Reduction of pyrimidine derivatives by $LiAlH_4$

Liu Yu-Xiu[a], Cui Ming-Bo[a], Zhao Qi-Qi[a], Wang Qing-Min[a,*], Liu Ying[b] and Huang Run-Qiu[a]

[a]*State Key Laboratory of Elemento-organic Chemistry, Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China*

[b]*State Key Laboratory for Structural Chemistry of Unstable and Stable Species, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China*

The reduction of ethyl 2-methylthio-(or 2-ethoxy)pyrimidine-5-carboxylate by $LiAlH_4$ afforded ethyl 2-methylthio-(or 2-ethoxy)-1,6-dihydropyrimidine-5-carboxylate as the main product. Similarly, the reduction of 2-methylthio-(or 2-methoxy)pyrimidine-5-carboxamide by $LiAlH_4$ gave 2-methylthio-(or 2-methoxy)-1,6-dihydropyrimidine-5-carbonitrile as main product.

Keywords: reduction, $LiAlH_4$, pyrimidine-5-carboxylate, dihydropyrimidine-5-carboxylate

$LiAlH_4$ is an excellent reducing agent for carboxylates and amides. The products are generally the corresponding alcohols and amines.[1] In our attempt to prepare (2-(methylthio) pyrimidin-5-yl)methanol, via the reduction of ethyl 2-(methylthio)pyrimidine-5-carboxylate (**1**) by $LiAlH_4$, the expected methanol was isolated as only a byproduct. This paper deals with the unique reactions of pyrimidine derivatives with $LiAlH_4$.

Result and discussion

Ethyl 2-(methylthio)pyrimidine-5-carboxylate (**1**) was prepared as shown in Scheme 1. Thiourea was treated with dimethyl sulfate to form S-methylisothiouronium sulfate (**5**).[2] The synthesis of ethyl 3-dimethylamino-2-formylacrylate (**7**) involved the reaction of a Vilsmeier reagent, which was derived from N,N-dimethylformamide and phosphorus oxychloride, with potassium ethyl malonate (**6**).[3,4] Reaction of **5** with **7** afforded ethyl 2-(methylthio)pyrimidine-5-carboxylate (**1**).[5] Subsequent treatment with sodium ethanolate provided ethyl 2-(ethoxy)pyrimidine-5-carboxylate (**2**) as shown in Scheme 1.

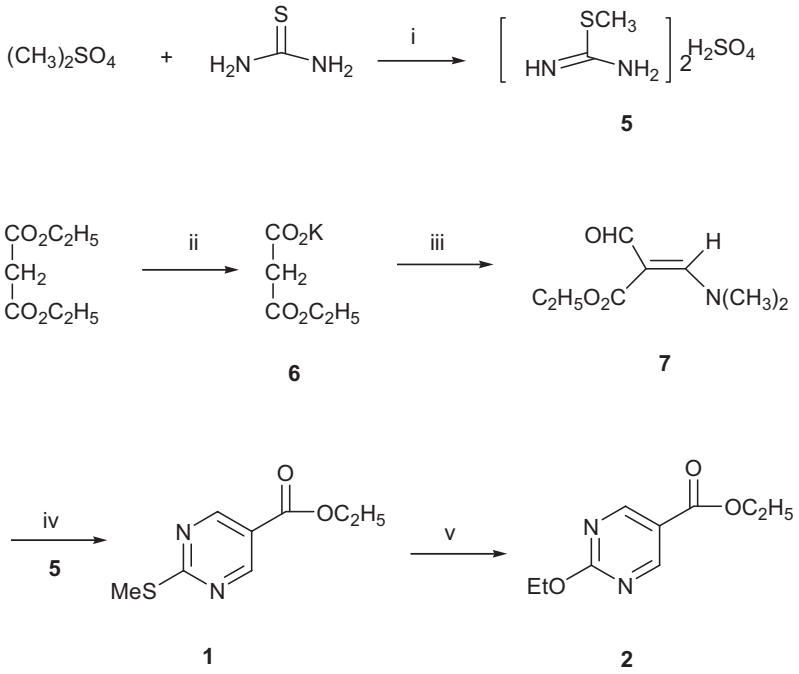
The reduction of **1** by $LiAlH_4$ was conducted in tetrahydrofuran or ether. After the reaction mixture was hydrolysed with a little water, the residue was purified by column chromatography to give ethyl 1,6-dihydro-2-(methylthio)pyrimidine-5-carboxylate (**3**) as the major product as shown in Scheme 2. At the same time, [2-(methylthio) pyrimidin-5-yl]methanol (MPOL) was isolated as byproduct.

In order to evaluate the regioselectivity of the reduction, a series of reactions were performed and the results were listed in Table 1.

In general, compound **3** was obtained as the main product. Moreover, the yield was higher in ether as solvent than in THF. A reasonable explanation was that the low solubility of the compound **3** in ether prevented the extensive reduction by $LiAlH_4$. This was supported by the fact that when the reaction time was prolonged in THF, yield of **3** was very low (Table 1, entry 4).

Compound **2** was synthesised to repeat the reaction. Similarly, the reduction of ethyl 2-(ethoxy)pyrimidine-5-carboxylate (**2**) by $LiAlH_4$ yielded ethyl 1,6-dihydro-2-ethoxypyrimidine-5-carboxylate **4** as shown in Scheme 2. Its structure was determined by X-ray diffraction to be ethyl 1,6-dihydro-2-ethoxypyrimidine-5-carboxylate as shown in Fig. 1.[6]

^1H NMR spectrum of the compounds **3** and **4** showed that 1,6-dihydropyrimidine-5-carboxylate can be converted to



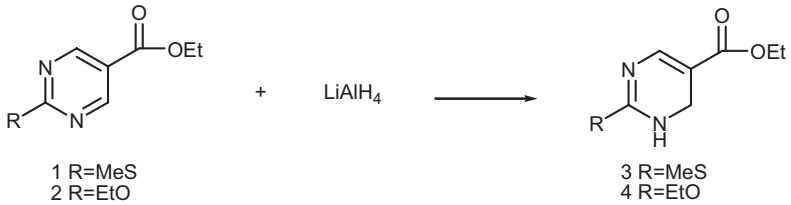
Scheme 1 Reagent and conditions: (i) water, reflux; (ii) KOH, EtOH; (iii) DMF, $POCl_3$; (iv) EtONa, EtOH; (v) EtONa, EtOH.

* Correspondent. E-mail: wangqm@syn.nankai.edu.cn

Table 1 The reduction of compound **1** by $LiAlH_4$

No.	Solvent	Method	T/°C Time	Yield of **3**/%	Yield of MPOL/%
1	Et_2O	A	–15~10º 16 h	42	3
2	Et_2O	B	–15~10º 16 h	44	12
3	Et_2O	B	0~10º 16 h	46	11
4	THF	B	–15~10º 16 h	5	15
5	THF	B	0~10º 1 h	30	14
6	THF	A	–15~10º 1 h	32	15
7	THF	A	0~10º 1 h	37	15

Method A: the solution of the compound **1** (0.99 g, 5.0 mmol) was added dropwise to the suspension of $LiAlH_4$ (0.27 g, 7.1 mmol); Method B: $LiAlH_4$ (0.27 g, 7.1 mmol) was added to the solution of the compound **1** (0.99 g, 5.0 mmol) in batch. T is temperature.



Scheme 2

1,4-dihydropyrimidine-5-carboxylate in solution as shown in Fig. 2. The chemical shifts of the compounds **3** and **4** were assigned according to relevant literature.[7,8]

The reduction of the pyrimidine ring has been rarely reported.[7,8] It always occurs when a electron-withdrawing group (such as CN, CH=NOH, $CONH_2$, CO_2Et, Cl, *etc.*) in the 4 or 5-position of the ring. The mechanism may involve attack by a hydride ion at the more electron-deficient position. The electron–withdrawing group may reduce the electron density of the ring. The hydride ion adds to the 4 or 6-position of the ring and affords 1,4 and 1,6-dihydropyrimidine derivative. An electron-donating group (NH_2, NHMe, $NHNH_2$ or CH_3) in 4-position may raise the electron density of the pyrimidine ring and reduce the tendency of the ring to undergo reduction. Hence, the normal product, *i.e.* the hydroxymethylpyrimidine derivative, would be obtained via the reduction of the corresponding pyrimidinecarboxylate.[7,9,10] Similar results were observed in the reduction reaction of uracil derivatives using borane.[11]

2-Methylthiopyrimidine-5-carboxamide (**9**) and 2-methoxy-pyrimidine-5-carboxamide (**10**) were synthesised from compound **1** and underwent the reduction with $LiAlH_4$ as shown in Scheme 3. Surprisingly, the reactions gave dihydropyrimidinecarbonitriles (**11** and **12**).

In conclusion, when pyrimidinecarboxylate and pyrimidine-carboxamide were reduced with $LiAlH_4$, the main product was not always the corresponding alcohol and amine. The product may be largely affected by the nature and position of substituent on the pyridine ring. For example, the reduction of 2-methylthio-(or 2-ethoxy)pyrimidine-5-carboxylate by $LiAlH_4$ afforded 2-methylthio-(or 2-ethoxy)-1,6-dihy-dropyrimidine-5-carboxylate as main product. Similarly, the reduction of 2-methylthio-(or 2-methoxy)pyrimidine-5-carboxamide by $LiAlH_4$ gave 2-methylthio-(or 2-methoxy)-1,6-dihydro-pyrimidine-5-carbonitrile.

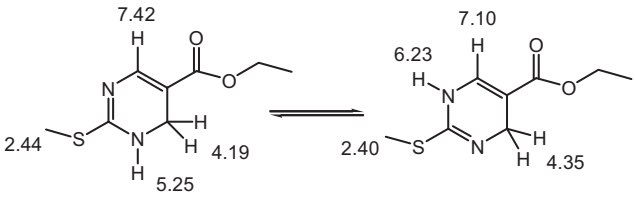
Experimental

Melting points were determined with an X-4 melting point apparatus and were uncorrected. IR spectra were recorded with a Shimadzu-435 spectrometer. ^1H NMR spectra were recorded with a BrukerAC-P300 instrument, tetramethylsilane being used as internal standard. Elemental analyses were carried out with a Yanaco CHN Corder MT-3 elemental analyser. GC-MS were recorded with Thermefinmingan Polaris Q. HRMS were recorded with IonSpec-7.0T.

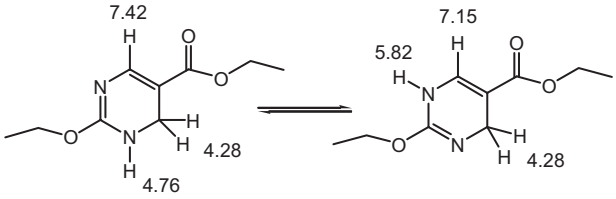
Compounds **5**,[2] **6**[4] and **7**[3] were prepared according to published literature.

Ethyl 2-(methythio)pyrimidine-5-carboxylate (**1**) was prepared according to the published literature[5] which was modified.

To anhydrous ethanol (50 ml) was added metallic sodium (0.92 g, 0.04 mol), then S-methylisothiouronium sulfate (**5**) (6.80 g, 0.025 mol) was added in batch. After being stirred at room temperature for 30 min, crude **7** was added to the mixture (7.0 g, 0.04 mol) and then



3



4

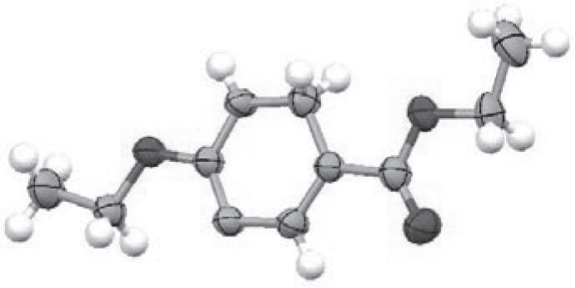
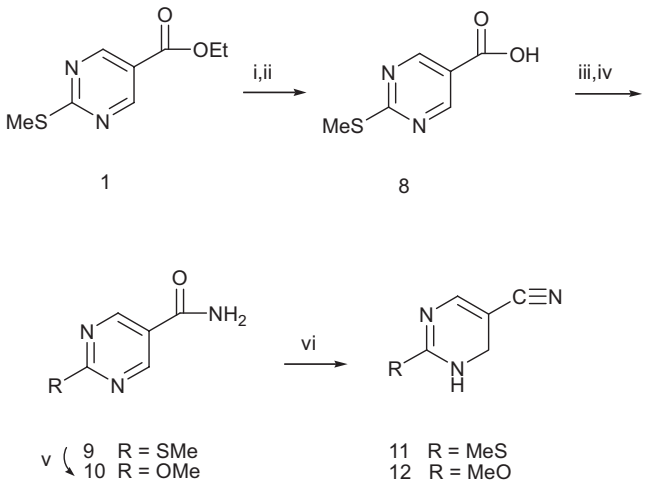


Fig. 1 Single crystal diffraction of compound **4**.

Fig. 2 Selected chemical shift (δ in $CDCl_3$) of the compounds **3** and **4**.



Scheme 3 Reagent and conditions: (i) NaOH, EtOH; (ii) HCl; (iii) $SOCl_2$; (iv) $NH_3.H_2O$; (v) MeONa; (vi) $LiAlH_4$.

refluxed for 30 min. The mixture was cooled and filtered, then the filtrate was condensed and purified by column chromatography to give **1** (6.0 g, 61.5% from **6**) as a white solid: m.p. 38–40ºC. (Ref: [12] 36–37ºC) ^{1}H NMR($CDCl_3$): δ1.34 (t, J = 7.2 Hz, 3H, CH_3), 2.55 (s, 3H, SCH_3), 4.34 (q, J = 7.2 Hz, 2H, CH_2), 8.96 (s, 2H, pyrimidine).

Ethyl 2-ethoxy-pyrimidine-5-carboxylate (**2**): To anhydrous ethanol (50 ml) was added sodium (0.8 g, 0.035 mol). After the sodium had disappeared, **1** (1.1 g, 5.5 mmol) was added, and the reaction mixture was refluxed for 1 h. Then the reaction mixture was cooled and hydrogen chloride (5 mol/l) was added dropwise to pH = 6. Sodium chloride was filtered and the filtrate was condensed. The residue was dissolved in ether and washed with water. Then ether layer was evaporated to afford **2** (0.4 g, 40%) as a yellow solid: m.p. 55–57ºC. ^{1}H NMR($CDCl_3$): δ 1.40 (t, 3H, J = 7.2 Hz, CH_3), 1.46 (t, 3H, J = 7.2 Hz, CH_3), 4.40 (q, 4H, J = 7.2 Hz, OCH_2), 4.51(q, 4H, J = 7.2 Hz, OCH_2), 9.07(s, 2H, pyrimidine). Anal. Calcd. For $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.17; H, 6.33; N, 14.18.

2-(Methylthio)pyrimidine-5-carboxylic acid (**8**): To ethanol (100 ml) was added **1** (10.2 g, 5.15 mmol) and 82% potassium hydroxide (4.57 g, 67 mmol) in ethanol (110 ml) and stirred at r.t. for 1.5 h, then sodium carboxylate was collected by filtration. The salt was dissolved in 25 ml water and hydrogen chloride (5 mol/l) added to pH = 4, then filtrated and collected carboxylic acid **8** (8.1 g, 92.5%) as a white solid: m.p. 264–266ºC (ref:[6] 267ºC); ^{1}H NMR (DMSO-d_6): δ 2.58 (s, 3H, SCH_3), 9.01 (s, 2H, pyrimidine).

*2-(Methylthio)pyrimidine-5-carboxamid*e (**9**): To **8** (1.2 g, 7.1 mmol) was added thionyl chloride (12 ml) and refluxed for 1 h, then the excess thionyl chloride was distilled off to give 2-(methylthio)pyrimidine-5-carbonyl chloride. The chloride was diluted with 30 ml toluene and then dropwise added to 28% ammonia solution (10 ml) at 0ºC. The reaction mixture was stirred at r. t. for 3 h, and filtered and washed with water to afford **9** (1.13 g, 95%) as a white solid: m.p. 220–222ºC (ref: [5] 218–220ºC); ^{1}H NMR (DMSO-d_6): δ 2.56 (s, 3H, SCH_3), 7.70 (bs, 1H, NH), 8.19 (bs, 1H, NH), 9.00 (s, 2H, pyrimidine).

2-Methoxypyrimidine-5-carboxamide (**10**): To anhydrous methanol (50 ml) was added sodium (0.5 g, 0.022 mol). After the sodium had disappeared, **9** (1.48 g, 8.76 mmol) was added and refluxed for 1 h. The solvent was removed, and to the residue was added water (10 ml) and diluted hydrogen chloride to pH = 7, then filtered and washed with water to give **10** (1.13 g, 84.3%) as a white solid: m.p. 228–230ºC; ^{1}H NMR (DMSO-d6): δ 4.01 (s, 3H, OCH_3), 7.50, 8.12 (2H, NH_2), 9.02 (s, 2H, pyrimidine). IR (KBr) cm^{-1}: 3159(NH), 1672(C=O), 1615(C=N). Anal. Calcd. For $C_6H_7N_3O_2$: C, 47.06; H, 4.61; N, 27.44. Found: C, 47.23; H, 4.52; N, 27.65.

Ethyl 1,6-dihydro-2-(methylthio)pyrimidine-5-carboxylate (**3**)

Method A: To a suspension of $LiAlH_4$ (0.27 g, 7.1 mmol) in 10 ml anhydrous tetrahydrofuran or ether, cooled to certain temperature as listed in Table 1, was added **1** (0.99 g, 5.0 mmol) in 10 ml solvent. The reaction mixture was then stirred at room temperature. After the reaction was complete detected by TLC, to the mixture water was carefully added (no more than 2 ml) and stirred for 1h, then the inorganic salt was filtrated and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (petroleum ether and ethyl acetate 2 : 1 to 1 : 1 as eluent) to give compound **3** and (2-(methylthio)pyrimidin-5-yl) methanol (MPOL).

Method B: To a suspension of **1** (0.99 g, 5.0 mmol) in anhydrous tetrahydrofuran or ether (15 ml), cooled to certain temperature as listed in Table 1, was added $LiAlH_4$ (0.27 g, 7.1 mmol) in batch. The reaction mixture was then stirred at room temperature and worked up as described in Method A.

MPOL: White solid, m.p. 62–64ºC [ref:[10] 63–64ºC]. ^{1}H NMR ($CDCl_3$): δ 2.57 (s, 3H, SCH_3), 4.67 (s, 2H, OCH_2), 8.52 (s, 2H, pyrimidine).

3: Colourless solid. m.p. 137–138ºC (ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H, J = 7.2 Hz, CH_3), 2.40–2.44 (ds, 3H, SCH_3), 4.12–4.35 (m, 4H, CH_2O, CH_2), 5.25 (bs, 0.47H, NH), 6.23 (bs, 0.53H, NH), 7.10 (d, 0.53H, J = 4.2 Hz, CH=C), 7.42 (s, 0.47H, CH=C); IR (KBr) cm^{-1}: 3351, 3321(NH), 1661(C=O), 1592(C=N), 1542(C=C). HRMS *m/z*: 201.0695, Calcd. For $C_8H_{12}N_2O_2S$ + H^+: 201.0692.

Ethyl 1,6-dihydro-2-(ethoxy)pyrimidine-5-carboxylate (**4**): To a suspension of $LiAlH_4$ (0.21 g, 5.5 mmol) in anhydrous tetrahydrofuran (10 ml) was dropwise added **2** (0.67 g, 3.4 mmol) in anhydrous tetrahydrofuran (10 ml) at 0ºC. The mixture was stirred for 10 min then worked up as described in Method A.

4: Colourless solid, m.p. 121–128ºC (ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 1.20–1.38 (m, 6H, CH_3), 4.08–4.22 (m, 4H, CH_2O), 4.28 (s, 2H, CH_2), 4.76 (bs, 0.7H, NH), 5.82 (bs, 0.3H, NH), 7.15 (bs, 0.3H, CH=C) 7.42 (bs, 0.7H, CH=C); IR (KBr) cm^{-1}: 3230, 3198 (N-H), 1704(C=O), 1641(C=N), 1537(C=C); GC-MS *m/z*: 199 (M + 1). Anal. Calcd. For $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.27; H, 6.99; N, 14.18.

1,6-Dihydro-2-(methylthio)pyrimidine-5-carbonitrile (**11**): To a suspension of $LiAlH_4$ (0.18 g, 7.1 mmol) in anhydrous tetrahydrofuran (10 ml) was added **9** (0.8 g, 4.7 mmol) in anhydrous tetrahydrofuran (10 ml) under reflux. After the reaction was complete detected by TLC, to the cooled mixture water (no more than 2 ml) was carefully added and stirred for 1h, then the inorganic salt was filtrated and the filtrate was concentrated in vacuum. The residue was purified by column chromatography to give compound **11** as colourless solid, m.p. 116–119ºC (ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 3.32 (s, 3H, SCH_3), 4.15 (s, 2H, CH_2), 5.50 (bs, 0.2H, NH), 6.50 (bs, 0.8H, NH), 6.80 (bs, 1H, CH=C); IR (KBr) cm^{-1}: 3150(N–H), 2201(CN), 1662(C=C), 1615(C=N); GC-MS *m/z*: 154 (M + 1). Anal. Calcd. For $C_6H_7N_3S$: C, 47.04; H, 4.61; N, 27.43. Found: C, 47.47; H, 4.77; N, 27.79.

1,6-Dihydro-2-(methoxy)pyrimidine-5-carbonitrile (**12**): **12** was isolated from the reaction mixture of $LiAlH_4$ with **10** as described above. ^{1}H NMR data showed **12** could maintain equilibrium with its 1,4-dihydro isomer in solution. Colourless solid, m.p. 184–187ºC (ethyl acetate); ^{1}H NMR ($CDCl_3$): 3.70, 3.80 (s, s, about 1:2 estimated by ^{1}H NMR, 3H, OCH_3),4.24, 4.26 (s, s, 2H, CH_2), 4.88, 6.15 (bs, bs, 1H, NH), 6.77 (d, 1H, J = 5.4 Hz, CH=C), 7.04 (s, 1H, CH=C); IR (KBr) cm^{-1}: 3183, 3114(N-H), 2207(CN), 1639(C=C), 1526(C=N). GC-MS *m/z*: 138 (M + 1). Anal. Calcd. For $C_6H_7N_3O$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.64; H, 5.13; N, 30.83.

This work was supported by the National Key Project for Basic Research (2003CB114404) and Program for New Century Excellent Talents in University (NCET-04-0228) and the National Natural Science Foundation of China (20472039 and 20421202) and the Key Project of Chinese Ministry of Education (106046).

Received 5 July 2007; accepted 21 August 2007
Paper 07/4728 doi: 10.3184/030823407X240872

References

1 Q.-Y. Xing; R.-Q. Xu and Z. Zhou, *Basic Organic Chemistry*, 1 st ed.; People's Education Press, Beijing, China, 1980, pp 438.
2 P.-R. Shildneck and W. Windus, *Org. Synth.,* 1932, **12**, 52.
3 Z. Arnold, Collect. Czech. Chem. Commun., 1961, **26**, 3051.
4 R.-E. Strube, *Org. Synth.,* 1957, **37**, 34.
5 J. Arukwe and K. Undheim, *Acta Chem. Scan.,* 1986, **B40**, 764-767.
6 Y.-X. Liu, Q.-Q. Zhao, M.-B. Cui, H.-B. Song, Q.-M. Wang and R.-Q. Huang, *Acta Cryst.,* 2006, **E62**, o2599.
7 H.-C. Koppel, R.-H. Springer, R.-K. Robins and C.-C. Cheng, *J. Org. Chem.,* 1962, **27**, 3614.
8 M. Barvian, D.-H. Boschelli, J. Cossrow, E. Dobrusin, A. Fattaey, A. Fritsch, D. Fry, P. Harvey, P. Keller, M. Garrett, F. La, W. Leopold, D. McNamara, M. Quin, S. Trumpp-Kallmeyer, P. Toogood, Z. Wu and E. Zhang, *J. Med. Chem.,* 2000, **43**, 4606.
9 Shadbolt, R.-S.; Ulbricht, T.-L.-V. *J. Chem. Soc. (C)* 1968, 733.
10 R.-S. Shadbolt and T.-L.-V. Ulbricht, *J. Chem. Soc. (C),* 1968, 1203.
11 C. Ghosh, D. G. Schmidt and B. C. Pal, *J. Org. Chem.,* 1984, **49**, 5256.
12 L. Sansebastiano, L. Mosti, G. Menozzi, P. Schenone and O. Muratore, *Farmaco,* 1993, **48(3)**, 335.