Synthesis of Orthogonally Protected Pyrrole Tricarboxylic Acid Derivatives: Versatile Building Blocks for Pyrrole-Containing Compounds

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Dedicated to Prof. Albrecht Berkessel on the occasion of his 50th birthday

Abstract: The large-scale synthesis of three new orthogonally protected pyrrole tricarboxylates 1–3 is described. Using different cleavage conditions, each of the three carboxylates can be set free selectively without affecting the others, making these pyrrole derivatives versatile synthetic building blocks for a wide range of applications in natural product or supramolecular chemistry.

Key words: pyrroles, carboxylic acids, protecting groups, transesterifications, oxidations

Substituted pyrroles are versatile synthetic building blocks for a variety of applications ranging from natural products to pharmaceutical agents and supramolecular chemistry.1 For our own specific purposes, the design of artificial receptors for biologically relevant substrates2 or self-assembling zwitterions3 we were interested in pyrrole tricarboxylic acids of the general structure shown in Figure 1. The two carboxyl groups in position 2 and 5 of the pyrrole ring are needed for further attachment of specific binding sites such as a guanidino or an amide group whereas the side-chain carboxyl group serves as a handle to attach the resulting guanidinocarbonyl pyrrole binding motif to either a solid support or for linking two or more of these recognition motifs into a multivalent display. For this purpose, however, a sequential and selective transformation of the three carboxylic acid groups is necessary. Whereas in principle the side-chain carboxylate is more reactive than the two pyrrole carboxylates and can be reacted at least with some selectivity, a distinction between the latter two is not possible based on their intrinsic reactivity. Even the selective transformation of the side-chain carboxylate, for example its hydrolysis into the corresponding acid, requires a careful control of the reaction conditions to avoid mixtures of products.4 The use of orthogonal protecting groups offers a solution to this problem. We were therefore interested in developing a versatile approach, which allows the large-scale synthesis of a variety of new pyrrole triesters with varying substitution patterns at the three ester groups. The corresponding target compounds 1–3 are summarized in Figure 1. All triesters are new compounds that have not been described in the literature so far.5

We chose the corresponding tert-butyI, benzyl and methyl/ethyl esters as orthogonal protecting groups.6 Whereas the tert-butyI ester can be cleaved easily under acidic conditions (e.g. TFA in CH₂Cl₂), the benzyl ester can be removed by hydrogenolysis (H₂/Pd) and the methyl/ethyl ester by basic hydrolysis (LiOH in MeOH). Choosing the correct substitution pattern of the three carboxyl groups as in 1, 2 or 3 each of the carboxylates can be set free subsequently without affecting the remaining esters in the molecule. These three derivatives therefore allow for maximum synthetic flexibility in any further desired transformation of these useful synthetic building blocks.

The general synthetic procedure is described in Scheme 1. The triesters can be traced back to the α-methyl pyrrole from which they can be synthesized by selective α-oxidation and subsequent esterification in position R₂. The α-methyl pyrroles can be prepared by Knorr-type cyclization of a β-diketone (e.g. the R₃-4-acetyl-5-oxohexan-2-one) with an α-amino-β-dicarbonyl compound, which can be obtained by reduction from the corresponding oxime.7 Due to the frequent instability of many of these aminocarbonyl compounds the reduction of the oxime to the amine is in general performed in situ in the presence of the second carbonyl compound to start the Knorr reaction immediately after release of the amine.8

Our first target compound was triester 1 (Scheme 2). The preparation started from the pyrrole diester 4 synthesized according to methods described in the literature.13b,9 The carboxylic acid 5 was obtained by treatment of 4 with NaOH in EtOH and water at 60 °C.10 To avoid the transesterification to the methyl ester we chose EtOH as a solvent even though the solubility of 4 in EtOH is rather limited compared to MeOH. Selective hydrolysis of the side-chain ethyl ester was thus achieved and the desired product was obtained in 80% yield. In the next step the free side-chain carboxylic acid group of 5 was transformed into the benzyl ester by reaction with benzyl chlo-

![Figure 1](https://example.com/figure1.png)
ride in DMF–Et₃N to give the diester 6 in 90% yield. Attempts to directly transform the starting diester 4 into 6 by transesterification with benzylate failed due to significant amounts of dibenzyl derivative in the product mixture. Even the transesterification of the ethyl ester derivative of 15 (Scheme 6, R₃ = Et instead of Me) with NaOBn in refluxing toluene led to transesterification at both ester positions, although position R⁵ is derived from a rather unreactive electron-rich pyrrole carboxylate and tert-butyl esters in general are assumed to be inert towards basic transesterification.

The next step required the oxidation of the α-methyl group to introduce the third carboxylic acid group. For methyl pyrroles in general a wide range of procedures and reaction conditions are described for this transformation in the literature. The most common one is the radical chlorination with subsequent hydrolysis (Scheme 3, route a). This oxidation can be carried out with or without basic quenching of the liberated hydrochloric acid. The yields reported vary from < 30–99%, significantly depending also on other functionalities present in the molecule. The problem of this reaction step is mainly the instability of the resulting pyrrole carboxylic acids. Upon prolonged reaction times especially under acidic conditions or even during work up, pyrrole carboxylic acids tend to decarboxylate which very often significantly reduces the yields of isolated product in this oxidation step. Good yields are often found for products, which easily crystallize and are thereby removed from the aggressive reaction mixture.

For the hitherto unknown compound 7, we first chose a standard procedure. The α-methyl group in 6 was oxidized by treatment with sulfuryl chloride in AcOH followed by aqueous workup at 0 °C. Fast precipitation avoided decomposition of the resulting carboxylic acid 7, otherwise quite sensitive to acidic conditions. After addition of water to the reaction mixture (which led to liberation of HCl from the hydrolysis of the trichloride and by decomposition of unreacted SO₂Cl₂) a change in the color of the reaction mixture from slightly yellow to brown indicated the beginning of decomposition during workup, but fortunately in this case the product precipitated immediately after pouring into ice-water, thereby removing it from the aggressive reaction medium and giving a yield of 92%. In contrast to this, for example, the direct oxidation of the diethyl ester 4 only gave trace amount of acid under the same conditions, because the product does not crystallize as easily as 7. Compound 7 was then transformed into the corresponding acyl chloride using oxalyl chloride in CH₂Cl₂ with a catalytic amount of DMF. Finally, the new pyrrole triester 1 was obtained by reaction of this acyl chloride with t-BuOK in tert-BuOH in 50% yield.
The three carboxylic acid groups in this triester 1 or the free acid 7 can be released in nearly any desired sequence except for one limitation: The cleavage of the benzyl ester in the side-chain has to occur prior to the hydrolysis of the ethyl ester in position 5. Therefore, triester 1 does not allow to further react both carboxylates attached to the pyrrole ring before the side-chain carboxylate is transformed. To circumvent this problem, we were interested in triester 2, in which the side-chain carboxylate is now protected as the tert-butyl ester and the α-positions of the pyrrole as benzyl and methyl esters, respectively. This triester 2 together with the corresponding free acid 10 allows any of the three carboxylates to react in any order.

The synthesis of 2 also started from the carboxylic acid 5 (Scheme 4). The remaining ethyl ester group in position 5 was exchanged for a benzyl ester by treatment with sodium benzylate in benzyl alcohol at 100 °C over a period of 6 hours under reduced pressure (10–20 mbar) to remove the liberated EtOH to give 8 in 64% yield. These conditions proved to be mild enough to avoid decomposition. The same reaction at atmospheric pressure and a temperature of 140 °C, conditions similar to those found in the literature for related systems, resulted only in very low yields (< 16%) when applied to 5. Compound 8 was then esterified via the acyl chloride (obtained from its reaction with oxazolyl chloride) and subsequent treatment with t-BuOK in tert-BuOH at 40 °C to give 9 in 72% yield. In analogy to the synthesis of 7, direct oxidation of the α-methyl group to the carboxylic acid using sulfuryl chloride was attempted in various solvents, but even under very mild and slightly basic conditions only decomposition of the product was observed. Only trace amounts of the desired carboxylic acid 10 could be isolated. Another approach to avoid decarboxylation of the free carboxylic acid is to use an alcohol instead of water for hydrolysis of the intermediate trichloride to directly obtain the corresponding ester. However, we tried this for the oxidation of 4 to the corresponding benzyl ester (R = Bn) by quenching the reaction mixture with benzyl alcohol instead of water (see Scheme 3, route a). After flash chromatography the 1H NMR indicated a mixture of the benzyl ester and some unwanted by-products (according to NMR the aldehyde resulting from incomplete oxidation of the methyl group even in the presence of excess sulfuryl chloride). We could not separate this mixture either by column chromatography or by crystallization.

We finally succeeded in preparing 10 in acceptable yields by performing the oxidation in two subsequent steps (Scheme 3, route b). First, chlorination of 9 with 2 equivalents of sulfuryl chloride in Et2O at 0 °C followed by aqueous workup gave the corresponding aldehyde, which was then oxidized without further purification in situ by treatment with K2MnO4 in aceton–water at room temperature. This provided the hitherto unknown pyrrole derivative 10 in 42% overall yield. The oxidation of the intermediate pyrrole aldehyde (which was identified via NMR in the reaction mixture) with K2MnO4 represents obviously much milder conditions than the direct oxidation using excess sulfuryl chloride preventing the decomposition of the resulting free carboxylic acid. Hence, route b is an alternative for highly sensitive compounds. Compound 10 was then reacted with MeI in DMF in the presence of K2CO3 to obtain the triester 2 in a yield of 45%. Triester 2 or the free acid 10 now allow to further transform both carboxylic acid groups attached to the pyrrole before the side-chain ester.

The two triesters 1 and 2, synthesized here for the first time, now offer a broad flexibility for the introduction of other functionalities into this pyrrole skeleton via their ester groups. Furthermore, besides hydrolysis and subsequent ester or amide formation via the free acid, the ester groups can also be transformed into other even more versatile functionalities via the corresponding aldehydes or alcohols. For example, in a first experiment we were able to obtain the side-chain aldehyde 11 by reaction of 4 with DIBAL-H at −78 °C in toluene (Scheme 5). Hence, the side-chain ester can be selectively reduced while keeping the pyrrole ester intact. The aldehyde functionality offers additional synthetic flexibility, for example via imine formation or reductive amination. However, in this first experiment substantial amounts (15%) of the corresponding alcohol were also formed, although TLC still indicated a trace of unreacted starting material. Further optimization would be required to find the best reaction conditions for aldehyde formation. For example, protection of the pyrrole nitrogen could be beneficial or the use of LiHAl(Ot-Bu)3 instead of DIBAL-H. However, we have not yet investigated this approach any further.

The two new pyrrole derivatives 1 and 2 can be prepared on multi gram scales via the synthesis described above, but the total sequences are still rather time-consuming and require extensive purification by flash chromatography. Furthermore, the starting material 4 is not commercially available and has also to be synthesized (two steps with a total yield of 59%). We therefore developed an even sim~
The acetoacetate 13 could be easily prepared in a one-pot synthesis from methyl acrylate and pentane-2,4-dione in 88% yield after distillation according to a known literature procedure. 8a,20 Commercially available 14 was reacted with sodium nitrite in AcOH to give the corresponding oxime which was reduced in situ with zinc in the presence of 13 to give the pyrrole 15 in a 32% yield after crystallization from hexane–isopropanol. 21 For the oxidation of the methyl group in 15 we found the complete chlorination using sulfuryl chloride in Et₂O in the presence of K₂CO₃ to be the best method. 12c,22 The trichlorinated product could easily be separated from the excess K₂CO₃ by filtration and was then directly hydrolyzed without further isolation with NaOAc in 50% water in dioxane to give the free acid 16 in a good yield of 49% after crystallization. The basic in situ quenching of the liberated HCl with carbonate is crucial for the yield. Not only to avoid decarboxylation of the pyrrole carboxylic acid once it is formed (see above), but also because of the acid-sensitive tert-butyl ester which is otherwise cleaved. The free acid 16 can then easily be converted into triester 3 with benzyl bromide and K₂CO₃ in DMF in quantitative yield. Aqueous workup followed by column chromatography gave the triester 3 in 98% yield. Hence, triester 3 was synthesized from commercially available starting materials on a multi gram scale in only four steps without any intermediate chromatographic purification needed in between in 14% overall yield in excellent purity.

In conclusion, we present here the versatile and large-scale synthesis of three new triply orthogonally protected pyrrole tricarboxylates 1–3. Even though their synthesis followed the same general approach (Scheme 1), each compound required a careful optimization of the reaction conditions especially for the oxidation of the α-methyl group. This step was crucial for the total yield. With the procedures developed here multi-gram quantities of these versatile synthetic building blocks can now easily be prepared.

Reaction solvents were dried and distilled under Ar before use. All other reagents were used as obtained from either Aldrich or Fluka. 1H and 13C NMR spectra were measured on a Bruker Avance-400 or AC 250 and the chemical shifts are reported relative to the deuterated solvents. Peak assignments are based on either DEPT, 2D NMR studies and/or comparison with literature data. Melting points were measured on a Büchi SMP-20 apparatus and are not corrected.

IR spectra were collected on a Perkin-Elmer FT-IR 1600 instrument. MS data were measured on a Bruker Daltonic micro TOF or a Finnigan MAT 8200 spectrometer.

**Scheme 5** Reagents and conditions: (i) toluene, −78 °C, 1 M DIBAL-H in toluene (stepwise 2.5 equiv), 4 h, 46%.

**Scheme 6** Reagents and conditions: (i) NaNO₂, AcOH–H₂O, 0 °C, 12 h, then 13, Zn, 65 °C, 12 h, 32%. (ii) Et₃O, SO₂Cl₂ (3.2 equiv), K₂CO₃, −20 °C to reflux, 8 h, 49%. (iii) BnBr, DMF, K₂CO₃, 98%.

The acetoacetate 13 could be easily prepared in a one-pot synthesis from methyl acrylate and pentane-2,4-dione in 88% yield after distillation according to a known literature procedure. 8a,20 Commercially available 14 was reacted with sodium nitrite in AcOH to give the corresponding oxime which was reduced in situ with zinc in the presence of 13 to give the pyrrole 15 in a 32% yield after crystallization from hexane–isopropanol. 21 For the oxidation of the methyl group in 15 we found the complete chlorination using sulfuryl chloride in Et₂O in the presence of K₂CO₃ to be the best method. 12c,22 The trichlorinated product could easily be separated from the excess K₂CO₃ by filtration and was then directly hydrolyzed without further isolation with NaOAc in 50% water in dioxane to give the free acid 16 in a good yield of 49% after crystallization. The basic in situ quenching of the liberated HCl with carbonate is crucial for the yield. Not only to avoid decarboxylation of the pyrrole carboxylic acid once it is formed (see above), but also because of the acid-sensitive tert-butyl ester which is otherwise cleaved. The free acid 16 can then easily be converted into triester 3 with benzyl bromide and K₂CO₃ in DMF in quantitative yield. Aqueous workup followed by column chromatography gave the triester 3 in 98% yield. Hence, triester 3 was synthesized from commercially available starting materials on a multi gram scale in only four steps without any intermediate chromatographic purification needed in between in 14% overall yield in excellent purity.

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IR spectra were collected on a Perkin-Elmer FT-IR 1600 instrument. MS data were measured on a Bruker Daltonic micro TOF or a Finnigan MAT 8200 spectrometer.
The remaining red oil was treated with hexane (15 mL), filtered off and washed with small amounts of hexane. After drying, 6 (12.2 g, 36.9 mmol, 90%) was obtained as colorless crystals; mp 75 °C.

IR (KBr): 3299 (s), 3938 (m), 1736 (s), 1702 (s), 1559 (m), 1471 (m), 1346 (70), 91 (67), 41 (18).

HRMS (EI): \[m/z\] = 343 (16) [M]+, 301 (26), 242 (18), 134 (40), 91 (81).

HRMS (ESI): \[m/z\] = [M + Na]+ calc for C_{10}H_{12}NNaO_{4}: 383.1261; found: 382.1264.

3-(2-Benzoxycarbonyl)ethyl)-4-methyl-1H-pyrrole-2,5-dicarboxylic Acid tert-Butyl Ester (1)

A solution of oxalyl chloride (2.13 mL, 26.5 mmol) in glacial AcOH (20 mL) was added dropwise over a period of 1 h to a solution of 6 (2.50 g, 7.59 mmol) in glacial AcOH (10 mL). The resulting solution was stirred for 4 h at r.t. Water (8 mL) was added to a solution of sodium (726 mg, 31.6 mmol) in benzyl alcohol (100 mL). The reaction mixture was heated to reflux at 10–20 °C for 2 h. The solvent was removed under reduced pressure, and the remaining solid was dissolved in water (100 mL). The organic phase was extracted with a sat. solution of NaHCO3 (3 × 100 mL). The combined aqueous phases were acidified with concd sulfuric acid to pH = 3 and stored at 4 °C for 2 h. The precipitate was filtered off and washed with water (2 × 30 mL) and hexane (2 × 30 mL). Compound 8 (3.03 g, 10.1 mmol, 64%) was obtained as a reddish, crystalline solid; mp 127 °C.

IR (KBr): 2918 (s), 1721 (m), 1673 (s), 1455 (s), 1270 (m), 1159 (s), 725 (m) cm–1.

HRMS (ESI): \[m/z\] = [M + Na]+ calc for C_{10}H_{12}NNaO_{4}: 383.1261; found: 382.1264.
IR (KBr): 2983 (m), 2927 (m), 1729 (s), 1657 (s), 1454 (s), 1367 (m), 1268 (s), 1150 (s), 1092 (s), 769 (m) cm\(^{-1}\).

\(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.42\) [s, 9 H, C(CH\(_3\))\(_3\)], 2.20 (s, 3 H, pyrrole-CH\(_3\)), 2.29 (s, 3 H, pyrrole-CH\(_3\)), 2.32 (t, \(J = 8.0\) Hz, 2 H, pyrrole-CH\(_2\)), 2.65 (t, \(J = 8.0\) Hz, 2 H, pyrrole-CH\(_2\)), 5.29 (s, 2 H, benzyl-CH\(_3\)), 7.32–7.42 (m, 5 H, aryl-H), 8.56 (s, 1 H, NH).

\(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta = 10.8, 11.7\) (pyrrole-CH\(_3\)), 19.8 (pyrrole-CH\(_3\)), 28.2 [C(CH\(_3\))\(_3\)], 36.4 (pyrrole-CH\(_2\)), 65.6 (benzyl-CH\(_3\)), 80.3 [C(CH\(_3\))\(_3\)], 116.7, 120.7, 130.2, 136.8 (pyrrole-C\(_q\)), 128.2, 128.7 (benzyl-C\(_q\)), 161.4 (CO\(_2\)Bn), 172.7 (CO\(_2\)t-Bu).

MS (EI, 70 eV): \(m/z\% = 357 (23) [M]^+\), 301 (26), 242 (44), 166 (70), 91 (100), 57 (97).

HRMS (EI): \(m/z\% = [M]^+\) calcd for C\(_{17}\)H\(_{17}\)NO\(_6\): 357.1933; found: 357.1934.

3-(2-tert-Butoxycarbonyl)-4-methyl-1H-pyrrole-2,5-dicarboxylic Acid 5-Benzyl Ester (10)

A solution of tert-butyl chloroformate (3.66 mL, 45.5 mmol) in anhyd Et\(_2\)O (200 mL) with K\(_2\)CO\(_3\) (13.5 g, 114 mmol) at 0 °C and it was stirred for 2 h at 0 °C. Water (10 mL) was added to the reaction mixture and it was stirred for 30 min at r.t. The solvent was removed under reduced pressure and the remaining solid was dissolved in acetonitrile (150 mL). A solution of KMnO\(_4\) (5.57 g, 14.0 mmol) in acetonitrile (25 mL) was added slowly in small portions and the resulting mixture was stirred for 1 h at r.t. Na\(_2\)S\(_2\)O\(_4\) was washed with water and dried in vacuo. The solid was dissolved in EtOAc (3 x 15 mL) and concentrated to dryness under reduced pressure. Compound 10 (2.45 g, 6.32 mmol, 42%) was obtained as an off-white solid; mp 94 °C.

1H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 1.43\) [s, 9 H, C(CH\(_3\))\(_3\)], 2.31 (s, 3 H, pyrrole-CH\(_3\)), 2.40 (t, \(J = 8.0\) Hz, 2 H, pyrrole-CH\(_2\)), 3.02 (t, \(J = 7.8\) Hz, 2 H, pyrrole-CH\(_2\)), 5.37 (s, 3 H, CO\(_2\)CH\(_3\)), 5.33 (s, 2 H, benzyl-CH\(_3\)), 7.35–7.44 (m, 5 H, aryl-H), 9.40 (s, 1 H, NH).

\(^{13}C\) NMR (100 MHz, DMSO-\(d_6\)): \(\delta = 10.3\) (pyrrole-CH\(_3\)), 19.8 (pyrrole-CH\(_3\)), 27.7 [C(CH\(_3\))\(_3\)], 35.5 (pyrrole-CH\(_2\)), 65.3 (benzyl-CH\(_3\)), 79.5 [C(CH\(_3\))\(_3\)], 121.0, 123.0, 126.2, 128.6 (pyrrole-C\(_q\)), 128.5, 128.6, 128.8 (benzyl-C\(_q\)), 160.8 (CO\(_2\)CH\(_3\)), 161.1 (CO\(_2\)Bn), 171.7 (CO\(_2\)t-Bu).

MS (EI, 70 eV): \(m/z\% = 401 (1) [M]^+\), 345 (17), 299 (17), 91 (100), 57 (21).

HRMS (ESI): \(m/z\% = [M + Na]^+\) calcd for C\(_{17}\)H\(_{25}\)NO\(_5\)Na\(_2\): 424.1731; found: 424.1736.

4-(2-Methoxy carbonyl)-3,5-dimethyl-1H-pyrrole-2-carboxylic Acid tert-Butyl Ester (15)

tert-Butyl acetooxacete 14 (64.8 g, 410 mmol) was dissolved in AcOH (115 mL) and cooled down to 5 °C. A solution of sodium nitrite (27.5 g, 399 mmol) in water (95 mL) was added slowly via an addition funnel and the resulting solution was stirred overnight at 5 °C. To assure complete conversion the disappearance of 14 was observed by TLC monitoring (deactivated SiO\(_2\), cyclohexane–EtOAc, 4:1; \(R_f = 0.29\)). The resulting solution was added to a suspension of 13 (75.5 g, 410 mmol), NaOAc (82.5 g, 1.01 mol) and zinc (82.5 g, 1.26 mol) in AcOH (90 mL). Further zinc (82.5 g, 1.26 mol) was added slowly in small portions and the resulting mixture was stirred overnight at 65 °C. The reaction was cooled down to r.t. and poured into an ice-water dispersion (15 L). The precipitate was filtered off, washed with water and dried in vacuo. The solid was dissolved in EtOH and the zinc residue was removed by filtration. After evaporation of the solvent, crystallization from hexane–i-PrOH led to 15 (36.2 g, 129 mmol, 32%) as a white solid; mp 96 °C.

IR (KBr): 2974 (m), 2951 (w), 2924 (m), 1738 (s), 1666 (s), 1449 (m), 1345 (m), 1364 (m), 1281 (m), 1163 (s) cm\(^{-1}\).

\(^{1}H\) NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 1.49\) [s, 9 H, C(CH\(_3\))\(_3\)], 2.11 (s, 3 H, pyrrole-CH\(_3\)), 2.13 (s, 3 H, pyrrole-CH\(_3\)), 2.35 (t, \(J = 7.4\) Hz, 2 H, pyrrole-CH\(_2\)), 2.56 (t, \(J = 7.4\) Hz, 2 H, pyrrole-CH\(_2\)), 3.56 (s, 3 H, CO\(_2\)CH\(_3\)), 10.81 (s, 1 H, NH).

\(^{13}C\) NMR (100 MHz, DMSO-\(d_6\)): \(\delta = 10.3, 10.7\) (pyrrole-CH\(_3\)), 19.2 (pyrrole-CH\(_3\)), 28.2 [C(CH\(_3\))\(_3\)], 34.5 (pyrrole-CH\(_2\)), 51.2 (CO\(_2\)CH\(_3\)), 78.8 [C(CH\(_3\))\(_3\)], 117.3, 118.8, 124.8, 129.7 (pyrrole-C\(_q\)), 160.5 (CO\(_2\)t-Bu), 172.8 (CO\(_2\)Me).

MS (EI, 70 eV): \(m/z\% = 281 (16) [M]^+\), 225 (40), 208 (19), 152 (100), 134 (45), 41 (5).
3-(2-Methoxy carbonyl)ethyl)-4-methyl-1H-pyrrole-2,5-dicarboxylic Acid 5-tert-Butyl Ester (16)

Compound 15 (3.29 g, 11.7 mmol) and K₂CO₃ (6.43 g, 46.6 mmol) were suspended under Ar in anhyd Et₂O (100 mL) and stirred overnight. The reaction mixture was cooled down to 0 °C. This aqueous solution was then acidified slowly and under vigorous stirring with concentrated hydrochloric acid to pH = 1–2.

The precipitate was filtered off, washed with cold water (150 mL) and recrystallized from MeOH–water to give 16 (1.77 g, 5.69 mmol, 49%) as white needles; mp 169 °C.

IR (KBr): 3473 (m), 3340 (s), 2977 (m), 2952 (w), 1737 (s), 1716 (s), 1616 (m), 1575 (s), 1455 (m), 1324 (s), 1164 (s), 1101 (m), 939 (s), 802 (m), 756 (m), 688 (m), 634 (m) cm⁻¹.

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