The Preparation of Partially Protected 3-Amino-1-methylpyrazole-5-carboxylic Acids to be Used as Intermediates in the Synthesis of Analogues of Distamycin A

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Partially protected 3-amino-1-methylpyrazole-5-carboxylic acid derivatives have been prepared by a convenient route from 3-amino-1-methylpyrazole. The structures of these compounds have been correlated with recent work in the field. Such derivatives, blocked on the amino function with *tert*-butyloxycarbonyl (**6**) or formyl (**8**) groups or on the carboxy function with benzyl (**4a**) or ethyl (**4b**) groups, should serve as suitable precursors for the synthesis of oligoamides related to distamycin A using a stepwise strategy. In addition several intermediates and side-products have been characterized.

In continuation of our efforts to obtain more potent synthetic analogues of the antiviral compound distamycin A, we are at present investigating the possibility of incorporating heterocyclic moieties other than the original pyrrole ring into the molecule. In this context, a preparative study dealing with suitably designed 4-amino-1-methylimidazole-2-carboxylic acid derivatives fitting our previous synthetic scheme has just been completed.[1] Essentially in parallel with this, we have also elaborated a similar scheme for the preparation of pyrazole precursors. A very interesting paper treating synthetic aspects of miscellaneous aminopyrazolecarboxylic acid synthons has recently been published.[2] The general interest in this topic therefore prompted us to communicate results regarding the chemistry of various aminopyrazole derivatives. The present paper describes in detail alternative practical methods leading to protected 3-amino-1-methylpyrazole-5-carboxylic acid synthons to be used in our programme of distamycin A analogues.

Results and discussion

The synthesis of precursors **4a**, **4b**, **6** and **8** is depicted in Scheme 1. The base-mediated cyclocondensation of 2-chloroacrylonitrile and methylhydrazine provided the requisite starting material **1** by a known convenient procedure.[3] As already described, the amino group of **1** was subsequently blocked by the acid-catalysed reaction with acetonylacetone and the protected derivative **2** was obtained in fair yield.[4] Lithiation of the 5-position of **2** was smoothly effected by BuLi in THF at low temperature and the resulting metallated intermediate furnished **3a** upon cautious addition of BzlOCOCl by analogy with the established procedure for **3b**.[5] The moderate yield in this conversion is partly due to the concomitant formation of the ketone **9** (Fig. 1). This could be explained by nucleophile attack by the transient 5-lithio species on the carbonyl function of ester **3a**, already present, with displacement of the benzyloxy group. In all runs, the crude reaction product contained 20–30 % of this undesired by-product. This side reaction could probably be prevented or at least suppressed by avoiding the excess of the lithiated intermediate in the reaction but, for practical reasons, the reversed order of addition of the reactants was not attempted.

Prolonged reflux in aqueous EtOH in the presence of hydroxylamine under buffering conditions, smoothly cleaved the 2,5-dimethylpyrrolyl moiety in **3a** and, by analogy with the known ethyl ester **4b**,[5] amine **4a** was liberated in fair yield. However, because of the extended reaction time in EtOH, under the influence of a base, noticeable transesterification occurred and significant amounts of **4b** were also formed under these conditions. Typical crude reaction mixtures generally contained up to 20 % of **4b** (the remainder was largely the desired **4a**), and attempts to suppress this side reaction by using other solvents in place of EtOH were not encouraging. This deprotection was considerably retarded when performed in a similar manner in aqueous dioxane or aqueous BzlOH whereas the reaction in aqueous DMSO furnished a dark, impure product.

The reaction between Boc_2O and **4** proceeded rather sluggishly at ambient temperature and was not complete despite the excess of the acylating agent and extended reaction times. The *tert*-butyloxycarbonylation was, how-

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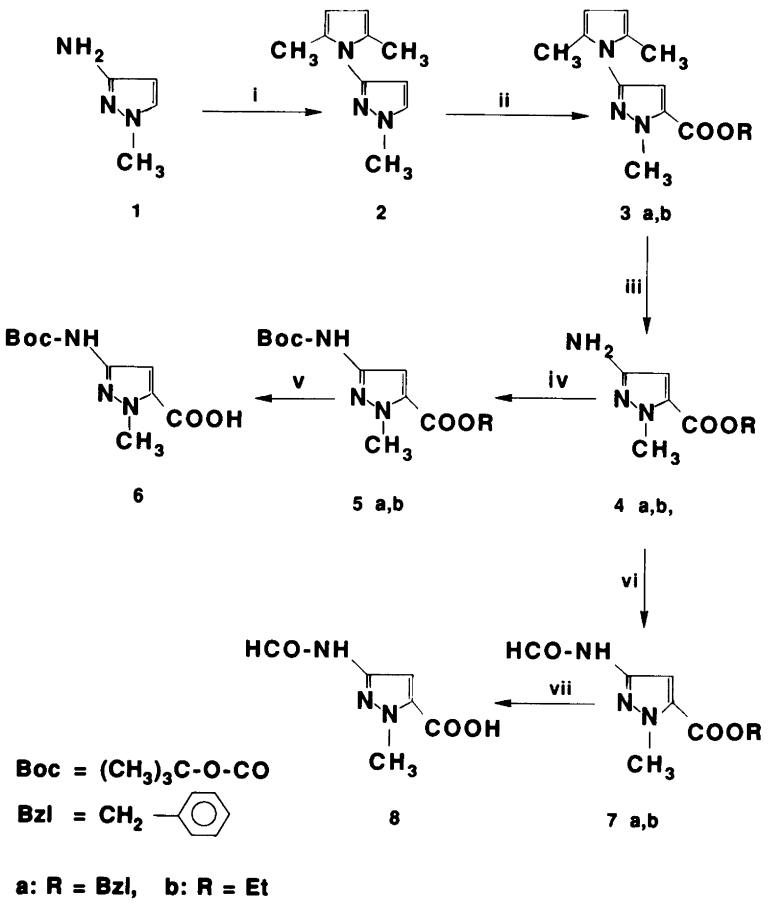
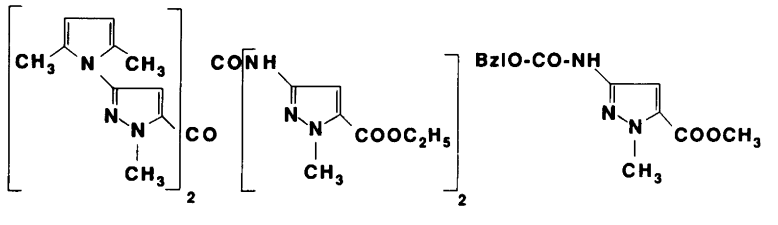
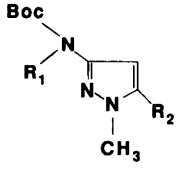


Scheme 1. Reagents: i, $MeCO(CH_2)_2COMe$/HOAc, C_6H_6, reflux; ii, 1: BuLi, hexane/THF, −70 °C, 2 h; 2: BzlOCOCl (a) or EtOCOCl (b), THF, −70 °C, 2 h; iii, NH_2OH·HCl/KOH, aq. EtOH, reflux, 36 h; iv, Boc-F/NEt_3, $MeCN/Et_2O$, 70 h; v, a: H_2(Pd/C), EtOH, 1 h; b: aq. NaOH (1.2 equiv.); vi, $HCO-OC_6F_5$, $CHCl_3$, 4 h; vii, a: H_2(Pd/C), MeOH, 2 h; b: as for v b.





12 a-d

a: $R_1 = R_2 = H$

b: R_1 = Boc; $R_2 = H$

c: R_1 = Boc; $R_2 = COOC_2H_5$

d: $R_1 = COOC_2H_5$; $R_2 = H$

Table 1. Properties of pyrazole intermediates.

Comp.	Formula (mol. wt.)[a]	Yield (%)[b]	Solvent for recrystallization[c]	M.p./°C	^{1}H NMR [$CDCl_3$, δ(ppm) rel. TMS]
3a	$C_{18}H_{19}N_3O_2$ (309.37)	68[d]	Hexane (20 ml g^{-1})	75–75.5	7.40 (perturbed signal, 5 H, $CH_2C_6H_5$), 6.76 (s, 1 H, pyrazole H-4), 5.85 (s, 2 H, pyrrole H-3, H-4), 5.35 (s, 2 H, $CH_2C_6H_5$), 4.20 (s, 3 H, NCH_3), 2.09 (s, 6 H, pyrrole CH_3)
4a	$C_{12}H_{13}N_3O_2$ (231.26)	60[d]	–[e]	–[f]	7.38 (s, 5 H, $CH_2C_6H_5$), 6.17 (s, 1 H, H-4), 5.29 (s, 2 H, $CH_2C_6H_5$), 3.99 (s, 3 H, NCH_3), 3.63 (br s, 2 H, NH_2)
5a	$C_{17}H_{21}N_3O_4$ (331.37)	91	Hexane (40 ml g^{-1})	119.5–120	8.01 (br s, ca. 1 H, NH) 7.38 (perturbed signal, 5 H, $CH_2C_6H_5$), 7.05 (s, 1 H, H-4), 5.29 (s, 2 H, $CH_2C_6H_5$), 4.09 (s, 3 H, NCH_3), 1.50 (s, 9 H, Boc CH_3)
5b	$C_{12}H_{19}N_3O_4$ (269.30)	84	Hexane–Et_2O 4:1 (40 ml g^{-1})	124–124.5	8.13 (br s, ca. 1 H, NH), 7.04 (s, 1 H, H-4), 4.31 (q, 2 H, CH_2CH_3), 4.09 (s, 3 H, NCH_3), 1.52 (s, 9 H, Boc CH_3), 1.35 (t, 3 H, CH_2CH_3)
6	$C_{10}H_{15}N_3O_4$ (241.25)	97[g](92[h])	EtOH (20 ml g^{-1})	252–254 (decomp.)	13.32 (br s, ca. 1 H, COOH), 9.73 (br s, ca. 1 H, NH), 6.74 (s, 1 H, H-4), 3.95 (s, 3 H, NCH_3), 1.45 (s, 9 H, Boc CH_3)[i]
7a	$C_{13}H_{13}N_3O_3$ (259.27)	97	Et_2O–CH_2Cl_2 5:1 (60 ml g^{-1})	132–132.5	8.68 (br signal, ca. 0.7 H, NH), 8.35 (d, 0.69 H, $J_{NH,HCO}$ 1.5 Hz, HCO), 7.39 (perturbed signal, 5 H, $CH_2C_6H_5$), 7.27 (s, 0.69 H, H-4), 5.31 (s, ca. 1.4 H, $CH_2C_6H_5$), 4.10 (s, 3 H, NCH_3)[j]
7b	$C_8H_{11}N_3O_3$ (197.19)	95	Et_2O–CH_2Cl_2 6:1 (70 ml g^{-1})	153.5–154	8.92 (br signal, ca. 0.7 H, NH), 8.39 (d, 0.67 H, $J_{NH,HCO}$ 1.5 Hz, HCO), 7.26 (s, 0.67 H, H-4), 4.34 (q, ca. 1.4 H, CH_2CH_3), 4.12 (s, 3 H, NCH_3), 1.38 (t, ca. 2 H, CH_2CH_3)[k]
8	$C_6H_7N_3O_3$ (169.14)	97[l](93[m])	MeOH (30 ml g^{-1})	ca. 225 (decomp.)	13.24 (br s, ca. 1 H, COOH), 10.74 (br s, ca. 0.8 H, NH), 8.21 (d, 0.78 H, $J_{NH,HCO}$ 1.6 Hz, HCO), 6.97 (s, 0.78 H, H-4), 4.00 (s, 3 H, NCH_3)[j,n]
9	$C_{21}H_{24}N_6O$ (376.46)	–[o]	Hexane–EtOAc 4:1 (80 ml g^{-1})	135.5–136	6.70 (s, 2 H, pyrazole H-4), 5.89 (s, 4 H, pyrrole H-3, H-4), 4.24 (s, 6 H, NCH_3), 2.14 (s, 12 H, pyrrole CH_3)
10	$C_{15}H_{20}N_6O_5$ (364.36)	30	MeCN (30 ml g^{-1})	218.5–219.5	8.90 (br s, ca. 2 H, NH), 6.80 (s, 2 H, H-4), 4.33 (q, 4 H, CH_2CH_3), 4.11 (s, 6 H, NCH_3), 1.37 (t, 6 H, CH_2CH_3)
11	$C_{14}H_{15}N_3O_4$ (289.29)[p]	97	Hexane–EtOAc 4:1 (80 ml g^{-1})	131–131.5[q]	8.63 (br s, ca. 1 H, NH), 7.36 (s, 5 H, $CH_2C_6H_5$), 7.07 (s, 1 H, H-4), 5.20 (s, 2 H, $CH_2C_6H_5$), 3.95 (s, 3 H, NCH_3), 3.85 (s, 3 H, OCH_3). In $(CD_3)_2CO$: 9.16 (br s, ca. 1 H, NH), 7.28–7.49 (perturbed signal, 5 H, $CH_2C_6H_5$), 6.97 (s, 1 H, H-4), 5.20 (s, 2 H, $CH_2C_6H_5$), 3.99 (s, 3 H, NCH_3), 3.86 (s, 3 H, OCH_3).
12a	$C_9H_{15}N_3O_2$ (197.24)	81	Hexane–EtOAc 7:1 (80 ml g^{-1})	121.5–122	8.29 (br s, ca. 1 H, NH), 7.20 (d, 1 H, $J_{4,5}$ 2.2 Hz, H-5), 6.43 (perturbed signal, 1 H, H-4), 3.81 (s, 3 H, NCH_3), 1.51 (s, 9 H, Boc CH_3)
12b	$C_{14}H_{23}N_3O_4$ (297.38)	100	Hexane (75 ml g^{-1})	90.5–91	7.29 and 6.09 (2 d, 2 H, $J_{4,5}$ 2.3 Hz, H-5, H-4), 3.87 (s, 3 H, NCH_3), 1.47 (s, 18 H, Boc CH_3)
12c	$C_{17}H_{27}N_3O_6$ (369.42)	94	Hexane (6 ml g^{-1})	92.5–93	6.71 (s, 1 H, H-4), 4.34 (q, 2 H, CH_2CH_3), 4.16 (s, 3 H, NCH_3), 1.48 (s, 18 H, Boc CH_3), 1.37 (t, 3 H, CH_2CH_3)

[a]Satisfactory microanalyses obtained for recrystallized specimens: C ± 0.3, H ± 0.2, N ± 0.3. [b]Crude, essentially pure by TLC or ^{1}H NMR spectroscopy. [c]Decolourizing carbon if necessary. [d]Yield after chromatography. [e]Not recrystallized. [f]Not recorded. [g]Catalytic hydrogenolysis of **5a**. [h]Alkaline hydrolysis of **5b**. [i]DMSO-d_6. [j]*cis* conformer. Additional resonances at δ 9.03 (d, NH) and 8.67 (d, HCO, $J_{NH,HCO}$ 11.4 Hz), 6.56 (s, H-4) and 5.32 (s, $CH_2C_6H_5$) indicated 31 % of *trans* conformer. [k]*cis* conformer. Additional resonances at δ 9.35 (d, NH) and 8.71 (d, HCO, $J_{NH,HCO}$ 11.3 Hz), 6.56 (s, H-4), 4.37 (q, CH_2CH_3) and 1.39 (t, CH_2CH_3) indicated 33 % *trans* conformer. [l]Catalytic hydrogenolysis of **7a**. [m]Alkaline hydrolysis of **7b**. [n]*cis* conformer. Additional resonances at δ 10.32 (d, NH) and 8.68 (d, HCO, $J_{NH,HCO}$ 11.1 Hz) and 6.56 (s, H-4) showed 22 % of the *trans* conformer. [o]Side product isolated in the synthesis of **3a** (and **3b**). [p]No CHN analyses. [q]Lit.[2] m.p. = 127–128 °C (not recrystallized).

ever, readily achieved with Boc-F/Et_3N in MeCN/Et_2O and **5a** and **5b**, respectively, were produced in excellent yields after a convenient work-up.[1] Also paralleling the behaviour of the corresponding aminoimidazole analogues, the symmetrical urea derivative **10** (Fig. 1) was obtained as the main product when **4b** was treated with Boc_2O/Et_3N in MeCN.[1]

The cleavage of the ester function in **5a** and **5b** was accomplished by standard methods.[1] Catalytic hydrogenolysis of **5a** gave the acid **6** in essentially quantitative yield. Alternatively, this acid was prepared by alkaline hydrolysis of **5b**.

The formylation of **4** presented no special problem. Preliminary experiments employing HCOOH/dicyclohexylcarbodiimide were abandoned because of difficulties of separating the product completely from the by-product dicyclohexylurea.[1] A large excess of HCOOH slowly converted **4b** into the corresponding formyl analogue **7b** on prolonged reaction at room temperature. This formylation was greatly facilitated when pentafluorophenyl formate in dry $CHCl_3$ was used as the acylating agent.[6] The isolated yields of **7a** and **7b** were very high and we assume that this mild, rapid and non-acidic method offers special advantages in work with acid-sensitive amine substrates.

The removal of the carboxy protection in **7a** and **7b** was accomplished according to the procedures described for **5a** and **5b**, respectively, and **8** was produced in high yield and purity in both conversions.[1]

Examination of the formyl region of the ^1H NMR spectra of **7a**, **7b** and **8**, recorded at room temperature (Table 1 and notes), clearly demonstrates the existence of an equilibrium between the major *cis*-conformer and the minor *trans*-conformer in the approximate ratios 2.2, 2.0 and 3.5, respectively. The discrimination between the conformers was based on the chemical shift of the formyl proton and the coupling between this proton and the amide hydrogen. The values for the *cis* form, $8.21 < \delta_{HCO} < 8.39$ ppm and $1.5 < J_{NH,HCO} < 1.6$ Hz, differ significantly from those of the *trans* form, $8.67 < \delta_{HCO} < 8.71$ ppm and $11.1 < J_{NH,HCO} < 11.4$ Hz, and are consistent with the ^1H NMR parameters recorded for a similar *N*-pyrazolyl formamide.[7]

A convenient route to certain 3-amino-1-methylpyrazole-5-carboxylic acid derivatives, among them compound **11** (Fig. 1), by a completely different approach starting from 3,5-dimethylpyrazole has recently been described,[2] which can be correlated with the present work. We synthesized **11** in excellent yield and high purity by treating the methyl analogue of **4**[5] with a slight excess of benzotriazol-1-yl benzyl carbonate in dry DMF according to a previous method.[8] The melting point of **11** (131–131.5 °C) agreed well with the literature value (127–128 °C, crude sample), whereas that of the isomeric methyl 5-benzyloxycarbonylamino-1-methylpyrazole-3-carboxylate was considerably lower (89.5–90 °C).[2] Furthermore, the ^1H NMR spectrum of **11** (Table 1) was identical with that reported.[2]

As the cleavage of the protecting 2,5-dimethylpyrrolyl function in **3** generally requires rather vigorous conditions,[5,9] the use of other protective groups removable by milder methods was considered. The application of the Boc group to block the amine site appeared attractive in this case since deprotection is readily accomplished by mild acidolysis. As expected, amine **1** underwent facile reaction with Boc-F/Et_3N in MeCN/Et_2O by analogy with the procedure for **5** to give **12a** (Fig. 1) in satisfactory yield. The protection of the remaining urethane site was smoothly achieved by the conventional DMAP-catalysed Boc_2O-mediated *tert*-butyloxycarbonylation and the fully masked **12b** was obtained in quantitative yield. This compound was then subjected to mesityllithium in dry THF under carefully controlled conditions in order to generate the intermediate 5-lithio derivative.[10] Subsequent cautious treatment with excess EtOCOCl was expected to exchange the ethoxycarbonyl group for the Li atom and give rise to **12c**. TLC examination of the crude reaction product indicated, however, the presence of several unidentified compounds and this was confirmed by inspection of ^1H NMR spectra. From this complex mixture, minor amounts of **12d** could be isolated by a laborious chromatography. Since the Boc group was reported to be stable to mesityllithium at low temperature,[10] the above outlined reaction sequence seemed feasible but the partial formation of **12d** clearly indicated that the di-*tert*-butyl imidodicarbonate moiety in **12b** was too labile under those circumstances. In fact, attempted chromatographic work-up of the intractable mixture afforded (besides **12d**) only impure samples of rather unstable substances. None of the fractions contained even traces of **12c** as obtained independently by conventional exhaustive *tert*-butyloxycarbonylation of **5b**.

Experimental

For general experimental details, see the preceding paper.[1] Yields, melting points, spectroscopic and other data are collected in Table 1.

Benzyl 3-(2,5-dimethylpyrrol-1-yl)-1-methylpyrazole-5-carboxylate (**3a**). Distilled **2**[4] (1.75 g, 10.0 mmol) was dissolved in dry THF (30 ml) and the solution was chilled in dry ice to −78 °C, whilst being rapidly stirred under N_2. A solution of BuLi (1.6 M in hexane, 7.5 ml, 12 mmol) was then slowly introduced (25 min) to the rapidly stirred solution under N_2. Stirring was continued for 2 h at −73 °C ± 5 °C. To this turbid mixture, was added dropwise BzlOCOCl (10.5 g, 84 % w/w, 51.5 mmol) with vigorous stirring over a period of 10 min. After the additions, the clear reaction mixture was allowed to reach room temperature and then stirred for about 2 h. Removal of the solvent left a semisolid residue which was partitioned between Et_2O (200 ml) and 0.2 M aq. citric acid (100 ml). The Et_2O extract was washed with citric acid, 1 M aq. $NaHCO_3$ and aq. satd. NaCl (3×50 ml each) and dried over Na_2SO_4. Evaporation to dryness afforded a yellow sticky solid which was subjected to column chromatography in CH_2Cl_2. First **3a** (2.10 g) was eluted as

an almost colourless solid. This product was chromatographically pure (B, C)[1] and suitable for further work. The recrystallized sample was obtained as pale yellow heavy crystals. Continued elution of the column afforded minor amounts of **9** which after crystallization gave light yellow crystals.

Benzyl 3-amino-1-methylpyrazole-5-carboxylate (**4a**). To a suspension of $NH_2OH \cdot HCl$ (10.6 g, 153 mmol) in EtOH (120 ml) was added a solution of KOH (4.52 g, 80.7 mmol) in 50 % aq. EtOH (140 ml). Finely ground **3a** (4.50 g, 14.5 mmol) was then slowly introduced and the resulting mixture was stirred at 90 °C (reflux) under N_2. The reaction was monitored by TLC (B) and when all of the starting material had been consumed (36 h), the solvent was stripped off at reduced pressure. The residue was partitioned between Et_2O (150 ml) and 30 % aq. K_2CO_3 (70 ml) and the aqueous phase was extracted with Et_2O (2×35 ml). The combined ether extracts were washed with satd. NaCl (3×50 ml), dried over Na_2SO_4 and taken to dryness. The yellow sticky residue was purified by chromatography in CH_2Cl_2–Me_2CO 9:1. First obtained was **4a** (2.00 g) as a light yellow solid suitable for further work. Continued elution of the column furnished a small quantity of **4b**.

*Benzyl 3-*tert*-butyloxycarbonylamino-1-methylpyrazole-5-carboxylate (***5a***).* Chromatographed **4a** (1.39 g, 6.00 mmol) in dry MeCN (30 ml) was treated with a solution of Boc-F[1] (1.0 M in Et_2O, 12 ml, 12 mmol) followed by Et_3N (1.25 ml, 9.0 mmol, distilled from CaH_2) with rapid stirring under N_2 at ambient temperature. After 20 h, TLC (B) showed incomplete reaction and the clear yellow reaction mixture was concentrated to about one third of its volume by evaporation at room temperature. More Boc-F and Et_3N (quantities above) were introduced and the stirring was continued overnight. As minor amounts of **4a** still remained in the mixture, a final batch of Boc-F solution (6.0 ml, 6.0 mmol) was added and after a further 20 h only traces of starting material could be detected. The solvent was stripped off at room temperature and the brownish solid residue was partitioned between Et_2O (300 ml) and 0.2 M aq. citric acid (100 ml). The pale yellow extract was washed in turn with 0.2 M citric acid, 1 M $NaHCO_3$ and satd. NaCl (3×50 ml each), dried over $MgSO_4$ and treated with decolourizing carbon. Removal of the solvent afforded a light yellow solid (1.81 g) consisting of essentially pure **5a**. TLC (B, C) displayed one spot. An analytical sample was obtained by chromatography in CH_2Cl_2–Et_2O 15:1. Recrystallization of the chromatographed material gave white shiny crystals.

*Ethyl 3-*tert*-butyloxycarbonylamino-1-methylpyrazole-5-carboxylate (***5b***).* Prepared from **4b** according to the above procedure. Thus, from the crude amine (1.46 g, 8.65 mmol), pure **5b** (1.96 g) was obtained after a similar work-up and chromatography using petroleum ether–Et_2O 5:2 as the mobile phase. Recrystallization gave the analytical specimen as flat lustrous needles. When **4b** (169 mg, 1.00 mmol) in dry MeCN (4.0 ml) was treated with Boc_2O/Et_3N (1.50 equiv.) and the mixture stirred overnight, a white precipitate appeared. After several hours in the cold, this solid was filtered off, rinsed repeatedly with small portions of cold MeCN and dried *in vacuo*. This product, weighing 110 mg, consisted mainly of **10**. The filtrate contained **5b**, **10** and other impurities. Recrystallization furnished an analytical specimen as tiny, colourless crystals.

*3-*tert*-Butyloxycarbonylamino-1-methylpyrazole-5-carboxylic acid (***6***). (A) Hydrogenolysis of* **5a**. A solution of **5a** (663 mg, 2.00 mmol) in 99 % EtOH (50 ml) was stirred under H_2 (1 atm, 20 °C) in the presence of Pd (5 % on C, 70 mg). After 1 h, TLC (D) indicated complete reaction and the catalyst was removed by filtration. The colourless filtrate was taken to dryness and the solid residue was thoroughly triturated with hexane (10 ml). After evaporation, further hexane (5 ml) was added and the insoluble white powder was filtered off, rinsed with cold hexane (3×1 ml) and dried *in vacuo*. The yield of chromatographically pure (D, E) **6** was 467 mg. Recrystallization afforded colourless rhombic crystals.

(B) Hydrolysis of **5b**. Finely ground **5b** (269 mg, 1.00 mmol) was suspended in 50 % aq. EtOH (3 ml) and 1.00 M NaOH (1.25 ml, 1.25 mmol) was added. The resulting slurry was stirred at 45 °C for 20 min to dissolve all solid material and the stirring was continued at ambient temperature for 30 min. After filtration, the colourless filtrate was cautiously acidified with 3 M HCl with rapid stirring at room temperature to pH ca. 2. A precipitate was formed and after the suspension had been stirred for 30 min it was left in the cold overnight. The crude acid **6** was collected by filtration, rinsed with ice–water (2×1 ml) and dried at about 0.01 mmHg. This product, weighing 221 mg, was identical with that obtained in the above procedure from **5a**.

*Benzyl 3-formamido-1-methylpyrazole-5-carboxylate (***7a***).* Chromatographed **4a** (1.16 g, 5.00 mmol) was dissolved in dry $CHCl_3$ (8 ml) and pentafluorophenyl formate (2.12 g, 10.0 mmol, freshly prepared) was added dropwise with rapid stirring at room temperature under N_2. The resulting mixture darkened slowly and the reaction was monitored by TLC (B). Only traces of **4a** remained after 4 h and after the reaction had been stirred overnight, most of the solvent was stripped off at reduced pressure. The violet semisolid residue was treated with dry Et_2O (25 ml) and again taken to dryness. This procedure was repeated and the remaining dark solid was thoroughly triturated with dry Et_2O (10 ml) and the resulting suspension was left in the cold overnight. The insoluble material was filtered off, rinsed with cold Et_2O (3×2 ml) and dried. A second crop of a slightly darker product was obtained by evaporation of the Et_2O filtrate and washings and treatment of the oily residue with petroleum ether–Et_2O 2:1 (5 ml). After being chilled to −20 °C for a few days, the product was filtered off, rinsed

with the above cold mixture and dried. The total amount of chomatographically pure (A, B) **7a** was 1.25 g (pink powder). Recrystallization gave an analytical specimen as white fluffy crystals.

*Ethyl 3-formamido-1-methylpyrazole-5-carboxylate (***7b***).* The compound was prepared from **4b** (719 mg, 4.25 mmol) according to the above procedure. After a similar work-up, 719 mg of chromatographically pure (A, B) product were obtained as a white finely grained solid suitable for further work. Recrystallization furnished an analytical sample as lustrous woolly crystals.

*3-Formamido-1-methylpyrazole-5-carboxylic acid (***8***). (A) Hydrogenolysis of* **7a**. A solution of **7a** (598 mg, 2.31 mmol) in MeOH (45 ml) was hydrogenated (1 atm, room temperature) over Pd (5 % on C, 60 mg). After 2 h, TLC (E) indicated complete reaction and the catalyst was removed by filtration. The colourless filtrate was evaporated and the remaining white solid was washed essentially as described for **7a**. Two crops, weighing 380 mg in total, were obtained after thorough drying. This material gave white crystals after recrystallization.

(B) Hydrolysis of **7b**. Finely ground **7b** (296 mg, 1.50 mmol) was suspended in H_2O (1.5 ml) and treated with 1.00 M NaOH (1.80 ml, 1.80 mmol) with stirring. The slurry was heated (45 °C, ca. 15 min) whereupon all of the solid dissolved completely. After being stirred for 30 min at ambient temperature, the solution was filtered and then cautiously acidified to pH ca. 2 with 3 M aq. HCl. A precipitate soon appeared and after being allowed to stand overnight at 0 °C, a wad-like solid was collected, rinsed with small portions of ice–water and dried. This crude product (236 mg) was identical in all respects with **8** as obtained above.

*Methyl 3-benzyloxycarbonylamino-1-methylpyrazole-5-carboxylate (***11***).* To a solution of chromatographed methyl 3-amino-1-methylpyrazole-5-carboxylate[5] (465 mg, 3.00 mmol) in dry DMF (15 ml) was added benzotriazol-1-yl benzyl carbonate (848 mg, 3.15 mmol) in small portions over 10 min with rapid stirring under N_2. The reaction was monitored by TLC (B) and after 2 h, only traces of the starting material remained. After being stirred overnight, the reddish solution was evaporated to dryness and the dark solid residue was partitioned between Et_2O (300 ml) and 0.2 M aq. citric acid (150 ml). The red aqueous phase was discarded and the pale yellow ether extract was washed as described for **5a**. Removal of the solvent left a colourless solid weighing 840 mg. Recrystallization gave an analytical sample as white woolly needles.

*3-*tert*-Butyloxycarbonylamino-1-methylpyrazole (***12a***).* This compound was synthesized from **1** using excess Boc-F/Et_3N according to the method described for the synthesis of **5a** (see above). From crude **1** (1.77 g, 18.2 mmol) a white crystalline solid (2.92 g) was obtained which, after recrystallization, furnished colourless glittering flakes.

*3-[Bis(*tert*-butyloxycarbonyl)amino]-1-methylpyrazole (***12b***).* Recrystallized **12a** (986 mg, 5.00 mmol) and DMAP (61 mg, 0.50 mmol, crystallized from EtOAc) were dissolved in dry MeCN (15 ml) and treated with Boc_2O (1.36 g, 6.25 mmol) in one portion with thorough mixing at room temperature. The resulting, essentially colourless solution, was left at ambient temperature with occasional agitation, and after 2 h TLC (B) indicated complete reaction. The mixture was left overnight and then taken to dryness at reduced pressure. The light brown solid residue was taken up in ether (200 ml) and the extract was washed as above. Removal of the solvent afforded chromatographically pure (B, F) **12b** (1.48 g) as a white solid which after recrystallization gave small white shiny crystals.

*Ethyl 3-[bis(*tert*-butyloxycarbonyl)amino]-1-methylpyrazole-5-carboxylate (***12c***).* The compound was prepared from **5b** (34.7 mg, 0.12 mmol) using Boc_2O/DMAP in MeCN as described above for **12b**. When the reaction was complete (1 h), an analogous work-up gave chromatographically pure (B, F) **12c** (44.9 mg). Recrystallization afforded an analytical specimen as pale yellow needles.

Attempted preparation of **12c** *from* **12b**. A solution of mesityllithium was generated from bromomesitylene (598 mg, 3.00 mmol, dried over molecular sieves 4A) in dry THF (5 ml, freshly distilled from $LiAlH_4$) and 1.6 M BuLi in hexane (2.00 ml, 3.20 mmol) as previously described.[10] Recrystallized, well-dried **12b** (595 mg, 2.00 mmol) dissolved in dry THF (3 ml) was slowly introduced under dry Ar over a period of 10 min with vigorous stirring at −40 °C ± 2 °C. The stirring was continued for 3 h under these conditions whereupon the white precipitate dissolved completely. A solution of EtOCOCl (381 µl, 4.00 mmol) was added dropwise with rapid stirring at −55 °C over 10 min and the reaction was allowed to proceed at −40 °C ± 2 °C for a further 1 h. The cooling bath was removed and when the temperature reached 0 °C (1 h), water (2 ml) was cautiously introduced. The resulting mixture was partitioned between Et_2O (200 ml) and 0.2 M aq. citric acid (50 ml) and the pale yellow extract was treated as usual (see **5a**). Removal of the solvent and meticulous drying of the residue furnished a yellow viscous oil (0.88 g). The TLC (B, F) of this crude product exhibited several spots and ^1H NMR spectroscopy confirmed that it was a complex mixture. Laborious chromatography in CH_2Cl_2–Me_2CO mixtures gave minor amounts of compound **12d**. ^1H NMR ($CDCl_3$): δ 7.31 (d, 1 H, H-5), 6.11 (d, 1 H, $J_{4,5}$ 2.2 Hz, H-4), 4.24 (q, 2 H, CH_2CH_3), 3.88 (s, 3 H, NCH_3), 1.46 (s, 9 H, Boc CH_3), 1.26 (t, 3 H, CH_2CH_3).

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