,47 (d of d, H_a,J_{ab} = 9. J_{ac} = 1,4) ;8,23 (d of d , H_g, J_{gf} = 4, J_{ge} = 1,6); 7,87 (d, $2H_i$, J_{ij} = 8,6) ; 7,85 (t of d, H_e , J_{ed}= 8, J_{ef} = 7,8); 7,7 (d of d , H_d , J_{de} = 8, J_{df} = 1,1); 7,59 (s, H_p); 7,57–7,4 (m , H_m , $2H_j$, H_b ;7,13(q of d , H_f, J_{fe} = 7,6, J_{fg} =4, J_{fd} =1,1); 7,09 (d of d, H_c , J_{cb} =7, J_{ca} =1,4); 4,38 (q, $2H_r$, J_{rs} =7,2); 1,39 (t, $3H_s$, J_{sr} =7,2).

Ethyl 3–(p–nitro–benzoyl)–5–(2′–pyridyl)–indolizine–1–carboxylate (18). Recrystallized from methanol.Yellow crystals were obtained. Yield 65%, mp 155°C. Anal. $C_{23}H_{17}N_3O_5$.Calcd. C 66,5 ; H 4,09 ;N 10,12 . Found C 66,61; H 4,1 ; N 10,21 . IR (KBr, cm^{-1}):, 1695 (C=Oester), 1645 (C=O ketone). ^{1}HNMR ($CDCl_3$): δ : 8,49 (d of d , H_a, J_{ab} =9, J_{ac} = 1,4) ; 8,3 (d, $2H_j$, J_{ji} =8,8) ; 8,22 (d of d, H_g, J_{gf} =4, J_{ge} =1,6); 8,03 (d , $2H_i$, J_{ij} =8,8) ; 7,94 (t of d , H_e , J_{ed} =7,6, J_{ef} =7,8); 7,76 (d of d , H_d, J_{de} =7,6, J_{df} =1,1); 7,57 (s , H_p,) ;7,54 (d of d , H_b , J_{ba} = 9, J_{bc} =7) ;7,17 (q of d , H_f, J_{fe} = 7,6, J_{fg} =4, J_{fd} =1,1); 7,15 (d of d , H_c, J_{cb} =7 , J_{ca} =1,4) ; 4,38 (q ,$2H_r$, J_{rs} = 7,2); 1,39 (t , $3H_s$, J_{sr} =7,2).

Ethyl 3–(p–bromo –benzoyl)– 5–(2′–pyridil)–indolizine–1–carboxylate (19). Recrystallized from methanol.Yellow crystals were obtained. Yield 40%, mp 233–235°C. . Anal.$C_{23}H_{17}N_2O_3Br$.Calcd. C 61,46 ; H 3,87; N 6,23 . Found C 61,53; H 3,9; N 6,11 . IR (KBr,cm^{-1}):, 1700 (C=Oester), 1645 (C=O ketone). ^{1}HNMR ($CDCl_3$): δ : 8,48 (d of d, H_a, J_{ab} =9, J_{ac} =1,4); 8,22 (d of d, H_g, J_{gf} =4, J_{ge} =1,6); 7,86 (t of d, H_e , J_{ed} =7,6, J_{ef} =7,8); 7,76 (d, $2H_i$, J_{ij} =8,6); 7,71 (d of d, H_d , J_{de} =7,6, J_{df} =1,1); 7,61 (d, $2H_j$, J_{ji} =8,6) ; 7,57 (s , H_p,); 7,46 (d of d, H_b, J_{ba} = 9, J_{bc} =7); 7,14 (q of d, H_f, J_{fe} = 7,6, J_{fg} = 4, J_{fd} =1,1); 7,08 (d of d, H_c, J_{cb} =7, J_{ca} =1,4) ; 4,38 (q, $2H_r$, J_{rs} = 7,2); 1,39 (t , $3H_s$, J_{sr} =7,2).

References

1. Henrick, C.; Ritchie, E.; Taylor, W. *Aust. J. Chem., 1967, 20*, 2467.
2. Boekelheide, V.; Fahrenholtz, K. *J. Am. Chem. Soc.*, **1961**, *83*, 458.
3. Boekelheide, V.; Miller, A. *J. Org. Chem.*, **1961**, *26*, 431.
4. Rucinski, E.; Gabe, I.; Zugravescu, I. *Ann. Sci. Univ. Iassi*, **1970**, *16*, 49.
5. Zugravescu, I.; Petrovanu, M.: *N-Ylid- Chemistry*, Mc. Graw Hill, London, **1976.**
6. Mangalagiu, I.; Druta, I.; Caprosu, M.; Petrovanu, M. *Ann. Sci. Univ. Iassi*, **1993**, *s2c*, 72-80.
7. Mangalagiu, I.; Druta, I.; Caprosu, M.; Petrovanu, M. *Ann. Sci. Univ. Iassi*, **1992**, *s1c*, 52.
8. Zugravescu, I.; Perovanu, M.: *Cicloaditii 3+2 Dipolare*, Ed, Academiei R.S.R., Bucharest, **1987.**
9. Mangalagiu, I.; Druta, I.; Constantinescu, M.; Humelnicu, I.; Perovanu, M.: *Tetrahedron*, **1996**, *52*, 8853.
10. Calder,I.; Sasse,W. *Aust. J. Chem.*, **1968**, *21*, 1023.
11. Padwa, A.: *1,3- Dipolar cycloaddition Chemistry,* John Wiley & Sons, New York, **1984,** *2*, pp 277-451.
12. Black, P. J.; Heferman, M. L.; Jackmam, L. M.; Porter, Q. , *Aust. J. Chem.*, **1964**, *17*, 1128.
13. Kramer, F.: West, R. *J. Phys. Chem.* **1965**, *69*, 673.
14. Saito, T,; Araki, M.; Uchida, Y.;Misono, A. *J. Phys. Chem*, **1967**, *71*, 2370.