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SYNTHESIS OF FUNCTIONAL DERIVATIVES OF TRIFLUOROMETHYLPYRIMIDINES FROM ACETYLACETONE, TRIFLUOROACETONITRILE, AND ARYL ISOCYANATES

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1,1,1-Trifluoro-2-amino-3-acetyl-2-penten-4-one was obtained by the addition of acetylacetone to trifluoroacetonitrile in the presence of catalytic amounts of nickel acetylacetonate. The reaction of 1,1,1-trifluoro-2-amino-3-acetyl-2-penten-4-one with aryl isocyanates gave 1-aryl-5-acetyl-6-methyl-4-trifluoromethyl-1H-pyrimidin-2-ones.

Trifluoromethylpyrimidines have broad range of biological activity [1]. In a continuation of a study of functional derivatives of pyrimidines [2, 3], we synthesized new pyrimidines with a trifluoromethyl group from acetylacetone (I), CF_3CN (II), and aryl isocyanates.

We have found that (I) adds smoothly at the C≡N bond of nitrile (II) in the presence of catalytic amounts of nickel acetylacetonate ($Ni(acac)_2$) to give 1,1,1-trifluoro-2-amino-3-acetyl-2-penten-4-one (III), a functional enaminone, which holds interest as a potential reagent for organic synthesis.

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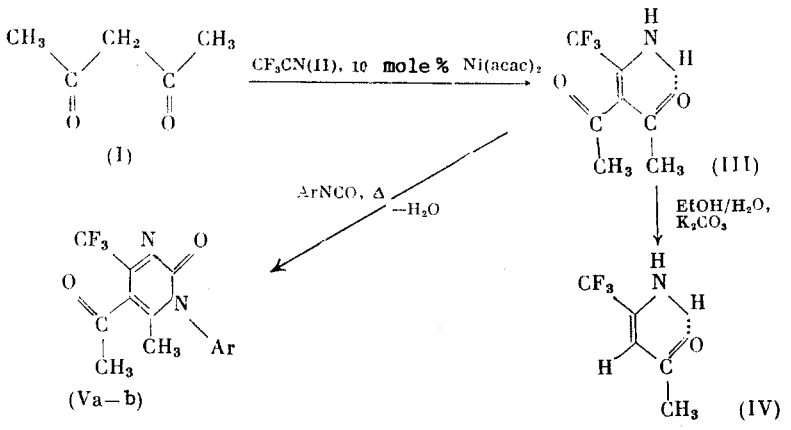

(I) (III) (IV) (Va–b)

Ar = Ph (a); 2-naphthyl (b)

We should note that the reaction of (I) with trihaloacetonitriles in the presence of base is accompanied by deacetylation [4, 5], which does not permit us to obtain (III) by this method. The use of $Ni(acac)_2$ permits us to carry out the addition of β-dicarbonyl compounds to activated nitriles (in particular, to trichloroacetonitrile [6, 7]) in neutral media without loss of the acetyl group.

Product (III) is a crystalline compound, which is soluble in benzene, chloroform, acetone, and ethanol, sublimes in vacuum without decomposition, and is not altered upon heating at reflux in toluene for 4 h. The spectral data indicate that the acetyl and amino groups in the cis position to the C=C bond form an intramolecular hydrogen bond. Thus, the IR spectrum of (III) has C=O bands at 1645 and 1700 cm^{-1}. The band at 1645 cm^{-1} should be assigned to the carbonyl group involved in the intramolecular hydrogen bond. The region for NH stretching vibrations has a broad band at 3000-3400 cm^{-1} (bound NH group) and the band at 3480 cm^{-1} (free NH group). The two acetyl groups are not equivalent in the PMR spectrum. The signal at 2.17 ppm is assigned to the methyl group of the acetyl substituent in the chelate ring, while the signal at 2.46 ppm is assigned to the free acetyl substituent.

Upon the action of K_2CO_3 in aqueous ethanol, (III) is deacetylated to give enaminone (IV), which was isolated by sublimation in vacuum.

Product (III) may be used to construct functional derivatives of heterocycles with a trifluoromethyl group. Thus, enaminoketones react with isocyanates in the presence of NaH to give 1-substituted 1H-pyrimidin-2-ones [8]. The reaction of (III) with aryl isocyanates, by analogy to the reactions of S,N-acetals of diacetylketene [3], proceeds in the absence of base to give 1-aryl-5-acetyl-6-methyl-4-trifluoromethyl-1H-pyrimidin-2-ones (Va) and (Vb). Pyrimidine derivatives (Va) and (Vb) are crystalline compounds with good solubility in chloroform, acetone, and benzene and only moderate solubility in ethanol. The structures of these products were indicated by IR, PMR, and ^{13}C NMR spectroscopy and mass spectrometry.

EXPERIMENTAL

The NMR spectra of all the compounds obtained were taken in $CDCl_3$. The PMR spectra were taken on a Bruker WM-250 spectrometer, while the ^{13}C NMR spectra were taken on a Bruker AM-300 spectrometer. The IR spectra were taken for CH_2Cl_2 solutions on a UR-20 spectrometer. The mass spectra were taken on a Varian MAT CH-6 mass spectrometer.

1,1,1-Trifluoro-2-amino-3-acetyl-2-penten-4-one (III). This reaction was carried out in a dry argon atmosphere. A mixture of 36 g (0.36 mmole) acetylacetone 0.78 g (0.003 mole) $Ni(acac)_2$, and 60 ml dry CH_2Cl_2 was introduced into a three-necked flask equipped with an inlet for CF_3CN, thermometer, cold finger condenser filled with dry ice and acetone. Then, 43 g (0.45 mole) CF_3CN was introduced and ice water cooling for 2 h. The mixture was stirred for an additional 1 h at ~20°C and 150 ml dry ether was added. The precipitated nickel complex was filtered off and the filtrate was evaporated using a water pump. The residue contained 66.9 g (98%) (III), which was purified by sublimation at 1-2 mm (bath temperature 60-70°C), mp 76.5-77.5°C. Mass spectrum, m/z: 195 $[M]^{+\cdot}$. Found: C, 43.25; H,

4.21; F, 29.24; N, 7.21%. Calculated for $C_6H_8F_3NO_2$: C, 43.08; H, 4.13; F, 29.21; N, 7.18%. IR spectrum (ν, cm^{-1}): 3480 (NH), 3400-3000 (NH), 1700 (C=O), 1645 (C=O), 1600 (C=C), 1160-1250 (C–F). PMR spectrum (δ, ppm): 2.17 s (3H, Me), 2.46 s (3H, Me), 7.89 br.s (2H, NH_2). ^{13}C NMR spectrum (δ, ppm, J, Hz): 28.8 (Me), 32.9 q (MeCO cis to CF_3, $^5J_{C,F}$ = 2.7), 112.4 (C^3), 120.2 q.t (C^1, $^1J_{C,F}$ = 278, $^3J_{C,N(NH_2)}$ = 8.2), 146 q (C^2, $^2J_{C,F}$ = 34), 196.2 q (CO, $^2J_{C,H}$ = 5.6), 202.3 q (CO, $^2J_{C,H}$ = 5.6).

1,1,1-Trifluoro-2-amino-2-penten-4-one (IV). A mixture of 48.5 g (0.23 mole) (III), 230 ml ethanol, and 460 ml sat. aq. K_2CO_3 was stirred for 14 h at ~20°C and then for 17 h at 40-50°C. The reaction was monitored by thin-layer chromatography. The upper layer was separated and the lower layer was extracted with chloroform. Both organic layers were combined and the solvent was removed at 100-120 mm. The residue was poured into cold water. The precipitate formed was filtered off and dried over P_2O_5. The yield of (IV) was 20.65 g (57%). The sample was purified by sublimation at 100 mm (bath temperature 60-70°C), mp 40-41°C (40-40.5°C [9]). ^{13}C NMR spectrum (δ, ppm, J, Hz): 30.3 q (Me, $^1J_{C,H}$ = 127.6), 93.9 d.q (C^3, $^1J_{C,H}$ = 124.2, $^3J_{C,F}$ = 3.0), 120.4 q (C^1, $^1J_{C,F}$ = 276.5), 147.2 q (C^2, $^2J_{C,H}$ = 34.2), 199.6 q.d (CO, $^2J_{C,H}$ = 5.5, $^2J_{C,H}$ = 3.5).

5-Acetyl-6-methyl-4-trifluoromethyl-1-phenyl-1H-pyrimidin-2-one (Va). A mixture of 0.29 g (1.5 mmoles) enaminoketone (III) and 0.33 ml (3 mmoles) PhNCO in 4 ml toluene was heated at reflux for 7 h in an argon atmosphere. The solvent was evaporated in vacuum and the residue was subjected to chromatography on a silica gel column using benzene and then 1:1 benzene–ether as the eluent to give 0.17 g (39%) (Va), mp 223-224°C (ethanol). Mass spectrum, m/z: 296 $[M]^{+\cdot}$. Found: C, 56.90; H, 4.04; F, 19.16; N, 9.12%. Calculated for $C_{14}H_{11}F_3N_2O_2$: C, 56.76; H, 3.74; F, 19.24; N, 9.46%. IR spectrum (ν, cm^{-1}): 1695 (CO), 1610, 1595. PMR spectrum (δ, ppm): 2.05 s (3H, Me), 2.56 s (3H, Me), 7.15-7.32 m (2H, Ph), 7.66-7.48 (3H, Ph). ^{13}C NMR spectrum (δ, ppm, J, Hz): 19.47 (Me), 32.70 (CO<u>Me</u>), 116.94 (C^5), 119.47 g (CF_3), $^1J_{C,F}$ = (279), 126.88, 130.17, 130.57, 136.56 (Ph), 154.30 (C^2), 158.24 q (C^4, $^2J_{C,F}$ = 36), 160.03 q (C^6, $^2J_{C,H}$ = 6), 198.41 (CO, $^2J_{C,H}$ = 10).

5-Acetyl-6-methyl-1-(2-naphthyl)-4-trifluoromethyl-1H-pyrimidin-2-one (Vb). A mixture of 0.39 g (2.0 mmoles) (III) and 0.68 g (4.0 mmoles) 2-naphthyl isocyanate in 5 ml toluene was heated at reflux for 7 h. The dinaphthylurea precipitate formed was filtered off. The filtrate was evaporated in vacuum. The residue was subjected to chromatography on a silica gel column using benzene and then 1:1 benzene–chloroform as the eluent to give 0.24 g (35%) (Vb), mp 271-272°C (ethanol). Mass spectrum, m/z: 346 $[M]^{+\cdot}$. Found: C, 62.75; H, 3.93; F, 15.93; N, 7.95%. Calculated for $C_{18}H_{13}F_3N_2O_2$: C, 62.43; H, 3.78; F, 16.46; N, 8.09%. IR spectrum (ν, cm^{-1}): 1695 (CO), 1600. PMR spectrum (δ, ppm): 2.10 s (Me), 2.59 s (Me), 7.28 m (1H), 7.68-7.52 m (2H), 7.73 m (1H), 7.80-7.98 m (2H), 8.03 m (1H) (naphthyl). ^{13}C NMR spectrum (δ, ppm): 19.65 (Me), 32.82 (CO<u>Me</u>), 117.02 (C^3), 119.47 (CF_3), 123.65, 126.17, 127.51, 127.92, 128.05, 128.28, 130.96, 133.47, 133.75 (naphthyl), 154.48 (C^2), 158.59 (C^4), 160.11 (C^6), 198.34 (CO).

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