Dimethyl Acetylsuccinate as a Versatile Synthon in Heterocyclic Chemistry – A Facile Synthesis of Heterocyclic Acetic Acid Derivatives

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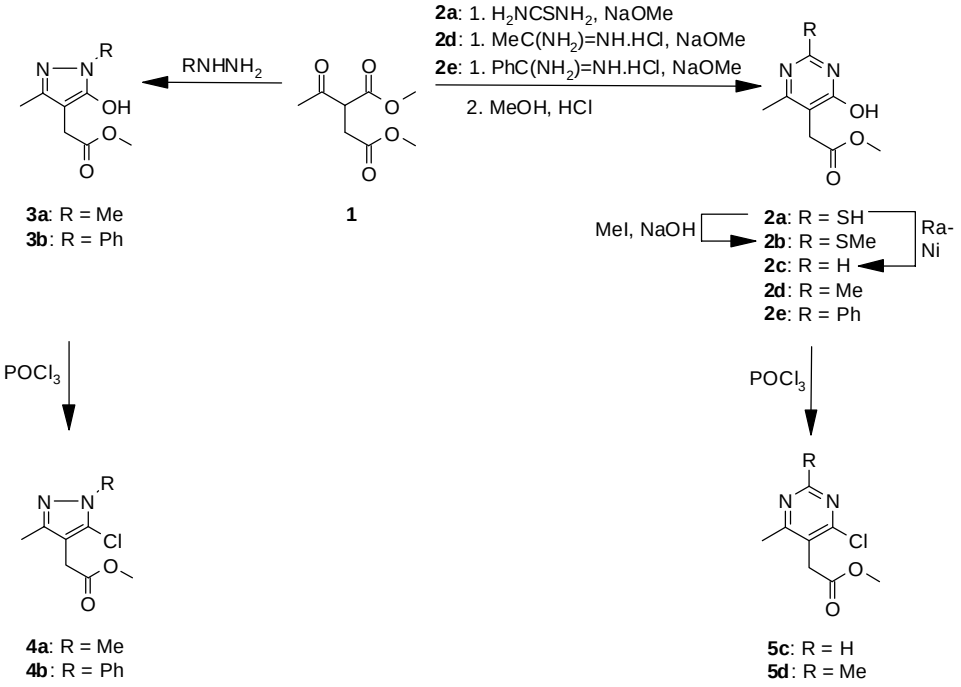
Abstract. The preparation of novel acetic acid derivatives of pyrazole **3a**,**b** and pyrimidine **2a**–**e** is achieved by condensation of dimethyl acetylsuccinate (**1**) with appropriate reaction partners. Also triethyl 1,1,2-ethanetricarboxylate (**6**) is a valuable starting material, which is demonstrated by the synthesis of previously unknown pyrimidin-5-yl acetates.

The contribution of β-ketoesters to heterocyclic synthesis is well documented. Not only such established reactions as the Hantzsch pyridine [1] and pyrrole [2] syntheses and the Knorr pyrrole [3] and quinoline [4] syntheses require β-ketoesters, there are also many other examples in which they are applied to the preparation of new five- [5], six- [6] and seven-membered [7] heterocyclic ring systems. However, esters of 2-acetylsuccinic acid have rarely been used for this purpose; only very few syntheses of carboxylated pyrrolinone [8], furanone [9], thiophene [10] or isoxazole [11] derivatives have been described. Dimethyl acetylsuccinate (**1**) is a commercially available compound, which was previously used mainly for the synthesis of cyclobutyl ketones [12] or monoterpenoidal cyclohexenones [13]. In this paper, we present its multifold possibilities in the construction of heterocyclic acetic acid derivatives.

Although pyrimidines with an acetic acid substituent in the 2- [14, 15] or 4-position [15, 16] have been known for a long time, the pyrimidin-5-yl acetates were until recently less readily accessible. Previous approaches to 5-pyrimidineacetic acid derivatives utilized a tedious four-step homologation process from the corresponding pyrimidin-5-yl carboxylate [17]. Also in pyrazole chemistry, the synthesis of pyrazolyl-4-acetates was achieved so far by formylation of a pyrazole and subsequent chain-elongation from the resulting aldehyde to the acetic acid ester [18]. In both cases the direct condensation of dimethyl acetylsuccinate (**1**) with ambident amino nucleophiles such as hydrazines and amidines offers a much shorter access to such specially substituted heterocycles (Scheme 1). The Traube type condensation [19] of dimethyl acetylsuccinate (**1**) with amidines or thiourea leads to pyrimidin-5-yl acetates **2** [20]. Usually the reaction passes through the cor-



Scheme 1 Synthesis of pyrimidin-5-yl and pyrazol-4-yl acetic acid asters from dimethyl acetylsuccinate

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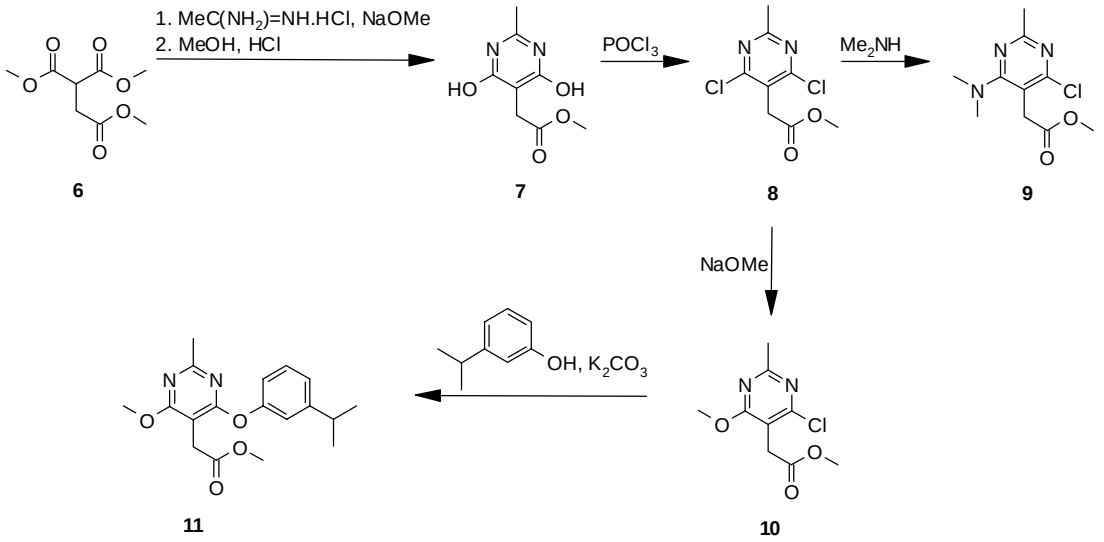
responding pyrimidin-5-yl acetic acids as intermediates, which are converted to the ester function by acid-catalyzed esterification. The 2-mercaptopyrimidine **2a** is easily transformed into the derivatives **2b** and **2c** by methylation or desulfurization [20]. The reaction of **1** with methylhydrazine or phenylhydrazine affords the 5-hydroxy-3-methyl-1*H*-pyrazol-4-yl acetic esters **3** selectively. The formation of the isomeric 3-hydroxy-5-methyl-1*H*-pyrazoles is not observed. Therefore, the products result from the attack of the less hindered and more nucleophilic nitrogen of the hydrazine at the ketone carbon atom of the β-ketoester. Both pyrimidines **2** and pyrazoles **3** are easily transformed into their chloro-derivatives **4** and **5** by standard $POCl_3$ chlorination (Scheme 1).

Also triethyl 1,1,2-ethanetricarboxylate (**6**) proves to be a versatile building block for the construction of heterocyclic acetic acid derivatives. Its condensation with acetamidine hydrochloride under basic conditions and subsequent re-esterification leads to the pyrimidine **7**, which can be chlorinated twice to the dichloro-derivative **8**. The sequential substitution of its chlorine atoms with different nucleophilic reaction partners results in a short synthesis of the pyrimidine **11**, bearing four different substituents (Scheme 2) [21].



Scheme 2 Synthesis of pyrimidin-5-yl acetic acid esters from triethyl 1,1,2-ethanetricarboxylate

In conclusion, we presented a concise approach to tetrasubstituted pyrazol-4-yl and pyrimidin-5-yl acetates from dimethyl acetylsuccinate (**1**) and triethyl 1,1,2-ethanetricarboxylate (**6**), which are both commercially available. The fact, that the acetate, hydroxy and halogen functions are well suited for further transformations, makes compounds **2** – **10** valuable building blocks for several different target molecules.

Experimental

All new compounds were characterized by standard spectroscopical and microanalytical methods. ^{1}H NMR spectra were recorded on a Varian Gemini 300 spectrometer at 300 MHz, using $CDCl_3$ or $(CD_3)_2SO$ as solvents and TMS as internal standard. Chemical shifts are reported in ppm downfield from the standard (δ = 0.00), coupling constants are in Hz. High-resolution mass spectra were obtained on a Finnigan MAT 90 spectrometer with DIP EI ionization (70 eV). Melting points were determined on a Buechi 535 melting-point apparatus, column chromatography was performed on E. Merck silica gel 60 (40 – 63 μm).

(4-Hydroxy-2-mercapto-6-methyl-pyrimidin-5-yl)-acetic acid methyl ester (**2a**)

Thiourea (16 g, 0.2 mol) and dimethyl acetylsuccinate (**1**, 38 g, 0.2 mol) are added at room temperature to a solution of sodium (9.5 g, 0.4 mol) in methanol (150 ml). The reaction mixture is refluxed for 16 hours. The crystalline precipitate is filtered and added with stirring to a concentrated aqueous solution of hydrochloric acid (75 ml). The resulting precipitate is filtered, washed with methanol and dried. This (4-hydroxy-2-mercapto-6-methyl-5-pyrimidinyl)-acetic acid is dissolved in 300 ml of methanol. Concentrated sulfuric acid (10 ml) is added and the reaction mixture is refluxed for 16 hours. The resulting suspension is cooled and filtered. Yield 33 g (0.15 mol, 77%) **2a**; *m.p.* >200 °C. – ^{1}H NMR ($(CD_3)_2SO$): δ/ppm = 2.31 (s, 3H), 3.54 (s, 2H), 3.79 (s, 3H), 12.48 (s, 1H), 12.67 (s, 1H). Exact Mass for $C_8H_{10}N_2O_3S$: Calcd.: 214.2451; Found: 214.2441.

(4-Hydroxy-6-methyl-2-methylsulfanyl-pyrimidin-5-yl)-acetic acid methyl ester (**2b**)

2a (10 g, 46 mmol) is dissolved in a solution of sodium hydroxide (2 g, 50 mmol) in water (100 ml). Methyl iodide (7.2 g, 50 mmol) is added and the mixture is stirred at room temperature for 4 hours. The precipitated solid is filtered and dried. Yield 6.4 g (28 mmol, 61%) **2b**; *m.p.* 195 °C. – ^{1}H NMR ($(CD_3)_2SO$): δ/ppm = 2.18 (s, 3H), 2.49 (s, 3H), 3.44 (s, 2H), 3.59 (s, 3H). Exact Mass for $C_9H_{12}N_2O_3S$: Calcd. 228.2719; Found: 228.2698.

(4-Hydroxy-6-methyl-pyrimidin-5-yl)-acetic acid methyl ester (**2c**)

A suspension of **2a** (16 g, 75 mmol) and Raney-Nickel (8 g) in water (180 ml) is heated to reflux for 16 hours. The reaction mixture is filtered and the filtrate is concentrated under reduced pressure to 1/10 of the original volume. The precipitating crystals are filtered and dried. Yield 11.5 g (63 mmol, 85%) **2c**; *m.p.* > 200 °C. – ^{1}H NMR ($(CD_3)_2SO$): δ/ppm = 2.11 (s, 3H), 3.38 (s, 2H), 3.63 (s, 3H), 8.02 (s, 1H), 12.38 (s, 1H). Exact Mass for $C_8H_{10}N_2O_3$: Calcd.: 182.1791; Found: 182.1802.

(4-Hydroxy-2,6-dimethyl-pyrimidin-5-yl)-acetic acid methyl ester (**2d**)

Dimethyl acetylsuccinate (**1**, 19 g, 0.1 mol) is dissolved in a mixture of sodium methoxide in methanol (20 ml of a 5.4M solution, 0.11 mol) and methanol (50 ml) and added within 20 minutes to a solution of acetamidine hydrochloride (10.5 g, 0.11 mol) at 60 °C with stirring. After refluxing the reaction mixture for 16 hours, the precipitated salt is removed by filtration, and the filtrate is evaporated to dryness under reduced pressure. The residual solid is suspended in acetone, filtered and dried. The resulting (2,6-dimethyl-4-hydroxy-5-pyrimidinyl)-acetic acid is suspended in a saturated solution of hydrochloric acid in methanol (50 ml). The mixture is heated to reflux for 16 hours. The volume of the reaction mixture is reduced to about the half by evaporating the solvent in vacuo. Subsequently, the product crystallizes. Yield 11.5 g (59 mmol, 59%) **2d**; *m.p.* > 200 °C. – ^{1}H NMR ($(CD_3)_2SO$): δ/ppm = 2.14 (s, 3H), 2.33 (s, 3H), 3.32 (s, 2H), 3.40 (s, 3H). Exact Mass for $C_9H_{12}N_2O_3$: Calcd.: 196.2059; Found: 196.2056.

(4-Hydroxy-6-methyl-2-phenyl-pyrimidin-5-yl)-acetic acid methyl ester (**2e**)

Benzamidine hydrochloride (17.5 g, 0.11 mol) and dimethyl acetylsuccinate (**1**, 19 g, 0.1 mol) are reacted according to the above procedure. Yield 14.2 g (55 mmol, 55 %) **2e**; *m.p.* 195 °C. – ^{1}H NMR ($(CD_3)_2SO$): δ/ppm = 2.35 (s, 3H), 3.58 (s, 2H), 3.64 (s, 3H), 7.48 - 8.10 (m, 5H). Exact Mass for $C_{14}H_{14}N_2O_3$: Calcd.: 258.2768; Found: 258.2781.

(5-Hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)-acetic acid methyl ester (**3a**)

Methylhydrazine (2.3 g, 50 mmol) is added to a solution of dimethyl acetylsuccinate (**1**, 9.5 g, 50 mmol) in toluene (80 ml) and the mixture is heated to reflux for 16 hours using a Dean-Stark water separation apparatus. Subsequently, the reaction mixture is cooled and the solvent is evaporated. The residue is purified by chromatography on silica gel (ethyl acetate/hexane 1 : 4). Yield 4.8 g (26 mmol, 52%) **3a**. – ^{1}H NMR ($(CD_3)_2SO$): δ/ppm = 2.02 (s, 3H), 3.21 (s, 2H), 3.63 (s, 3H), 3.69 (s, 3H). Exact Mass for $C_8H_{12}N_2O_3$: Calcd.: 184.1949; Found: 184.1960.

(5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-acetic acid methyl ester (**3b**)

Phenylhydrazine (5.5 g, 50 mmol) and dimethyl acetylsuccinate (**1**, 9.5 g, 50 mmol) are reacted according to the above procedure. Yield 9.1 g (37 mmol, 74%) **3b**; *m.p.* 132 °C. – ^{1}H NMR ($CDCl_3$): δ/ppm = 1.98 (s, 3H), 3.26 (s, 2H), 3.54 (s, 3H), 6.99 - 7.22 (m, 5H). Exact Mass for $C_{13}H_{14}N_2O_3$: Calcd.: 246.2658; Found: 246.2651.

(4,6-Dihydroxy-2-methyl-pyrimidin-5-yl)-acetic acid methyl ester (**7**)

Triethyl 1,1,2-ethanetricarboxylate (**6**, 20 g, 81 mmol) and acetamidine hydrochloride (7.7 g, 82 mmol) are added successively to a mixture of sodium methoxide in methanol (30 ml of a 5.4M solution, 0.16 mol) and methanol (60 ml). The mixture is stirred for 16 hours at room temperature and acidified with concentrated hydrochloric acid. The resulting crystals are filtered, washed with cold water and dried. Yield 14.8 g (75 mmol, 92%) **7**; *m.p.* >200 °C. – ^{1}H NMR ($(CD_3)_2SO$): δ/ppm = 2.09 (s, 3H), 3.01 (s, 2H), 3.36 (s, 3H), 11.80 (br.s, 2H). Exact Mass for $C_8H_{10}N_2O_4$: Calcd.: 198.1785; Found: 198.1799.

General Chlorination Procedure

Phosphorus oxychloride (6.2 g, 40 mmol) is added slowly to a suspension of **3a**, **3b**, **2c**, **2d** (25 mmol) or **7** (15 mmol) in toluene (80 ml). This reaction mixture is heated to reflux for 3 hours. The solvent was removed under reduced pressure and the resulting oil poured onto crushed ice with stirring. If a crystalline product is obtained, then it is filtered, washed with water and dried. Otherwise, the pH is adjusted to 8 by addition of potassium carbonate and the mixture is extracted twice with diethyl ether. The combined organic layer is washed with water, dried over magnesium sulfate and evaporated, the residue purified either by distillation or by crystallization from ethyl acetate/hexane to give **4a**, **4b**, **5c**, **5d** or **8**.

(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)-acetic acid methyl ester (**4a**)

Yield 46%. – ^{1}H NMR ($CDCl_3$): δ/ppm = 2.11 (s, 3H), 3.29 (s, 2H), 3.64 (s, 3H), 3.88 (s, 3H).

(5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-acetic acid methyl ester (**4b**)

Yield 57%. – ^{1}H NMR ($CDCl_3$): δ/ppm = 2.18 (s, 3H), 3.34 (s, 2H), 3.76 (s, 3H), 7.13 – 7.44 (m, 5H).

(4-Chloro-6-methyl-pyrimidin-5-yl)-acetic acid methyl ester (**5c**)

Yield 82%; *b.p.* 88 – 90 °C/1 torr. – ^{1}H NMR ($CDCl_3$): δ/ppm = 2.58 (s, 3H), 3.77 (s, 3H), 3.87 (s, 2H), 8.79 (s, 1H).

(4-Chloro-2,6-dimethyl-pyrimidin-5-yl)-acetic acid methyl ester (**5d**)

Yield 80%; *m.p.* 54 °C. – ^{1}H NMR ($CDCl_3$): δ/ppm = 2.50 (s, 3H), 2.67 (s, 3H), 3.73 (s, 3H), 3.82 (s, 2H). Exact Mass for $C_9H_{11}ClN_2O_2$: Calcd.: 214.6513; Found: 214.6525.

(4,6-Dichloro-2-methyl-pyrimidin-5-yl)-acetic acid methyl ester (**8**)

Yield 63%; *m.p.* 71 °C. – ^{1}H NMR ($CDCl_3$): δ/ppm = 2.91 (s, 3H), 3.97 (s, 3H), 4.16 (s, 2H). Exact Mass for $C_8H_8Cl_2N_2O_2$: Calcd.: 235.0692; Found: 235.0703.

(4-Chloro-6-dimethylamino-2-methyl-pyrimidin-5-yl)acetic acid methyl ester (**9**)

Dimethylamine in water (5 ml of a 7.9M solution, 40 mmol)

is added dropwise to a solution of **8** (8.0 g, 34 mmol) and triethylamine (4.0 g, 40 mmol) in 1,2-dimethoxyethane (30 ml) at room temperature. After stirring for 1 hour, the mixture is diluted with water and extracted with ethyl acetate. The combined organic layer is dried over magnesium sulfate and evaporated, the remaining oil is purified by chromatography on silica gel (ethyl acetate/hexane 1 : 5). Yield 7.5 g (31 mmol, 91%) **9**. – ^{1}H NMR ($CDCl_3$): δ/ppm = 2.47 (s, 3H), 3.05 (s, 6H), 3.71 (s, 2H), 3.90 (s, 3H). Exact Mass for $C_{10}H_{14}ClN_3O_2$: Calcd.: 243.6929; Found: 243.6933.

(4-Chloro-6-methoxy-2-methyl-pyrimidin-5-yl)acetic acid methyl ester (**10**)

Sodium methoxide in methanol (5 ml of a 5.4M solution, 28 mmol) is added at room temperature to a solution of **8** (6.5 g, 28 mmol) in 1,2-dimethoxyethane (15 ml). After stirring for 30 minutes, the mixture is diluted with diethyl ether and washed with water. The organic layer is dried over magnesium sulfate and evaporated, the remainder purified by distillation. Yield 4.9 g (21 mmol, 76%) **10**; *b.p*. 108–110 °C/0.5 torr. – ^{1}H NMR ($CDCl_3$): δ/ppm = 2.60 (s, 3H), 3.68–3.72 (m, 5H), 3.98 (s, 3H). Exact Mass for $C_9H_{11}ClN_2O_3$: Calcd.: 230.6507; Found: 230.6499.

[4-(3-Isopropyl-phenoxy)-6-methoxy-2-methyl-pyrimidin-5-yl]-acetic acid methyl ester (**11**)

A mixture of **10** (3.2 g, 14 mmol), 3-isopropylphenol (1.9 g, 14 mmol) and potassium carbonate (2.9 g, 21 mmol) is stirred in *N*,*N*-dimethylformamide (30 ml) for 3 hours at 130 °C. After cooling to room temperature, the reaction mixture is diluted with diethyl ether and washed with water. The organic layer is dried over magnesium sulfate and evaporated, the remainder chromatographed on silica gel (ethyl acetate/hexane 1 : 5). Yield 3.1 g (9.4 mmol, 67%) **11**. – ^{1}H NMR ($CDCl_3$): δ/ppm = 1.05 (d, 6H), 2.21 (s, 3H), 2.68 (dq, 1H), 3.44–3.50 (m, 5H), 3.77 (s, 3H), 6.78–7.14 (m, 4H). Exact Mass for $C_{18}H_{22}N_2O_4$: Calcd.: 330.3837; Found: 330.3849.

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