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ETHYLCROTONATES IN SYNTHESIS OF 4,4-DISUBSTITUTED 3,5-DICYANO-6-OXO-1,4,5,6-TETRAHYDROPYRIDINE-2-THIOLATES

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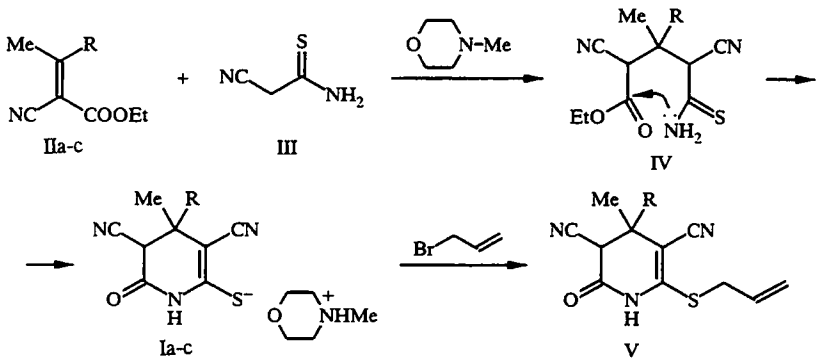
Despite the high biological activity of derivatives of 4,4-dialkylpiperidin-2-ones and spiro-1,4-cycloalkanepiperidin-2-ones [1-5], there is little data available on their synthesis [6-9]. This especially due to the lack of convenient methods for obtaining them up to the present time.

We have obtained for the first time N-methylmorpholinium 4,4-disubstituted 3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates (Ia-c) by reaction of ethylcrotonates (IIa-c) with cyanothioacetamide (III) in the presence of N-methylmorpholine. The reaction includes formation of Michael adducts (IV), which undergo *in situ* cyclocondensation with formation of salts (Ia-c).



I, II a R = Me, b R = Ph, c R = 2-thienyl

By alkylation of thiolate Ia with allyl bromide in DMF, we obtained the previously described [10] sulfide V, which can serve as support for the structure of the salts Ia-c.

The PMR spectra were taken on a Bruker WP-100 SY (100 MHz) rf spectrometer in DMSO-D_6 relative to TMS as the internal standard. The IR spectra were obtained on an IKS-29 for Vaseline oil mulls.

N-Methylmorpholinium 4,4-dimethyl-3,5-dicyano-6-oxo-1,4,5,6-tetrahydro-pyridine-2-thiolate (Ia). 15 millimoles N-methylmorpholine and 10 millimoles cyanothioacetamidine III were added to a solution of 10 millimoles of ester IIa in 15 ml absolute ethanol at 20°C and stirred for 10 min. After 48 h, the precipitate formed was separated and washed with ethanol and hexane. Yield, 88%. T_{mp}, 190-192°C. IR spectrum: 3150 (NH), 2253, 2200 (CN), 1700 cm^{-1} (CONH). PMR spectrum: 9.47 (1H, broad s, NH); 4.17 (1H, s, $C_{(5)}$–H); 3.80 (4H, m, CH_2OCH_2); 3.22 (4H, m, CH_2NCH_2); 2.83 (3H, s, NCH_3); 1.22 (3H, s, CH_3); 1.05 ppm (3H, s, CH_3). Found, %: C 54.70; H 6.33; N 17.95; S 10.31. $C_{14}H_{20}N_4O_2S$. Calculated, %: C 54.52; H 6.54; N 18.17; S 10.40.

N-Morpholinium 3,5-Dicyano-4-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-2-thiolate (Ib) was obtained using a procedure similar to that employed for salt Ia, using the ester IIb. Yield, 85%. T_{mp} 164-166°C. IR spectrum: 3150, 3360 (NH), 2205, 2262 (CN), 1700 cm^{-1} (CONH). PMR spectrum: 9.53 (1H, broad s, NH); 7.31 (5H, m, Ph); 4.68 and 4.99

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(1H, s, $C_{(5)}$–H); 7.78 (4H, m, CH_2OCH_2); 3.21 (4H, m, CH_2NCH_2); 2.80 (3H, s, NCH_3); 1.64 and 1.49 ppm (3H, s, CH_3). Found, %: C 61.47; H 6.13; N 15.30; S 8.45. $C_{19}H_{22}N_4O_2S$. Calculated, %: C 61.60; H 5.99; N 15.12; S 8.65.

N-Methylmorpholinium 3,5-dicyano-4-methyl-4-(2-thienyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate (Ic) was obtained using a procedure similar to that employed for salt Ia, accordingly using ethylcrotonate (IIc). Yield, 82%. T_{mp} 174-176°C. IR spectrum: 3460 (NH), 2170, 2248 (CN), 1700 cm^{-1} (CONH). PMR spectrum: 9.61 (1H, broad s, NH); 6.34 (1H, dd, $C_{(4)}$–H thienyl); 6.91 (2H, m, $C_{(3)}$ and $C_{(5)}$–H thienyl); 4.70 and 4.42 (1H, s, $C_{(5)}$–H); 3.76 (4H, m, CH_2OCH_2); 3.19 (4H, m, CH_2NCH_2); 2.74 (3H, s, NCH_3); 1.67 and 1.52 ppm (3H, s, CH_3). Found, %: C 54.10; H 5.08; N 14.92; S 16.86. $C_{17}H_{21}N_4O_2S_2$. Calculated, %: C 54.23; H 5.35; N 14.88; S 17.03.

6-Allylthio-3,5-dicyano-4,4-dimethyl-3,4-dihydropyridin-2-(1H)-one (V). 10 millimoles allyl bromide was added to a suspension of 10 millimoles of salt Ia in 8 ml DMF and stirred at 20°C for 4 h, and then diluted with 10 ml water. The precipitate was separated and then washed with water, ethanol, and hexane. Yield, 81%. T_{mp} 208-210°C. IR spectrum: 3450, 3200 (NH); 2502, 2254 (CN); 1685 cm^{-1} (CONH). PMR spectrum: 11.18 (1H, broad s, NH); 5.76 (1H, m, CH=); 5.14 (2H, m, CH_2=); 4.56 (1H, s, $C_{(3)}$–H); 3.69 (2H, d, SCH_2); 1.32 (3H, s, CH_3); 1.14 ppm (3H, s, CH_3). Found, %: C 58.11; H 5.15; N 17.13; S 12.80. $C_{12}H_{13}N_3OS$. Calculated, %: C 58.28; H 5.30; N 16.99; S 12.96.

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REFERENCES

1. V. V. Kuznetsov, Khim.-Farm. Zh., No. 7, 61 (1991).
2. G. Guillamet, T. Podona, G. Adam, B. Guardiola, and P. Renard, Eur. Pat. Appl. 546,358; Chem. Abstr. **120**, 164006 (1994).
3. G. Gulliamet, J. Pharm. Belg., **49**, 216 (1994).
4. R. C. Effland, J. F. Klein, L. Danis, and G. E. Oisen, US Pat. 4,868,190; Ref. Zh. Khim., 17 O 52P (1990).
5. F. H. Gawin, R. Byck, M. Alderdice, and J. Schwimmer, US Pat. 5,185,329; Ref. Zh. Khim., 10 O 222P (1994).
6. S. Pavlov, M. Bogavac, L. Arsenijevic, and V. Arsenijevic, Pharmazie, **45**, 286 (1990).
7. Y. Xu, Z. Zhu, Z. Tong, D. Peng, and L. Duan, Zhongguo Yiyao Gongye Zazhi, **24**, 49 (1993); Chem. Abstr. **120**, 8556 (1994).
8. G. R. Newkome, V. K. Gupta, R. W. Giffin and S. Arai, J. Org. Chem., **52**, 5480 (1987).
9. V. D. Dyachenko, A. E. Mitroshin, and V. P. Litvinov, Khim. Geterotsikl. Soedin., No. 9, 1235 (1996).
10. V. N. Nesterov, V. E. Shklover, Yu. T. Struchkov, Yu. A. Sharanin, A. M. Shestopalov, and L. A. Rodinovskaya, Acta Crystallogr., **41**, 1191 (1985).