A Short, Facile Synthesis of 5-Substituted 3-Amino-1*H*-pyrrole-2-carboxylates

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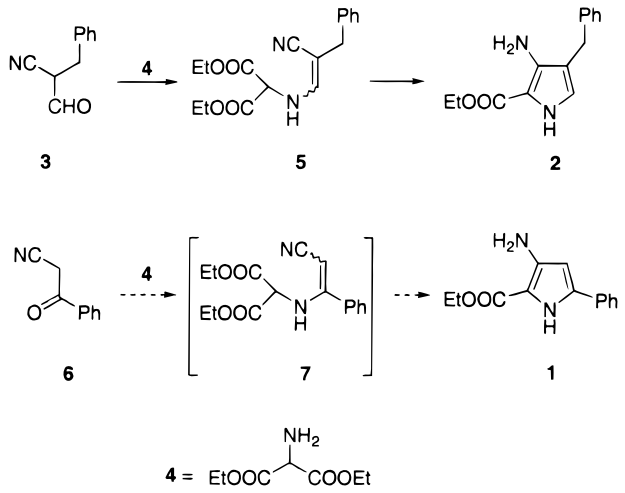
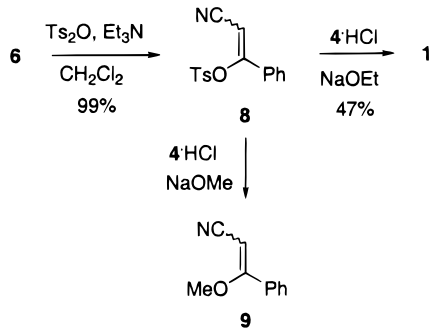
Derivatives of 3-amino pyrroles have been shown to exhibit antibacterial, antiviral, anticonvulsant, antiinflammatory, analgesic, and antipyretic activities.[1] In addition, many azo dyes are derived directly from 3-aminopyrroles.[2] In the midst of our research efforts, we found ethyl 3-amino-5-phenyl-1*H*-pyrrole-2-carboxylate (**1**) to be a useful intermediate in the synthesis of other nitrogen heterocycles.[3] Therefore, we needed a rapid synthesis of pyrrole **1** and its analogues.

Initially, we investigated an approach toward the synthesis of pyrrole **1** similar to the one described by Elliott and co-workers[4,5] for the preparation of 3-amino-4-benzyl-1*H*-pyrrole-2-carboxylate (**2**). In their synthesis, condensation with aldehyde **3** and diethyl aminomalonate (**4**) gave 3-substituted enamine **5**, which was cyclized in the presence of sodium methoxide to give pyrrole **2** (Scheme 1). However, using a similar approach toward the synthesis of pyrrole **1**, we were unable to synthesize the 2-substituted enamine **7** from benzoyl acetonitrile (**6**) and diethyl aminomalonate (**4**) using standard conditions such as azeotropic removal of water,[6] dehydration with molecular sieves, or Lewis acid catalysis ($TiCl_4$,[7] $BF_3 \cdot OEt_2$).

Scheme 1



Scheme 2



Considering the lower electrophilicity of the aryl ketone **6** compared to the aldehyde **3**, an alternative strategy for preparing enamine **7** was examined. Since amines are known to undergo substitution reactions with chloro- and alkylthio-substituted olefins to yield enamines,[8] we took a similar approach and investigated the reaction of *p*-toluenesulfonyl enol ester of α-cyano ketone **8** with diethyl aminomalonate (**4**) (Scheme 2). Tosylate **8** was prepared by reacting benzoyl acetonitrile with *p*-toluenesulfonic anhydride (1.2 equiv) in dichloromethane and triethylamine (1.5 equiv) in 99% yield. Initial attempts to obtain enamine **7** from the addition of diethyl aminomalonate to **8** using K_2CO_3 in THF failed. However, when a mixture of tosylate **8** and diethyl aminomalonate hydrochloride (1.2 equiv) were treated with an ethanolic solution of sodium ethoxide (0.2 M, 3.5 equiv),[9] the pyrrole **1** was *directly* obtained without isolation of enamine **7**. Addition of the amine, cyclization and decarboxylation occurred in one pot at room temperature to give a 46% overall yield of **1** from benzoyl acetonitrile. Upon further investigation we found that the initial use of tosylate **8** and diethyl aminomalonate was fortuitous. Attempts to improve the synthesis by substituting the

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(9) In a similar process, Elliott and co-workers also reported obtaining a pyrrole directly from the addition of diethyl aminomalonate to ethyl (ethoxymethylene)cyanoacetate. See: Elliott, A. J.; Montgomery, J. A.; Walsh, D. A. *Tetrahedron Lett.* **1996**, *37*, 4339−4340.

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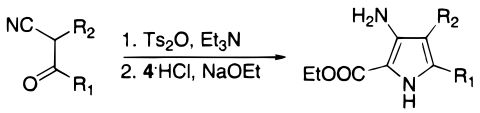
Table 1. 5-Substituted 3-Amino-1*H*-pyrrole-2-carboxylates



10-19

R_1	R_2	product	overall yield
4-methoxyphenyl	H	**10**	30
3-trifluoromethylphenyl	H	**11**	37
3,4-dichlorophenyl	H	**12**	31
4-trifluoromethoxyphenyl	H	**13**	38
3-methylphenyl	H	**14**	37
2-chlorophenyl	H	**15**	31
2-furanyl	H	**16**	61
2-thienyl	H	**17**	43
tert-butyl	H	**18**	30
methyl	phenyl	**19**	21

tosylate for a mesylate, or by using ethyl glycinate instead of diethyl aminomalonate, led to an intractable mixture of products. With sodium methoxide as the base a major byproduct **9** formed as a result of the addition of methoxide to the tosylate **8** (Scheme 2). Use of the stronger nonnucleophilic base potassium *tert*-butoxide led to unisolable mixture of products.

Ten other examples of 5-substituted 3-amino-1*H*-pyrrole-2-carboxylates were prepared using the method described above (**10**−**19**, Table 1). While tosylate **8** was used after being purified by column chromatography, for analogue preparation we found it more convenient to use tosylates simply after aqueous workup. Examples **10**−**14** illustrate that the electronic nature of the phenyl ring has little affect on the overall yields. The electron-rich 4-methoxyphenyl (**10**) and 3-methylphenyl (**14**) derivatives had comparable yields to the electron-poor 3-trifluoromethylphenyl (**11**), 3,4-dichlorophenyl (**12**), and 4-trifluoromethoxyphenyl (**13**) derivatives. The reaction process was not sensitive to the steric effects of the 2-chlorophenyl (**15**) or the *tert*-butyl (**18**) groups since yields were comparable to products containing less sterically demanding groups. However, attempts to form the product with a 2-nitro group on the aryl ring led to decomposition of the starting material. Heteroaromatics such as furanyl (**16**, 61% yield) and thienyl (**17**, 43% yield) behaved similarly to phenyl (**1**, 46% yield). Finally, a tetrasubstituted pyrrole (**19**) was also formed using this method.

In summary, we have developed an extremely facile, two-step synthesis for 5-substituted 3-amino-1*H*-pyrrole-2-carboxylates. The key step in this synthesis is the one-pot formation of the pyrrole ring from diethyl aminomalonate and *p*-toluenesulfonyl enol esters of α-cyano ketones. Other applications of this process are currently being explored and will be reported in due course.

Experimental Section

General. All chemicals were commercially available and reagent grade unless otherwise specified. All solvents were anhydrous grade and were used without further purification. High-resolution mass spectra (HRMS) were performed by Mass Consortium, La Jolla, CA. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Melting points were determined with a capillary melting point apparatus and are uncorrected.

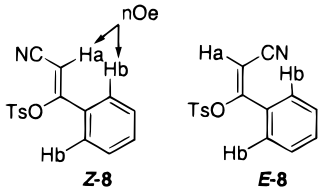
Representative Example for the Preparation of Ethyl 3-Amino-5-substituted-1*H*-pyrrole-2-carboxylates. 2-Cyano-1-phenylvinyl *p*-Toluenesulfonate (8). To a 100-mL, round-bottomed flask were added benzoyl acetonitrile (0.73 g, 5.0 mmol), *p*-toluenesulfonic anhydride (2.02 g, 6.0 mmol), and CH_2Cl_2 (25 mL). To the above solution was then added Et_3N (1.05 mL, 7.5 mmol) dropwise. After 16 h stirring at ambient temperature, the reaction mixture was partitioned between H_2O and CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give an orange solid. This material was purified by flash chromatography on silica gel with 1:6 EtOAc−hexanes as eluant to give 1.47 g (99%) of the title compound as an off-white solid. This material was a 3:1 mixture of the *Z* and *E* isomers[10] as determined by integration of the corresponding methyl singlets at 2.47 and 2.44 ppm, respectively. ^{1}H NMR ($CDCl_3$; 500 MHz) (chemical shifts of the *E*-isomer are given parenthetically): δ 2.47 (2.45) (s, 3H), 5.57 (5.56) (s, 1H), 7.35−7.60 (7.31−7.50) (m, 5H) 7.58 (7.65) (d, 2H, J = 8.0), 7.90 (7.76) (d, 2H, J = 8.0); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 21.07 (24.25), 89.50 (91.91), 113.56 (118.19), 126.36 (130.81), 128.20 (131.20), 128.36 (131.40), 129.61 (132.94), 131.04 (134.47), 131.57 (134.52), 131.74 (134.75), 146.25 (149.56), 162.02 (166.18); MS (ESI) *m*/*z*: 300 (M + 1), 298 (M − 1). Anal. Calcd for $C_{16}H_{13}NO_3S$: C, 64.20; H, 4.38; N, 4.68; S, 10.71. Found: C, 64.29; H, 4.41; N, 4.68; S, 10.88.

Ethyl 3-Amino-5-phenyl-1*H*-pyrrole-2-carboxylate (1). Sodium ethoxide was prepared freshly from Na (0.37 g, 16.2 mmol) and absolute ethanol (10 mL) in a 100-mL, round-bottomed flask equipped with a positive flow of N_2 gas. To the above solution was then added a solution of 2-cyano-1-phenylvinyl *p*-toluenesulfonate **8** (1.38 g, 4.6 mmol) and diethyl aminomalonate hydrochloride (1.20 g, 5.5 mmol) in ethanol (15 mL) and THF (7 mL) dropwise through an addition funnel. After the addition was completed, the reaction mixture was stirred at ambient temperature for 2 h and concentrated in vacuo to give an orange solid. Water and EtOAc were added, and the aqueous layer was back-extracted with EtOAc (3×). The combined EtOAc layers were dried (Na_2SO_4) and concentrated in vacuo to give an orange solid. This material was purified by flash chromatography on silica gel with 1:6 EtOAc−hexanes as eluant to give 0.50 g (47%) of the title compound as an off-white solid. Mp: 155.0−155.5 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) δ 1.30 (t, 3H, J = 7.1), 4.23 (q, 2H, J = 7.1), 5.75 (br s, 2H), 6.00 (d, 1H, J = 2.8), 7.24−7.44 (m, 3H), 7.75 (d, 2H, J = 8.0), 10.73 (br s, 1H); MS (ESI) *m*/*z*: 231 (M + 1), 229 (M − 1); IR (Nujol, cm^{-1}): 3433, 3340, 1666. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.96; H, 6.03; N, 12.07.

Compounds 10−19: Prepared Using the Methods Described Above for Tosylate 8 and Pyrrole 1. Only the amounts of α-cyano ketones are given below. All other reagents were used in the same molar ratio as detailed in the experimental methods above.

Ethyl 3-Amino-5-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (10). The title compound (0.78 g, 30%) was prepared using 4-methoxybenzoyl acetonitrile (1.75 g, 10 mmol) and was recrystallized from toluene. Mp: 173.0−174.5 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) δ 1.29 (t, 3H, J = 7.0), 3.77 (s, 3H), 4.21 (q, 2H, J = 7.0), 5.07 (br s, 2H), 5.89 (d, 1H, J = 1.2), 6.93 (d, 2H, J = 8.4), 7.69 (d, 2H, J = 8.4), 10.58 (br s, 1H); MS (ESI) *m*/*z*: 261 (M + 1); IR (Nujol, cm^{-1}): 3432, 3340, 1667. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.86; H, 6.21; N, 10.57.

(10) In an independent experiment, the *Z* and *E* isomers were separated by flash chromatography on silica gel with 1:9 EtOAc−hexanes as the eluant. The *ortho*-protons (H_b) of the major isomer ((*Z*)-**8**) showed a strong NOE when the vinyl proton (H_a) was irradiated. However, irradiation of the vinyl proton (H_a) on the minor isomer ((*E*)-**8**) led to no enhancement of the *ortho*-protons (H_b).



Ethyl 3-Amino-5-[3-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxylate (11). The title compound (5.22 g, 37%) was prepared using [3-(trifluoromethyl)benzoyl]acetonitrile (10 g, 46.9 mmol) and was recrystallized from toluene. Mp: 181.5−182.0 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) δ 1.31 (t, 3H, J = 7.0), 4.25 (q, 2H, J = 7.0), 5.12 (br s, 2H), 6.15 (d, 1H, J = 2.6), 7.58 (d, 2H, J = 8.1), 8.00−8.01 (m, 1H), 8.22 (s, 1H), 11.06 (br s, 1H); MS (ESI) *m*/*z*: 299 (M + 1); IR (Nujol, cm^{-1}): 3441, 3356, 1641. Anal. Calcd for $C_{14}H_{13}F_3N_2O_2$: C, 56.38; H, 4.39; N, 9.39. Found: C, 56.10; H, 4.48; N, 9.14.

Ethyl 3-Amino-5-(3,4-dichlorophenyl)-1*H*-pyrrole-2-carboxylate (12). The title compound (2.43 g, 31%) was prepared using 3,4-dichlorobenzoyl acetonitrile (5.57 g, 26.0 mmol) and was recrystallized from toluene. Mp: 184.0−185.0 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) δ 1.30 (t, 3H, J = 7.0), 4.24 (q, 2H, J = 7.0), 5.12 (br s, 2H), 6.11 (s, 1H), 7.60 (d, 1H, J = 8.5), 7.72 (d, 1H, J = 8.5), 8.14 (s, 1H), 10.95 (br s, 1H); MS (ESI) *m*/*z*: 299 (M + 1); IR (Nujol, cm^{-1}): 3440, 3337, 1638. Anal. Calcd for $C_{13}H_{12}Cl_2N_2O_2$: C, 52.19; H, 4.04; N, 9.36; Cl, 23.70. Found: C, 52.20; H, 4.12; N, 9.23; Cl, 23.53.

Ethyl 3-Amino-5-[4-(trifluoromethoxy)phenyl]-1*H*-pyrrole-2-carboxylate (13). The title compound (2.58 g, 38%) was prepared using [4-(trifluoromethoxy)benzoyl]acetonitrile (5.00 g, 21.8 mmol) and was recrystallized from toluene. Mp: 175.0−178.0 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) δ 1.30 (t, 3H, J = 7.0), 4.24 (q, 2H, J = 7.0), 5.12 (br s, 2H), 6.04 (d, 1H, J = 2.3), 7.35 (d, 2H, J = 8.6), 7.88 (d, 2H, J = 8.6), 10.86 (br s, 1H); MS (ESI) *m*/*z*: 315 (M + 1); IR (Nujol, cm^{-1}): 3446, 3313, 1669. Anal. Calcd for $C_{14}H_{13}F_3N_2O_3$: C, 53.51; H, 4.17; N, 8.91. Found: C, 53.24; H, 4.28; N, 8.81.

Ethyl 3-Amino-5-(3-methylphenyl)-1*H*-pyrrole-2-carboxylate (14). The title compound (2.86 g, 37%) was prepared using (3-methylbenzoyl)acetonitrile (5.00 g, 31.4 mmol) and was recrystallized from toluene. Mp: 121.0−123.0 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) δ 1.30 (t, 3H, J = 7.0), 2.32 (s, 3H), 4.22 (q, 2H, J = 7.0), 5.08 (br s, 2H), 5.98 (d, 1H, J = 2.8), 7.07 (d, 1H, J = 7.7), 7.23−7.26 (m, 1H), 7.53 (d, 1H, J = 7.7), 7.61 (s, 1H), 10.67 (br s, 1H); MS (ESI) *m*/*z*: 245 (M + 1); IR (Nujol, cm^{-1}): 3422, 3336, 1668. Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.74; H, 6.72; N, 11.29.

Ethyl 3-Amino-5-(2-chlorophenyl)-1*H*-pyrrole-2-carboxylate (15). The title compound (0.82 g, 31%) was prepared using 2-chlorobenzoyl acetonitrile (1.80 g, 10 mmol) and was recrystallized from toluene/cyclohexane. Mp: 90.0−91.5 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) δ 1.28 (t, 3H, J = 7.0), 4.22 (q, 2H, J = 7.0), 5.12 (br s, 2H), 5.98 (d, 1H, J = 2.2), 7.32−7.38 (m, 2H), 7.51 (d, 1H, J = 7.5), 7.59 (d, 1H, J = 7.5), 10.74 (br s, 1H); MS (ESI) *m*/*z*: 265 (M + 1); IR (Nujol, cm^{-1}): 3466, 3378, 1678. Anal. Calcd for $C_{13}H_{13}ClN_2O_2$: C, 58.99; H, 4.95; N, 10.58; Cl, 13.39. Found: C, 58.80; H, 5.08; N, 10.40; Cl, 13.17.

Ethyl 3-Amino-5-(2-furanyl)-1*H*-pyrrole-2-carboxylate (16). The title compound (1.28 g, 61%) was prepared using 2-furoylacetonitrile (1.35 g, 10 mmol) and was recrystallized from toluene. Mp: 124.0−125.0 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) δ 1.29 (t, 3H, J = 7.0), 4.22 (q, 2H, J = 7.0), 5.11 (br s, 2H), 5.84 (d, 1H, J = 2.7), 6.53−6.54 (m, 1H), 6.95 (d, 1H, J = 3.4), 7.65 (d, 1H, J = 1.4), 10.85 (br s, 1H); MS (ESI) *m*/*z*: 221 (M + 1); IR (Nujol, cm^{-1}): 3425, 3338, 1667. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.95; H, 5.55; N, 12.79.

Ethyl 3-Amino-5-(2-thienyl)-1*H*-pyrrole-2-carboxylate (17). The title compound (0.97 g, 43%) was prepared using 2-thenoylacetonitrile (1.51 g, 10 mmol) and was recrystallized from toluene. Mp: 149.0−151.0 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) δ 1.29 (t, 3H, J = 7.0), 4.22 (q, 2H, J = 7.0), 5.10 (br s, 2H), 5.79 (d, 1H, J = 2.6), 7.05−7.07 (m, 1H), 7.44 (d, 1H, J = 4.0), 7.58 (d, 1H, J = 4.0), 10.90 (br s, 1H); MS (ESI) *m*/*z*: 237 (M + 1); IR (Nujol, cm^{-1}): 3425, 3337, 1662. Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.92; H, 5.12; N, 11.86; S, 13.57. Found: C, 56.04; H, 5.04; N, 11.75; S, 13.60.

Ethyl 3-Amino-5-(*tert*-butyl)-1*H*-pyrrole-2-carboxylate (18). The title compound (0.63 g, 30%) was prepared using 4,4-dimethyl-3-oxopentane nitrile (1.25 g, 10 mmol). ^{1}H NMR (DMSO-d_6; 500 MHz) δ 1.20 (s, 9H), 1.26 (t, 3H, J = 7.0), 4.19 (q, 2H, J = 7.0), 4.93 (br s, 2H), 5.32 (d, 1H, J = 2.9), 9.98 (br s, 1H); ^{13}C NMR (DMSO-d_6; 100 MHz) δ 15.70, 30.50, 32.32, 58.92, 95.12, 104.56, 126.72, 148.72, 161.90; MS (HRMS) *m*/*z*: 211.1446 (expected), 211.1443 (observed); IR (neat, cm^{-1}): 3477, 3329, 1659.

Ethyl 3-Amino-5-methyl-4-phenyl-1*H*-pyrrole-2-carboxylate (19). The title compound (0.51 g, 21%) was prepared using (α-acetylphenyl)acetonitrile (1.59 g, 10 mmol) and was recrystallized from toluene. Mp: 157.0−158.5 °C. ^{1}H NMR (DMSO-d_6; 500 MHz) δ 1.26 (t, 3H, J = 7.0), 2.21 (s, 3H), 4.16 (q, 2H, J = 7.0), 4.90 (br s, 2H), 7.17−7.42 (m, 5H), 10.18 (br s, 1H); MS (ESI) *m*/*z*: 245 (M + 1); IR (Nujol, cm^{-1}): 3449, 3352, 1655. Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.06; H, 6.47; N, 11.54.

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