Synthesis of *N*-Urethane-Protected γ-Amino-Functionalized Butenoates and Tautomeric Studies by Means of NMR, X-ray Crystallography and ab initio Calculations

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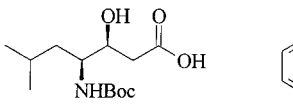
Keywords: *C*-Acylation reactions / γ-Amino-α-cyano-β-hydroxybutenoates / Tautomeric studies

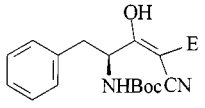
N-Urethane-protected γ-amino-α-cyano-β-hydroxybutenoates were synthesized as potential statine analogues and the stability of their possible tautomers was assessed using NMR, X-ray crystallography and ab initio calculations. The results establish that the *cis*-enol tautomeric form is the most stable one both in solution ($CDCl_3$) and in the solid phase. In full agreement with the experimental data, the theoretical calculations predicted that the *cis*-enol tautomer would be the minimum energy tautomer.

Introduction

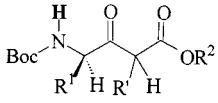
The synthesis and structure determination of functionalized enols of *N*-protected α-amino acids has recently attracted our attention as these compounds have proved to exhibit interesting biological activity; they have a topographical similarity to Boc-statine, for example, and can thus be effective as inhibitors of HIV-1 protease (Scheme 1, compounds of type **I**).[1] Moreover, *N*-urethane-protected α-alkyl-γ-amino-β-ketobutanoates (Scheme 1) have been reported to be potential precursors of "2-alkylated statine" derivatives and constitute interesting building blocks for use in combinatorial chemistry. These compounds have been observed to mimic the transition state analogue of the substrate when interacting with the enzyme.[2]



Boc-Statine



I (E=electron withdrawing group)[1a]

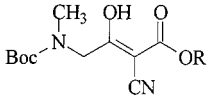


II N-protected-α-alkyl-γ-amino-β-keto-butanoates [1b]

Scheme 1

In addition, *N*-methylated α-amino acids are known to occur naturally in a wide range of peptides and depsipeptides and are valuable building blocks for the synthesis of peptidomimetics. Incorporation of *N*-methylated α-amino acids into strategic positions in peptides can result in enhanced proteolytic ability, an increase in lipophilicity and profound conformational changes (*N*-methylation permits left-handed α-helical structures, promotes *cis*/*trans* isomerization about the peptide bond, disrupts hydrogen bonding to the amide hydrogen atom and increases the hydrophobicity of the peptide).[3,4]

In this context, we decided to apply our previously described methodology for the synthesis of *N*-urethane-protected γ-amino-α-cyano-β-hydroxybutenoates using Boc-sarcosine (Boc-*N*-methyl glycine) (Scheme 2).[5] In this work we report the synthesis and structure determination of methyl and ethyl 4-[(*tert*-butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoate in solution (^1H and ^{13}C NMR) and in the solid state (X-ray crystallography), and also by ab initio calculation. The interest in structural study of these molecules arises from the fact that they are representative examples of asymmetric β-dicarbonyl compounds, capable of undergoing keto−enol and enol−enol tautomerism and also of forming intramolecular hydrogen bonds.[6]



R=Me, Et

N-*t*-butoxycarbonyl-γ-amino-α-cyano-β-hydroxy butenoates

Scheme 2

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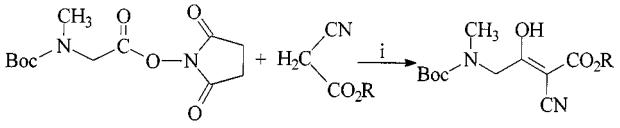
Results and Discussion

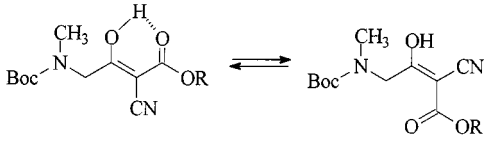
The target compounds, methyl 4-[(*tert*-butoxycarbonyl)-methylamino]-2-cyano-3-hydroxy-2-butenoate (**2**) and ethyl 4-[(*tert*-butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoate (**3**), were synthesized by our methodology, which involves a *C*-acylation reaction between an active methylene compound and the *N*-hydroxysuccinimide ester of an *N*-alkoxycarbonylated α-amino acid. The starting material, Boc-sarcosine *N*-hydroxysuccinimide ester (**1**), was synthesized by treatment of Boc-sarcosine with *N*-hydroxysuccinimide and DCC in DME at 0 °C.[7] The preparation of the functionalized enols **2** and **3** was accomplished by *C*-acylation of the appropriate active methylene compound with Boc-sarcosine *N*-hydroxysuccinimide ester **1** in *t*BuOK/*t*BuOH (see Exp. Sect.) (Scheme 3).



1 **2** R=Me **3** R=Et

Scheme 3.(i) *t*BuOK/*t*BuOH, room temp.

Boc-sarcosine *N*-hydroxysuccinimide ester (**1**) proved to be a very powerful acylating agent, providing the desired products in high yields (60−75%). β-Dicarbonyl compounds bearing a CN group tend to exist as stable enols, which offers the possibility of *cis*/*trans* isomerism about the enolic double bond (Scheme 4).



cis-enol *trans*-enol

Scheme 4. *cis*- and *trans*-enol isomerization in *N*-Boc-γ-amino-α-cyano-β-hydroxybutenoates

The same is true for compounds **2** and **3**, as can be deduced from the ^{1}H and ^{13}C NMR chemical shifts of the backbone nuclei of the molecules (Tables 1 and 2). The *C*-acylation compounds **2** and **3** must exist in $CDCl_3$ solution in their enolic forms, as there were no signals attributable to methine protons in their ^{1}H NMR spectra whereas their ^{13}C NMR spectra lacked any resonance characteristic of the sp^3-CH methine groups expected of the keto tautomers (Scheme 5). The electron-withdrawing effects of the cyano substituents should be expected to cause increases in the enol populations and decreases in the OH chemical shifts. Moreover, two sets of signals can be observed in each of the ^{1}H and ^{13}C NMR spectra, indicating the existence of two enol isomers (Scheme 6). The relative populations of the two enol forms are approximately 50:50, as deduced from the intensity ratios of the peaks.

Enolization of asymmetrical β-dicarbonyl compounds may occur in various ways. Open-chain derivatives generally adopt the *cis* conformation [*cis*- or (*Z*)-enol], which is stabilized by intramolecular hydrogen bonding (Scheme 6). However, the formation of a *trans*- [or (*E*)-]enol may occur by intramolecular rotation about a carbon−carbon bond that has partial double bond character due to conjugation (Scheme 4). The intramolecularly hydrogen-bonded *cis*-enol structure is usually the most stable one for open-chain β-dicarbonyl compounds. This appears to be true for compounds **2** and **3**, in view of the fact that the ^{1}H NMR signals attributable to the enolic protons appear downfield (δ = 13.7 for compound **2**; δ = 13.8 for compound **3**), as expected for enolic protons involved in strong hydrogen bonds. If, on the other hand, the *trans*-enols were predominant, the chemical shifts of the enolic protons should be higher, because hydrogen bonding between the cyano group nitrogen atoms and the α-hydrogen atoms is not favoured.[8]

In order to determine the structure and identify the predominant tautomer of ethyl 4-[(*tert*-butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoate (**3**) in the solid state, the X-ray structure of the compound was obtained. (Suitable crystals were obtained by recrystallization of the compound from dichloromethane/light petroleum ether.) A view of the molecular structure of ethyl 4-[(*tert*-butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoate (**3**) in the asymmetric unit is shown in Figure 1.

The results confirmed that the *cis*-enol structure **A** is favoured in the solid state. Thus, the C(7)−C(8) bond length is 1.36 Å, characteristically shorter than the normal single C−C bond, and so may be attributed to an sp^2-conjugated system, whereas the C(8)−C(9) bond length (1.41 Å) is consistent with a single C−C bond. The C(9)−O(4) bond length is 1.23 Å, definitely shorter than C(7)−O(3) (1.31 Å), and so C(9)−O(4) has a carbonyl double bond character whereas C(7)−O(3) is a single C−O bond. These observations indicate that the enolic proton is attached to O(3), the oxygen atom on the opposite side of the ester function. Moreover, the distance between O(3) and O(4) is 2.59 Å, much shorter than the interatomic O···O distance of 2.74 Å in ice. This shortening of the O···O distance is associated with an increased delocalization of the π-conjugated HO−C=C−C=O system.[9]

The low frequency of the FT-IR ν(OH) stretching [2984 and 2934 cm^{-1}, whereas the ν(OH) stretching frequency in the absence of hydrogen bonding is 3640 cm^{-1}, ref.[9]] and the downfield shift of the enolic proton resonance (Table 1) correlate very well with the structural data and are all indicative of the strength of the intramolecular hydrogen bond in ethyl 4-[(*tert*-butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoate (**3**).

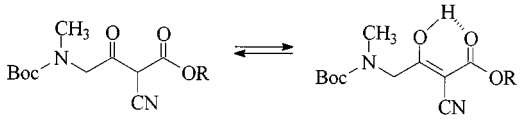
The molecular structure of methyl 4-[(*tert*-butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoate (**2**) was optimized at the SCF level using the 6-31G* basis set.[10] The total energy calculated for the keto tautomer is −947.668371 a.u. whereas for the *trans*-enol it is

Table 1. ^{1}H NMR chemical shifts for methyl and ethyl 4-[(*tert*-butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoates (**2** and **3**, numbering see Scheme 6) (300 MHz, $CDCl_3$)

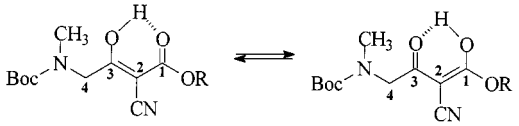
	$(CH_3)_3C$	$N-CH_3$	$N-CH_2-$	R	OH
2 (R = CH_3)	1.44 and 1.47 (9 H, 2 s)	2.94 and 2.98 (3 H, 2 s)	4.30 and 4.35 (2 H, 2 s)	3.89 and 3.91 (3 H, 2 s)	13.7 (1 H, br.)
3 (R = C_2H_5)	1.44 and 1.47 (9 H, 2 s)	2.94 and 2.98 (3 H, 2 s)	4.30 and 4.36 (2 H, 2 s)	1.37 (3 H, 2 t, J = 7.0 Hz) 4.36 (2 H, 2 q, J = 7.0 Hz)	13.8 (1 H, br.)

Table 2. ^{13}C NMR chemical shifts for methyl and ethyl 4-[(*tert*-butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoate (**2** and **3**, numbering see Scheme 6) (75 MHz, $CDCl_3$)

	C-3	C-1	OCO	$(CH_3)_3C$	CN	C-2	C-4	$(CH_3)_3C$	$N-CH_3$
2 (R = CH_3)	187.41	170.51	155.09, 156.00	80.83	113.43	81.00	50.70, 50.93	28.16	35.81
3 (R = C_2H_5)	187.36, 187.28	170.41, 170.12	155.98, 155.18	80.96	113.50, 113.39	80.79	50.65, 50.89	28.12	35.74, 35.78



Scheme 5. Keto−enol tautomerism in *N*-Boc-γ-amino-α-cyano-β-hydroxybutenoates



Scheme 6. Enol−enol tautomerism in *N*-Boc-γ-amino-α-cyano-β-hydroxybutenoates

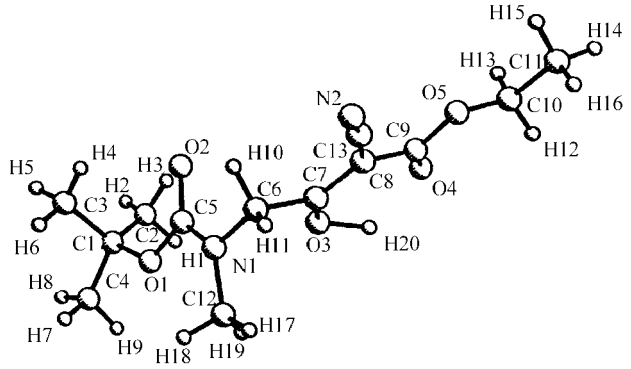


Figure 1. Molecular structure and atomic numbering scheme of ethyl 4-[(*tert*-butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoate (**3**)

−947.693978 a.u. Computation of the energies of the two *cis*-enol forms revealed that the minimum energy tautomer is *cis*-enol **A**, with a total energy of −947.707883 a.u., whereas the energy of *cis*-enol **B** is −947.69818 a.u. Tables 3 and 4 list bond lengths and dihedral angles calculated by the 6-31G*/SCF method for the keto tautomer and the *cis*- and *trans*-enol tautomers of compound **2**, whereas Table 5 presents Mulliken population analyses for the different tautomers (Figure 2).

The carbonyl oxygen of *cis*-enol A [Table 5, O(24)] has a more negative charge than the carbonyl oxygen atom of the *trans*-enol [Table 5, O(25)], because the former takes part in a hydrogen bond. The enol hydrogen atom of *cis*-enol A [Table 5, H(37)] bears more positive charge than the corresponding enol hydrogen atom of the *trans*-enol [Table 5, H(34)] for the same reason. On the other hand, the carbonyl oxygen atom of the keto tautomer appears to be less negatively charged, as is to be expected for non-hydrogen-bonded carbonyl oxygen atoms.

The information provided by the above ab initio method for compound **2** is in good agreement with the X-ray crystallographic data for compound **3**, as well as with the spectroscopic data obtained for both compounds.

Conclusions

We have shown that *N*-urethane-protected γ-amino-α-cyano-β-hydroxybutenoates derived from *N*-Boc-sarcosine can be easily obtained in good yields by means of our well-established methodology. A combination of experimental (NMR, IR, X-ray crystallography) and theoretical (ab initio) methods was used in order to investigate the keto−enol and enol−enol tautomeric equilibria of the synthesized β-dicarbonyl compounds. The results from the experimental techniques confirm that the *cis*-enol tautomer of these molecules predominates in solution and the solid state, whereas ab initio calculations predicted that the same tautomer should be favoured energetically. Moreover, the ab initio calculations yielded reliable bond lengths and angles, and so can be regarded as useful complementation to the experimental studies of tautomerism of the β-dicarbonyl systems that we have synthesized.

In order for statine and its analogues to display their inhibitory activity against aspartate proteases, a *syn* diastere-

Table 3. Optimized bond lengths (in Å) at the SCF/6-31G* level for the *cis*- and *trans*-enol isomers and the keto tautomer of methyl 4-[(*tert*-butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoate (**2**)

Keto tautomer		Enol tautomers *cis* isomer A		*cis* isomer B		*trans* isomer	
C(6)−O(3)	1.34	C(6)−O(3)	1.34	C(6)−O(3)	1.34	C(6)−O(3)	1.34
C(6)−O(7)	1.23	C(6)−O(7)	1.23	C(6)−O(7)	1.23	C(6)−O(7)	1.23
O(3)−C(1)	1.48	O(3)−C(1)	1.48	O(3)−C(1)	1.48	O(3)−C(1)	1.48
C(28)−O(26)	1.45	C(23)−O(22)	1.45	C(23)−O(22)	1.46	C(27)−O(26)	1.45
O(26)−C(24)	1.34	C(21)−O(22)	1.33	C(21)−O(22)	1.31	C(24)−O(26)	1.34
C(24)−O(25)	1.20	C(21)−O(24)	1.23	C(21)−O(24)	1.32	C(24)−O(25)	1.21
C(24)−C(21)	1.53	C(21)−C(18)	1.45	C(21)−C(18)	1.38	C(24)−C(21)	1.46
C(21)−C(22)	1.46	C(18)−C(19)	1.42	C(18)−C(19)	1.42	C(21)−C(22)	1.43
C(22)−N(27)	1.46	C(19)−N(20)	1.15	C(19)−N(20)	1.15	C(22)−N(23)	1.15
C(21)−C(20)	1.54	C(17)−C(18)	1.36	C(17)−C(18)	1.45	C(21)−C(20)	1.36
C(20)−O(23)	1.21	C(17)−O(25)	1.32	C(17)−O(25)	1.24	C(20)−O(28)	1.34
C(20)−C(19)	1.51	C(17)−C(26)	1.51	C(17)−C(26)	1.51	C(20)−C(19)	1.52
C(19)−N(17)	1.44	C(26)−N(27)	1.44	C(26)−N(27)	1.44	C(19)−N(18)	1.44
N(17)−C(6)	1.36	N(27)−C(6)	1.36	N(27)−C(6)	1.36	N(18)−C(6)	1.46
N(17)−C(18)	1.46	N(27)−C(28)	1.46	N(27)−C(28)	1.46	N(18)−C(17)	1.35

Table 4. Optimized bond angles [°] at the SCF/6-31G* level for the *cis*- and *trans*-enol isomers and the keto tautomer of methyl 4-[(*tert*-butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoate (**2**)

Keto tautomer		Enol tautomers *cis* isomer A		*cis* isomer B		*trans* isomer	
C(21)−C(20)−C(19)	119.5	C(18)−C(17)−C(26)	122.6	C(18)−C(17)−C(26)	118.6	C(21)−C(20)−C(19)	127.1
C(24)−C(21)−C(20)	112.8	C(21)−C(18)−C(17)	120.3	C(21)−C(18)−C(17)	119.4	C(24)−C(21)−C(20)	126.3
C(24)−C(21)−C(22)	110.9	C(21)−C(18)−C(19)	119.7	C(21)−C(18)−C(19)	119.7	C(24)−C(21)−C(22)	115.8
N(17)−C(6)−O(7)	123.7	N(27)−C(6)−O(7)	122.6	N(27)−C(6)−O(7)	122.9	N(18)−C(6)−O(7)	122.9
O(26)−C(24)−O(25)	120.8	O(22)−C(21)−O(24)	122.1	O(22)−C(21)−O(24)	115.3	O(26)−C(24)−O(25)	122.0
C(21)−C(20)−O(23)	117.2	C(18)−C(17)−O(25)	123.1	C(18)−C(17)−O(25)	121.0	C(21)−C(20)−O(28)	121

Table 5. Mulliken population analyses in units of e from a 6-31G*/SCF wave function for the *cis*- and *trans*-enol isomers and the keto tautomer of methyl 4-[(*tert*-butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoate (**2**)

Keto tautomer		*cis* isomer A		Enol tautomers *cis* isomer B		*trans* isomer	
O(23)	−0.495	O(25)	−0.760	O(25)	−0.689	O(28)	−0.749
		H(37)	0.504	H(37)	0.520	H(34)	0.462
C(20)	0.562	C(17)	0.561	C(17)	0.596	C(20)	0.529
C(21)	−0.445	C(18)	−0.172	C(18)	−0.206	C(21)	−0.128
H(34)	0.305						
C(22)	0.150	C(19)	0.061	C(19)	0.056	C(22)	0.044
N(27)	−0.277	N(20)	−0.275	N(20)	−0.279	N(23)	−0.289
C(24)	0.864	C(21)	0.887	C(21)	0.928	C(24)	0.840
O(25)	−0.499	O(24)	−0.668	O(24)	−0.761	O(25)	−0.554

omeric relationship between the amine and the hydroxy groups is required.[11] The novel compounds presented here contain a vinyl isosteric peptide bond and adopt the *cis*-enol form in solution and the solid phase, establishing a *syn* relationship between the amine and hydroxy groups. In addition, the *N*-methyl group present in our compounds can also be found in the statine analogue dolaisoleucine [(3*R*,4*S*,5*S*)-*N*,*O*-dimethylisostatine], which is a component of dolastatin 10, a marine natural product with cytotoxic and antineoplastic activity.[12] The above-mentioned features shared by our compounds and other statine derivatives strongly suggest that *N*-urethane-protected γ-amino-α-cyano-β-hydroxybutenoates may be useful for the design and synthesis of new inhibitors of aspartyl proteases, as well as in structure−activity relationship studies.

Experimental Section

Instrumental: Melting points were determined with a Gallenkamp MFB-595 melting point apparatus; the results are given without correction. − The IR spectra were recorded with a Perkin−Elmer 267 spectrometer and the FT IR spectrum was recorded with a Nicolet Impact 420 spectrometer. − The ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 2000 300 MHz spectrometer at 300 and 75 MHz, respectively. The chemical shifts are given relative to TMS; *J* values are given in Hz. − Elemental analyses were obtained from the University of Liverpool, Chemistry Department.

***N*-Hydroxysuccinimide Ester of *N*-(*tert*-Butoxycarbonyl)sarcosine (1):** A solution of *N*,*N*-dicyclohexylcarbodiimide (9.2 g, 0.044 mol) in ca. 15 mL of 1,2-dimethoxyethane (DME) was added dropwise with cooling, over a period of 30 min, to a solution of *N*-(*tert*-butoxycarbonyl)sarcosine (7.56 g, 0.04 mol) and *N*-hydroxysuccinimide (4.6 g, 0.04 mol) in 50 mL of DME. The reaction mixture was allowed to stand in the refrigerator overnight. The formed dicyclohexylurea was filtered off and washed with DME, after which

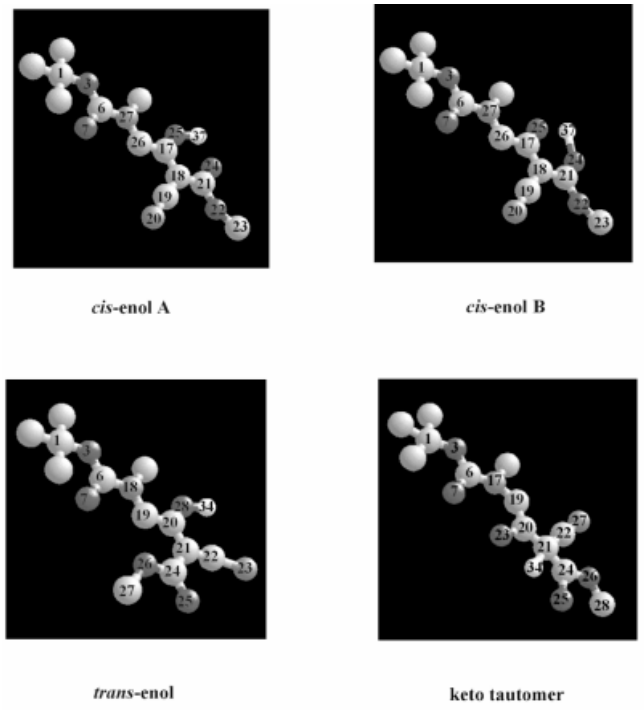


Figure 2. Optimized structures of *cis*- and *trans*-enol and keto tautomers of methyl 4-[(*tert*-butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoate (**2**) (top left and right: nitrogen atoms: labels 27, 20; oxygen atoms: labels 3, 7, 22, 24, 25; bottom left: nitrogen atoms: labels 18, 23; oxygen atoms: labels 3, 7, 25, 26, 28; bottom right: nitrogen atoms: lables 17, 27; oxygen atoms: labels 3, 7, 23, 25, 26)

the filtrate was concentrated in vacuo. Diethyl ether was added to the oily residue, which soon crystallized to give a white solid that was filtered off and washed with diethyl ether to afford 10.1 g (88% yield) of the pure ester **1**. − M.p. 124−127 °C (from isopropyl alcohol) − IR(Nujol): $\tilde{\nu}_{max}$ = 1820 m (CO ester), 1785 m (CO ring), 1730 cm^{-1} s (CO urethane) − ^1H NMR ($CDCl_3$): δ = 1.44 [9 H, s, $(CH_3)_3$], 2.82 [4 H, s, $(CH_2)_2$], 2.93 and 2.96 (3 H, 2 s, NCH_3) and 4.21 and 4.33 (2 H, 2 s, NCH_2). − $C_{12}H_{18}N_2O_6$ (286.28): calcd. C 50.34, H 6.34, N 9.79; found C 50.10, H 6.44, N 9.91.

General Procedure for the *C*-Acylation of Alkyl Cyanoacetates with the *N*-Hydroxysuccinimide Ester of *N*-Boc-Sarcosine (1): Potassium *tert*-butoxide (1.45 g, 0.0128 mol) was stirred in *tert*-butyl alcohol (80 mL) at room temperature until it dissolved (ca. 15 min), after which the alkyl cyanoacetate (0.0192 mol) was added dropwise to the mixture. Stirring was continued for 1 h, after which the *N*-hydroxysuccinimide ester of *N*-(*tert*-butoxycarbonyl)sarcosine (1.83 g, 0.0064 mol) was added to the mixture and stirring was continued at room temperature for 2 h. Water and diethyl ether were added to the reaction mixture, and the aqueous layer was separated and acidified with 10% hydrochloric acid, in an ice/water bath. The *C*-acylation compounds were isolated as crystalline products, formed directly upon acidification.

Methyl 4-[(*tert*-Butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoate (2): Yield 1.07 g (62%). − M.p. 70−73 °C (from CH_2Cl_2/light petroleum ether). − $C_{12}H_{18}N_2O_5$ (270.31): calcd. C 53.33, H 6.71, N 10.36; found C 53.32, H 6.71, N 10.37. − IR (Nujol): $\tilde{\nu}_{max}$ = 2210 cm^{-1} m (CN), 1690 s (CO urethane), 1650 s (CO β-keto ester, enol form), 1580 s (C=C ring stretching).

Ethyl 4-[(*tert*-Butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoate (3). Yield 1.36 g (75%). − M.p. 68−70 °C (from CH_2Cl_2/light petroleum ether). − $C_{13}H_{20}N_2O_5$ (284.31): calcd. C 54.88, H 7.23, N 9.60; found C 54.92, H 7.09, N 9.85. − IR (Nujol): $\tilde{\nu}_{max}$ = 2210 cm^{-1} m (CN), 1690 s (CO urethane), 1660 s (CO β-keto ester, enol form) and 1570 s (C=C ring stretching); ($CHCl_3$ solution): $\tilde{\nu}_{max}$ = 2984 cm^{-1} and 2934 w (OH), 2258 and 2227 w (CN), 1694 s (CO urethane), 1595 s (CO β-keto ester, enol form), 1559 w (C=C ring stretching).

Crystal Structure Determination of Ethyl 4-[(*tert*-Butoxycarbonyl)-methylamino]-2-cyano-3-hydroxy-2-butenoate (3): Single crystals of **3** suitable for X-ray crystallographic analysis were obtained by recrystallization from dichloromethane/light petroleum ether. The crystal data and data collection parameters are summarized in Table 6. − A colourless needle crystal of $C_{13}H_{20}N_2O_5$ was mounted on a glass fibre. All measurements were made with a Rigaku AFC6S diffractometer, with graphite-monochromated Mo-K_α radiation and a 12-kW rotating-anode generator. The data were collected at a temperature of 23±1 °C, using the ω-2θ scan technique to a maximum 2θ value of 50.0°. 4622 reflections were collected, 4357 of which were unique (R_{int} = 0.099). The intensities of three representative reflections measured after every 150 reflections remained constant throughout data collection, indicating crystal and electronic stability (no decay correction was applied). The linear absorption coefficient for Mo-K_α is 0.9 cm^{-1}. A numerical absorption correction was applied, resulting in transmission factors ranging from 0.00 to 1.00. The data were corrected for Lorentz and

Table 6. Crystal data and data-collection parameters for ethyl 4-[(*tert*-butoxycarbonyl)methylamino]-2-cyano-3-hydroxy-2-butenoate (**3**)

Formula	$C_{13}H_{20}N_2O_5$
M	284.31
Space group	*P*1 (#2)
Crystal dimensions [mm]	0.250 × 0.100 × 0.050
Crystal colour, habit	colourless, needle
Crystal system	triclinic
a [Å]	13.099(8)
b [Å]	17.52(1)
c [Å]	7.060(4)
α [°]	97.26(6)
β [°]	92.71(7)
γ [°]	77.49(5)
V [Å^3]	1569(2)
Z	4
D_c [g·cm^{-3}]	1.203
F(000)	608
Diffractometer	Rigaku AFC65
Beam width [mm]	1.0
μ(Mo-K_α) [cm^{-1}]	0.87
Scan mode	ω-2θ
2θ range [°]	8.20−19.20
λ(Mo-K_α) [Å]	0.71069
No. data collected	4622
No. unique data used	4357
R_{int}	0.099
No. unique data used	906 [$I > 3.00\sigma(I)$]
Absorption correction	Lorentz polarization
Weighting scheme, *w*	$4F_o^2/\sigma^2(F_o^2)$
R	0.063
R_w	0.058

polarisation effects. − The structure was solved by direct methods.[13] The non-hydrogen atoms were refined either anisotropically or isotropically. Hydrogen atoms were included in the structure factor calculation in idealized positions (d_{C-H} = 0.95 Å), and were assigned isotropic thermal parameters 20% greater than the B_{eq} value of the atom to which they were bonded. The final cycle of full-matrix, least-squares refinement was based on 906 observed reflections [$I > 3.00\sigma(I)$] and 246 variable parameters and converged (largest parameter shift was 0.04 times its esd) with unweighted and weighted agreement factors of R, R_w = 0.063, 0.058, respectively. The standard deviation of an observation of unit weight was 1.52. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.23 and −0.20 $e^-/Å^3$, respectively. All calculations were performed using the TEXSAN crystallographic software package.[14] The diagram was produced using PLUTO.[15] − Crystallographic data (excluding structure factors) for the structure (**3**) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-161880. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail:deposit@ccdc.cam.ac.uk].

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