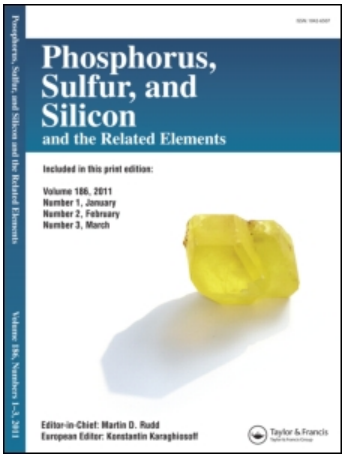


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# STUDIES ON THE SYNTHESIS OF SOME PYRAZOLO[1,5=a]PYRIMIDINES BEARING SULFONAMIDO MOIETIES

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# STUDIES ON THE SYNTHESIS OF SOME PYRAZOLO[1,5-a]PYRIMIDINES BEARING SULFONAMIDO MOIETIES

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A novel synthesis of pyrazolo[1,5-a]pyrimidine derivatives **4,5** and **9** bearing sulfonamido moieties from the reaction of aminopyrazoles **1** with [bis(methylsulfanyl)methylidene]malononitrile **2**, [arylamino(methylsulfanyl)methylidene]malononitrile **6** and ethyl [bis(methylsulfanyl)methylidene]cyano acetate **7** is reported.



## INTRODUCTION

Sulfonamides have a variety of biological activities such as antibacterial[1], insulin releasing[2], carbonic anhydrase inhibitory[3,4], antiinflammatory[5] and antitumar activities[6]. On the other hand, pyrazolo[1,5-a]pyrimidines are of considerable chemical and pharmacological importance as purine analogues[7]. In continuation of our research programme on the synthesis of novel heterocyclic systems exhibiting biological activity[8–10], we aimed to synthesize some new pyrazolo[1,5-a]pyrimidines bearing sulfonamido moieties.

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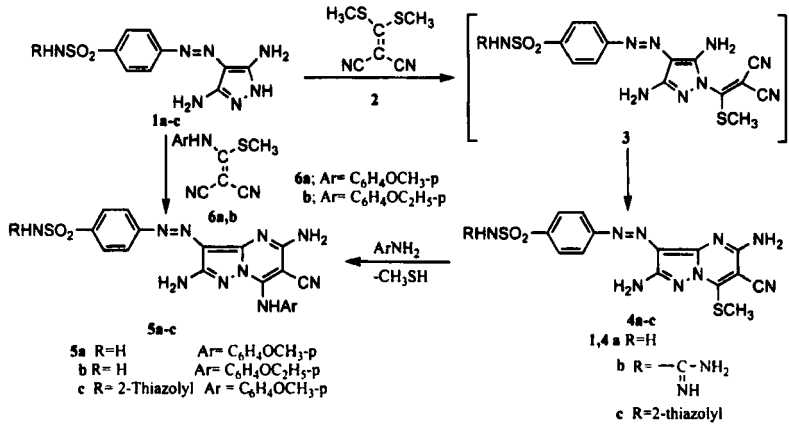
## DISCUSSION

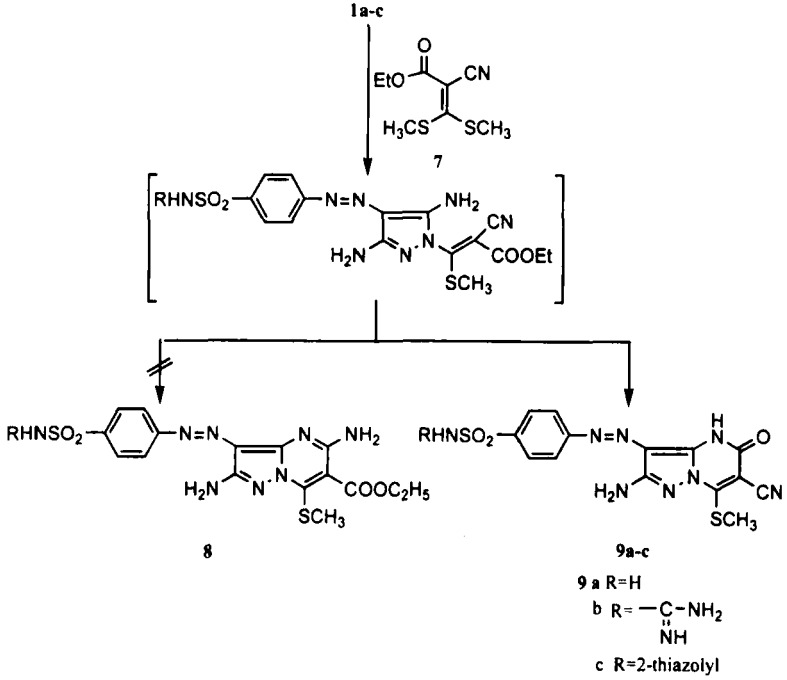
Thus, treatment of aminopyrazoles **1a-c** with [bis(methylsulfanyl)methylidene]malononitrile **2** in refluxing DMF, in the presence of a catalytic amount of triethylamine furnished the pyrazolo[1,5-a]pyrimidines **4a-c** in good yields. The structures of **4** were established on the basis of elemental analysis and spectral data. Thus, IR spectra of **4a-c** revealed characteristic bands for $NH_2$, NH, C≡N, N=N and S=O functional groups and the presence of methylsulfanyl function in $^1H$ NMR spectra of compounds **4a,c**, which are compatible with the assigned structure. The formation of **4** from the reaction of **1** with dithioacetals **2** is proceed *via* the initial alkylation of the endocyclic NH of the pyrazole ring to give **3**, followed by an intramolecular cyclization[11] to afford the pyrazolopyrimidines **4a-c**. Fusion of **4a,c** with aromatic amines afforded the corresponding anilino derivatives **5a-c** *via* elimination of methyl mercaptan. The structures of the latter products were established on the basis of analytical and spectral data. Also, conformation for structures **5a-c** was obtained through a one pot reaction by refluxing of the corresponding aminopyrazoles **1a-c** with [arylamino(methylsulfanyl)methylidene]malononitrile **6a,b** in DMF containing catalytic amounts of triethylamine, (Scheme 1).




SCHEME 1

On the other hand, when aminopyrazoles **1a-c** were reacted with ethyl[bis(methylsulfanyl)methylidene]cyanoacetate **7** for which two products **8** and **9** can be formulated (Scheme 2). Structure **8** was readily dis-

carded on the bases of analytical and spectral data. IR spectra of **9a-c** exhibited absorption band for C≡N and the absence of $OC_2H_5$ fragment in $^1H$ NMR spectra.




SCHEME 2

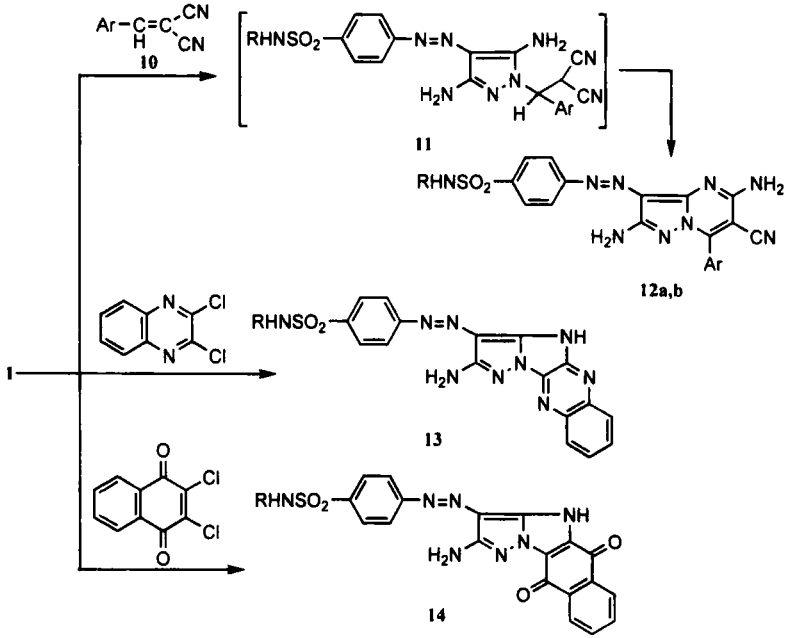
Aminopyrazoles **1a,b** reacts with arylidenemalononitrile **10** in refluxing DMF catalysed by piperidine to yield pyrazolopyrimidines **12a,b** on the basis of elemental analysis and spectral data. The formation of **12** is assumed *via* initial *Michael* addition of the endocyclic NH in **1** to the double bond in **10** to yield *Michael* adduct[12] **11**, which then cyclizes and loses $H_2$ to afford **12a,b** The novel ring system pyrazolo[2′,3′:4,5]imidazo[2,3-b]quinoxaline **13** was obtained when aminopyrazole **1a** was refluxed with 2,3-dichloroquinoxaline in DMF containing potassium carbonate. Finally, aminopyrazole **1c** was reacted with 2,3-dichloro-1,4-naphthoquinone under reflux for 5 minutes to yield naphtho[2′,3′:4,5]imidazo[1,2-b]pyrazole **14**. Formation of **13** and **14** takes place through elimination of hydrogen chloride, (Scheme 3).

## EXPERIMENTAL

All mps are uncorrected. IR spectra were obtained (KBr discs) on a Shimadzu IR 200 spectrophotometer. $^1$H NMR spectra were recorded in deutrated dimethylsulfoxide at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane as an internal reference. Mass spectra were performed on a Shimadzu GC MS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

### Aminopyrazoles[13] 1a-c, [bis(methylsulfanyl)methylidene]malononitrile[14]2, [arylamino(methylsulfanyl)methylidene]malononitrile[15] 6a,b and ethyl [bis(methylsulfanyl)methylidene]cyanoacetate[14] 7

Were prepared according to literature procedures.




**12a** R=H, Ar= 2-Thienyl **13** R= H

**b** R= —C(=NH)—NH$_2$ , Ar= Thienyl **14** R= 2-Thiazolyl

SCHEME 3

TABLE I Characterization data for compounds **4a-c, 5a-c, 9a-c, 12a,b, 13** and **14**

| *ınd. (colour)* | *Cryst. Solvent* | *Mp (T/°C)* | *Yield (%)* | *Molecular formula (M.Wt.)* | *Found /required,* | |
|---|---|---|---|---|---|---|
| | | | | | *C* | *H* |
| **4a** | Dioxane | >300 | 82 | $C_{14}H_{13}N_9O_2S_2$ | 41.50 | 3.20 |
| Violet) | | | | (403) | 41.69 | 3.23 |
| **4b** | Dioxane | 280 | 78 | $C_{15}H_{15}N_{11}O_2S_2$ | 40.40 | 3.30 |
| ellow) | | | | (445) | 40.45 | 3.37 |
| **4c** | Dioxane | 240 | 75 | $C_{17}H_{14}N_{10}O_2S_3$ | 41.80 | 2.80 |
| range) | | | | (486) | 41.98 | 2.88 |
| **5a** | EtOH | 120 | 87 | $C_{20}H_{18}N_{10}O_3S$ | 50.30 | 3.60 |
| range) | | | | (478) | 50.21 | 3.77 |
| **5b** | EtOH | 210 | 62 | $C_{21}H_{20}N_{10}O_3S$ | 51.30 | 4.10 |
| range) | | | | (492) | 51.22 | 4.07 |
| **5c** | EtOH/$H_2O$ | 150 | 65 | $C_{23}H_{19}N_{11}O_3S_2$ | 49.10 | 3.40 |
| range) | | | | (561) | 49.20 | 3.39 |
| **9a** | EtOH | 220 | 76 | $C_{14}H_{12}N_8O_3S_2$ | 41.50 | 3.00 |
| Brown) | | | | (404) | 41.59 | 2.97 |
| **9b** | Dioxane | 250 | 64 | $C_{15}H_{14}N_{10}O_3S_2$ | 40.50 | 3.20 |
| Brown) | | | | (446) | 40.36 | 3.14 |
| **9c** | Dioxane | >300 | 81 | $C_{17}H_{13}N_9O_3S_2$ | 41.60 | 2.80 |
| Brown) | | | | (487) | 41.89 | 2.67 |

| *und. (colour)* | *Cryst. Solvent* | *Mp (T/°C)* | *Yield (%)* | *Molecular formula (M.Wt.)* | *Found /required,* | |
|---|---|---|---|---|---|---|
| | | | | | *C* | *H* |
| **12a** | EtOH | 230 | 60 | $C_{17}H_{13}N_9O_2S_2$ | 46.40 | 3.00 |
| Brown) | | | | (439) | 46.47 | 2.96 |
| **12b** | Dioxane | >300 | 76 | $C_{18}H_{15}N_{11}O_2S_2$ | 45.00 | 3.10 |
| Brown) | | | | (481) | 44.91 | 3.12 |
| **13** | EtOH | 100 | 55 | $C_{17}H_{13}N_9O_2S$ | 50.10 | 3.30 |
| Orange) | | | | (407) | 50.13 | 3.20 |
| **14** | Dioxane | >300 | 63 | $C_{22}H_{14}N_8O_4S_2$ | 60.00 | 2.50 |
| Violet) | | | | (518) | 50.97 | 2.70 |



TABLE II Spectral data for compounds **4a-c, 5a-c, 9a-c, 12a,b, 13** and **14**

| *No.* | *IR ($\nu_{max}/cm^{-1}$)* | *$^1$HNMR (δ/ppm)* | *M* |
|---|---|---|---|
| | 3450, 3400, 3250 ($NH_2$), 2203 (C≡N), 1580 (N=N), 1321, 1152 ($SO_2$) | 2.96(3H,s,$SCH_3$), 3.43(2H,s,br,$NH_2$), 7.41 (2H,s,br,$NH_2$), 7.81–7.96 (4H,q. AB-system), 8.01(2H,s,br,$SO_2NH_2$) | |
| | 3410,3325,3249 ($NH_2$,NH), 2210 (C≡N), 1579 (N=N), 1324, 1125 ($SO_2$) | | |
| | 3460,3400,3250 ($NH_2$,NH), 2207 (C≡N), 1570 (N=N), 1337, 1120 ($SO_2$) | 2.94(3H,s,$SCH_3$), 3.35(2H,s,br,$NH_2$), 6.85–6.91 (2H,m,thiazole ring), 7.28 (2H,s,br, $NH_2$), 7.71–7.91(4H,q,AB- system), 8.20(1H,s,br,NH) | |

| No. | IR ($\nu_{max}/cm^{-1}$) | $^1$HNMR ($\delta$/ppm) | M |
|---|---|---|---|
| | 3460,3380,3200 ($NH_2$,NH), 2200 (C≡N), 1600 (N=N), 1360, 1167 ($SO_2$) | 2.82 (2H, s, br, $NH_2$), 4.10 (3H, s, $OCH_3$), 6.95–7.22 (8H, m, Ar-H), 7.26 (2H, s, br, $NH_2$), 7.81 (2H, s, br, $SO_2NH_2$), 10.39 (1H, s, br, NH) | |
| | 3350,3300,3220 ($NH_2$,NH), 2200 (C≡N), 1570 (N=N), 1330, 1150 ($SO_2$) | 1.15 (3H, t, $CH_3$), 3.32 (2H, s, br, NH2), 4.20 (2H, q, CH2), 6.91–7.40 (8H, m, Ar-H), 7.64 (2H, s, br, $NH_2$), 7.81 (2H, s, br, $SO_2NH_2$), 10.70 (1H, s, br, NH) | |
| | 3430,3380,3250 ($NH_2$,NH), 2205 (C≡N), 1595 (N=N), 1340, 1150 ($SO_2$) | 3.31(2H,s,br,$NH_2$), 4.10(3H,s,$OCH_3$), 6.80–6.91(2H, m, thiazole ring), 6.95 (2H, s, br, $NH_2$), 6.97–7.26 (8H, m, Ar-H), 7.78 (1H, s, br, $SO_2NH$). | |
| | 3405,3300,3165 ($NH_2$,NH), 2215 (C≡N), 1635 (C=O), 1596 (N=N), 1327, 1146 ($SO_2$) | 2.72 (3H,s,$SCH_3$), 4.05 (2H, s, br, $NH_2$), 7.51 (2H, s, br, $SO_2NH_2$), 7.79- 8.07 (NH, q, AB-system), 8.91(1H, s, br, NH) | |
| | 3445,3315,3195 ($NH_2$,NH), 2215 (C≡N), 1638 (C=O), 1584 (N=N), 1369, 1125 ($SO_2$) | | |
| | 3435,3325,3150 ($NH_2$,NH), 2220 (C≡N), 1637 (C=O), 1576 (N=N), 1328, 1113 ($SO_2$) | 2.91(3H,s,$SCH_3$), 3.95(2H,s,br,$NH_2$), 6.84–6.90 (2H,m,thiazole ring), 7.21 (1H, s, br, $SO_2NH$), 7.42–7.94(4H, q, AB-system), 8.41(1H,s,br,NH) | |
| | 3436,3400,3205 ($NH_2$), 2205 (C≡N), 1574 (N=N), 1324, 1127 ($SO_2$) | 4.51 (2H, s, br, $NH_2$), 7.21(2H, s, br, $NH_2$), 7.40–7.74 (7H, m, Ar-H), 7.91 (2H, s, br, $SO_2NH$) | |
| | 3440,3380,3225 ($NH_2$,NH), 2206 (C≡N), 1581 (N=N), 1376, 1124 ($SO_2$) | | |
| | 3367,3250,3100 ($NH_2$,NH), 1598 (C=O), 1340, 1120 ($SO_2$) | 7.21(2H,s,br,$NH_2$), 7.82–7.94 (8H, m, Ar-H), 8.10(2H,s,br, $SO_2NH_2$), 11.84 (1H, s, br, NH) | |
| | 3420,3300,3176 ($NH_2$,NH), 1665 (C=O), 1595 (N=N), 1326, 1135 ($SO_2$) | 6.81–6.90 (2H, m, thiazole ring), 7.30 (2H, s, br, $NH_2$), 7.74–7.90 (8H,m,Ar- H), 8.01(1H, s, br, $SO_2NH$), 11.60 (s,br,1H,NH) | |

### 2,5-Diamino-7-methylsulfanyl-3-[4-(N-substituted)sulfamyl] phenylazo-pyrazolo[1,5-a]pyrimidin-6-carbonitriles 4a-c

To a suspension of compounds **1** (0.01 mol) and [bis(methylsulfanyl)methylidene]malononitrile **2** (0.01 mol) in dimethylformamide (20 ml), three drops of triethylamine were added. The mixture was refluxed for 3 h and then allowed to cool. The solid precipitate was isolated by suction and crystallized from the appropriate solvent (*cf.* Tables I and II).

### 2,5-Diamino-7-arylamino-3-[4-(N-substituted)sulfamyl]phenylazo-pyrazolo[1,5-a]pyrimidin-6-carbonitriles 5a-c

***Method A***

A mixture of **4** (0.01 mol) and the requisite aromatic amine (0.01 mol) was fused at 160°C for 1 h., then triturated with ethanol, poured into water and then acidified with hydrochloric acid. The solid product, so formed was collected by filtration and crystallized from the appropriate solvent (*cf.* Tables I and II).

***Method B***

The experimental procedure used for the synthesis of **4** was carried out except for the use of [arylamino(methylsulfanyl)methylidene]malononitrile **6a,b** instead of [bis(methylsulfanyl)methylidene]malononitrile **2**.

### 2-Amino-4,5-dihydro-7-methylsulfanyl-5-oxo-3-[4-(N-substituted) sulfamyl]phenylazo-pyrazolo[1,5-a]pyrimidin-6-carbonitriles 9a-c

To a mixture of the compounds **1** (0.01 mol) and ethyl [bis(methylsulfanyl)methylidene]cyanoacetate **7** (0.01 mol) in dioxane (20 ml), three drops of triethylamine were added. The resulting mixture was refluxed for 2 h. and then allowed to cool to room temperature and diluted with water (30 ml). The solid product so formed was collected by filtration and crystallized from the appropriate solvent (*cf.* Tables I and II).

### 2,5-Diamino-7-thienyl-3-[4-(N-substituted)sulfamyl]phenylazo-pyrazolo[1,5-a]pyrimidin-6-carbonitriles 12a-c

A mixture of compound **4** (0.01 mol), nitrile **10** (0.01 mol) and piperidine (0.5 ml) in dimethylformamide (20 ml) was heated under reflux for 3h.

The solid obtained was collected by filtration and crystallized from the appropriate solvent (*cf.* Tables I and II).

### 2-Amino-3-(4-sulfamyl)phenylazo-4H-pyrazolo[2′,3′:4,5]imidazo [2,3-b]quinoxaline 13

A mixture of compound **1a** (0.01 mol) and 2,3-dichloroquinoxaline (0.01 mol) in dimethylformamide (20 ml) containing anhydrous potassium carbonate (0.5 g) was heated under reflux for 1 h., then left to cool to room temperature. The precipitated product was filtered off and crystallized from the appropriate solvent (*cf.* Tables I and II).

### 2-Amino-3-[4-(2-thiazolylsulfamyl)]phenylazo-4,5,10-trihydro-5,10-dioxo-naphtho[2′,3′:4,5]imidazo[1,2-b]pyrazole 14

A mixture of compound **1c** (0.01 mol) and 2,3-dichloro-1,4-naphthoquinone (0.01 mol) in dioxane (20 ml) was heated under reflux for 5 min., then cooled. The violet crystals precipitated product was filtered off and crystallized from the appropriate solvent (*cf.* Tables I and II).



## *References*


[1] F. Zani and P. Vicini; *Arch. Pharm.*, **331**, 219 (1998).

[2] T.H. Maren, *Annu. Rev Pharmacol Toxicol.*, **16**, 309 (1976).

[3] C.T. Supuran, A. Scozzafava, B.C. Jurca and M.A. Iiies, *Eur. J. Med. Chem.*, **33**, 83 (1988).

[4] C. T. Supuran, A. Scozzafava, A. Popescu,, R. B. Tureac, A. Banciu, A. Creanga, G. B. Tureac and M.D. Banciu, *Eur. J. Med. Chem.*, **32**, 445 (1997).

[5] J. J. Li, D. Anderson, E.G. Burton, J. N. Cogburn, J. T. Collins, D. J. Garland, S. A. Gregory, H. C. Huang, P. C. Isakson, C. M. Koboldt, E. W. Logusch, M. B. Nortor, W. E. Perkins, E. J. Reinhard, K. Seibert, A. W. Veenhuizem, Y. Zang and D.B. Reitz, *J. Med. Chem.*, **38**, 4570 (1995).

[6] H. Yashino, N. Ueda, J. Niijima, H. Sugumi, Y. Kotake, N. Koyanagi, K. Yoshimatsu, M. Asada, T. Watanabe, T. Nagasu, K. Tsukahara, A. Lijima and K. Kitoh, *J. Med. Chem.*, **35**, 2496 (1992).

[7] M. H. Elnagdi, M. R. H. Elmoghayar and G.H. Elgemeie; *Adv. Heterocyclic Chem.*, **41**, 320 (1987).

[8] A. A. Hassnien, M.A. Zahran, M. S. A. El-Gaby and M.M. Ghorab, *J. Indian Chem. Soc.*, **76**, 350 (1999).

[9] M. M. Ghorab, S. G. Abd El-Hamid; M.S.A. El-Gaby and S.M. El-Sayed, *Acta Pharm.*, **49**, 1 (1999).

[10] A. M. Sh. El-Sharief, Y. A. Ammar, Y. A. Mohamed and M. S. A. El-Gaby, *Phosphorus, Sulfur and Silicon*, **148**, 117 (1999).

[11] G.H Elgemeie; S.E. Elezbay, H.A. Ali. and A. Mansour, *Bull Chems. Soc. Jpn.*, **67**, 738 (1994).

[12] G. R. Elgemeie; A. H. Elghandour and H M. Elshimy, *J. Prakt Chem.*, **331**, 466 (1989).

[13] A. A. Hassnien, I. S. Abdel Hafuz and M.H. Elnagdi, *J. Chem. Res. (S)*, 1999, 8; *J. Chem. Res. (M)*, 129 (1999).
[14] R. Gompper and W. Toepfl, *Chem. Ber*, **95**, 2861 (1962).
[15] Y. A. Ammar, A. M. Sh.El-Sharief, M. A. Zahran, M. Z. El-Said and U. H. El-Said, *J. Chem. Res. (S)*, 324 (1995).