Regiospecific Functionalization of 1,3-Dihydro-2*H*-benzimidazol-2-one and Structurally Related Cyclic Urea Derivatives

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Received October 20, 1994[⊗]

Methods for selectively protecting one of the degenerate nitrogen atoms of the cyclic urea derivatives 1,3-dihydro-2*H*-benzimidazol-2-one (**6a**), 1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**11**), 1,3-dihydro-2*H*-imidazo[4,5-*b*]quinolin-2-ones (**20**), 1,3-dihydro-2*H*-imidazo[4,5-*c*]pyridin-2-one (**22**), and 1,3-dihydro-4-phenyl-2*H*-imidazol-2-one (**27**) were developed. Heating these cyclic ureas with ethyl 2-pyridyl carbonate in the presence of a base in CH_3CN at reflux or DMF at 100 °C cleanly provided the monoethoxycarbonyl derivatives **7a**, **12**, **21**, **23**, and **28**, respectively. Alternatively, treatment of **6a** with an excess of diethyl pyrocarbonate or di-*tert*-butyl dicarbonate afforded the bis-alkoxycarbonyl derivatives **8a** and **8b**, respectively, which underwent disproportionation to **7a** and **7b** upon heating with 1 mol equiv of **6a** and K_2CO_3 in CH_3CN at reflux. The regiochemistry of the introduction of alkoxycarbonyl groups to benzimidazol-2-one derivatives was not significantly influenced by an electron-withdrawing (CF_3, **6b**) or an electron-donating (OCH_3, **6c**) substituent at C-5 of the heterocyclic ring. However, the reaction was found to be sensitive to steric factors since a chlorine substituent *ortho* to one of the urea N atoms (**6e**) completely directed the alkoxycarbonyl moiety to the less sterically encumbered N atom, affording a single product (**7f**, **7g**). Alkylation of **7a–g** proceeded efficiently to provide products **10a–10ag** after removal of the protecting group. Halogenation of monoprotected benzimidazol-2-one **7a** occurred regiospecifically to give the monohalo derivatives **7h**, **7i**, and **7k**, the identity of which were readily established from the characteristic chemical shift and spin coupling pattern in their ^1H NMR spectra. A protecting group interchange strategy that took advantage of the distinctive chemical reactivities of the EtO_2C and t-BuO_2C protecting groups toward isopropylamine was developed that provided access to the isomerically substituted series of monohalo, mono-N-alkylated benzimidazol-2-ones **7l** and **7m**. The efficient derivatization of the unprotected N atom of these monoprotected cyclic urea derivatives was accomplished by treating with activated and unactivated halides in the presence of K_2CO_3 or exposure to alcohols under Mitsunobu conditions. In several cases, mixtures of O- and N-alkylated products were produced which were readily separated by chromatography. Alkylation of **7h** with activated halides, using K_2CO_3 in CH_3CN at reflux, occurred without protecting group equilibration; however, a mixture of isomeric alkylated products was obtained when **7h** was heated at 110 °C in DMF with cyclohexylmethyl bromide in the presence of K_2CO_3 as the base. Derivatization of **7h** under Mitsunobu reaction conditions proceeded with retention of the topological substituent relationships. Subsequent removal of the alkoxycarbonyl moiety afforded monoalkylated cyclic urea derivatives.

Introduction

1,3-Dihydro-2*H*-benzimidazol-2-ones (**5**, Scheme 1) and related cyclic urea derivatives are useful heterocyclic building blocks that are prominent structural elements of compounds demonstrating a wide variety of interesting biochemical and pharmacological properties.[1] Included are benzimidazol-2-one derivatives that antagonize neurotransmitters,[2] inhibit aldose reductase,[3] show antiulcer and antisecretory properties,[4] enhance pulmonary surfactant secretion,[5] and modulate ion channels.[6] The structurally closely related imidazo[4,5-*b*]pyridin-2-ones[7] and homologous imidazo[4,5-*b*]quinolin-2-ones[8] have been described as potent inhibitors of blood platelet and

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⊗ Abstract published in *Advance ACS Abstracts*, February 15, 1995.

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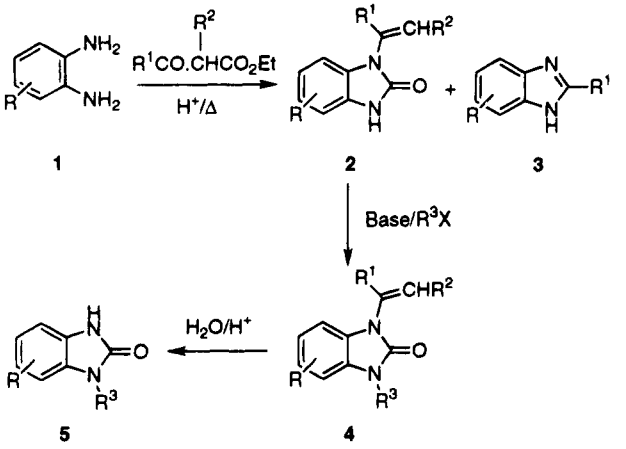
myocardial cAMP phosphodiesterase,[9] and the latter heterocycle is also the chromophoric element of the iron-chelating siderophore, azotobactin.[10] As a consequence of their interesting biological properties, a number of synthetic approaches have been developed that provide access to derivatives of these classes of cyclic urea exhibiting widely varied substitution patterns.[11-14] Nevertheless, with the design and elucidation of structurally more sophisticated target molecules that challenge existing synthetic methodology, new strategies continue to be devised and developed.[4,15,16]

A particular problem encountered in attempts to prepare derivatives of 1,3-dihydro-2*H*-benzimidazol-2-one has been the difficulty associated with selectively functionalizing a single ureido nitrogen atom. The direct monoalkylation of one of the nitrogen atoms of this heterocycle is not straightforward and mixtures of mono- and dialkylated products are generally produced along with unreacted starting material if the alkylating agent is not taken in excess.[17,18] This problem is further compounded when the aromatic ring is substituted in a topologically unsymmetrical fashion, resulting in complicated mixtures of isomers that are difficult to separate. While several solutions to this problem have been described, many are indirect and rely upon the elaboration of benzene derivatives substituted with a latent or protected vicinal diamino moiety. After unmasking, the vicinal diamine is cyclized to an imidazolone ring, a transformation generally accomplished using phosgene or a phosgene equivalent.[4,11-16] The method most commonly employed to prepare mono-N-substituted benzimidazol-2-one derivatives that depends upon the selective alkylation of a single nitrogen atom of the intact heterocycle is delineated in Scheme 1. This procedure, which was developed over 30 years ago[19] but continues

Scheme 1



to be of contemporary practical value,[17] involves the alkylation[2c,3,17,19-21] of *N*-alkenylbenzimidazol-2-ones **2**. The ability to discriminate between the nitrogen atoms of **2** is the result of a condensation and subsequent rearrangement that occurs when *o*-phenylenediamines **1** and structurally related compounds are heated with a β-keto ester, either in the presence or absence of an acid catalyst.[12,22-26] After derivatization of **2**, the alkenyl moiety of **4** is hydrolyzed under aqueous acidic conditions to deliver the monoalkylated heterocycle **5**.

While this protocol provides a convenient entry to mono-N-substituted benzimidazol-2-ones **5** and, by further synthetic elaboration, disubstituted benzimidazolone derivatives, there are several inherent practical disadvantages that may limit its synthetic applicability and practical utility. The reaction of *o*-diamines **1** that are unsymmetrical, by virtue of either substitution or heteroatom incorporation, with β-keto esters generally furnishes mixtures[21,25,26] of alkenylated derivatives **2**, although some measure of selectivity has been achieved[25,26] or claimed.[27-29] Moreover, the preparation of benzimidazol-2-ones **2** in this manner is frequently complicated by the concomitant production of varying amounts of the 2-substituted benzimidazole derivatives **3**. In our hands, separation of these components was not a particularly difficult task due to the markedly different solubility properties of **2** and **3**. However, the propensity for this reaction pathway to occur does detract from the overall efficiency of the process by reducing the yield of **2**. A further disadvantage of this strategy is the rather harsh aqueous acidic reaction conditions that are often required to remove the alkenyl protecting group from **4** in order to liberate **5**.[15,17a,19] These conditions limit the spectrum of functionality that can reliably be incorporated into the R^3 group of **5**. Moreover, the chemical reactivity associ-

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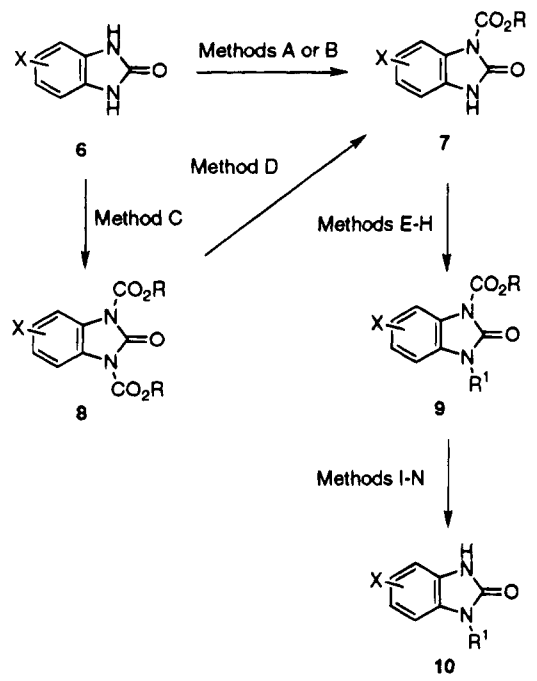
Scheme 2



[a] See footnote a of Table 1 for descriptions of synthetic methods A–N.

ated with the alkenyl moiety would be expected to interfere with electrophilic substitution of the aromatic ring, limiting its role to that of acting merely as a protecting group.

In order to surmount some of the limitations associated with currently available synthetic approaches, we have developed a practical and efficient procedure for effectively discriminating between the degenerate nitrogen atoms of 1,3-dihydro-2*H*-benzimidazol-2-ones (**6**, Scheme 2). A specific advantage inherent to this methodology is that it is based upon the direct and selective introduction of an alkoxycarbonyl protecting group to a single ureido nitrogen of the intact heterocycle, obviating the need to resort to more cumbersome indirect methods. Furthermore, the chemical properties associated with this protecting group moiety not only facilitate the subsequent derivatization of the unprotected nitrogen atom under mild conditions, but also provide a powerful means of controlling the regiospecific electrophilic functionalization of the aromatic ring. This process represents a significant refinement over previously described protocols and offers the advantage that it is more broadly applicable to structurally related cyclic urea derivatives. After fulfilling its function, the alkoxycarbonyl protecting group can be unmasked under a variety of conditions that are compatible with a wide range of chemical functionality.

Results and Discussion

(i) Protection of 1,3-Dihydro-2*H*-benzimidazol-2-one by Mono-N-alkoxycarbonylation, a Survey of Chemical Stability, and the Development of Methods for Protecting Group Removal. The alkoxycarbonyl group was identified as an attractive and potentially useful protecting functionality for the nitrogen atoms of cyclic ureas since it effectively combines reasonable chemical stability with ready removal under either mildly alkaline[30] or, if *tert*-butoxycarbonyl, under acidic[31] conditions. The initial observation that a single alkoxycarbonyl moiety could be conveniently and selectively introduced directly to cyclic urea derivatives was made during an attempt to prepare potential prodrugs[32] of 1,3-dihydro-2*H*-imidazo[4,5-*b*]quinolin-2-ones[8] from a mixed carbonate derivative.[33] Capitalizing on this finding, we heated a mixture of 1,3-dihydro-2*H*-benzimidazol-2-one (**6a**), ethyl 4-nitrophenyl carbonate, and K_2CO_3 in CH_3CN at reflux to afford the monoethoxycarbonyl derivative **7a**[16,30] in 72% yield, as depicted in Scheme 2, method A. Although the *p*-nitrophenol side product could readily be separated from **7a** by column chromatography, this purification technique was inconvenient and impractical for the large scale preparation of **7a**, prompting further refinement of the methodology. To this end, a series of mixed carbonates that incorporated more water-soluble leaving groups was prepared and examined individually for their preparative practicality. The less acidic[34] *p*-fluorophenol and even phenol itself functioned as effective leaving groups, although the much harsher conditions of heating the reaction mixtures in DMF were essential for the complete and rapid conversion of **6a** into **7a**. Under these conditions, **7a** was isolated in 73 and 100% yields, respectively. However, although some improvement was achieved, these phenols were not sufficiently soluble in water and also interfered with the purification of **7a**. The nonaromatic alcohol 1,1,1,3,3,3-hexafluoro-2-propanol[35] proved to be a satisfactory leaving group that exhibited good aqueous solubility but suffered from the disadvantage that heating the urea and carbonate in DMF at 110 °C was required in order to reproducibly afford **7a** in 93% yield. The use of the mixed carbonate derived from 2-hydroxypyridine, which is conveniently and completely removed by washing the crude reaction product with aqueous acid, proved to be a general and practical solution. Thus heating **6a** with ethyl 2-pyridyl carbonate[36] in CH_3CN at reflux for 30 min provided **7a** in 94% yield, isolated conveniently by a simple filtration after concentration and acidification of the reaction mixture (Table 1, entry 6). This reaction is easily performed on a large scale and the material isolated in this fashion is of high purity and satisfactory for further derivatization. The *tert*-butyl homologue **7b** was obtained by an alternative procedure that entailed treatment of **6a** with NaH and di-*tert*-butyl dicarbonate[37] in DMF[38] at room temperature, which afforded **7b** in 76% yield after chromatography (Scheme 2, method B).

Subsequently, a more convenient synthetic approach was developed and adopted as the preferred preparative procedure since it provided efficient access to both **7a** and **7b** and was particularly suitable for working on a large scale. Treating a suspension of **6a** in dry THF with diethyl pyrocarbonate[39] or di-*tert*-butyl dicarbonate[37] in

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the presence of a catalytic quantity of DMAP[40] afforded the bis-alkoxycarbonyl derivatives **8a** and **8b**, respectively, which could be isolated in crystalline form by simply evaporating the THF (Scheme 2, method C). Heating **8a** or **8b** with 1 mol equiv of **6a** and K_2CO_3 in CH_3CN at reflux (Scheme 2, method D) effected a rapid and complete disproportionation to cleanly furnish the target compounds **7a** and **7b**, which were isolated in high yield without the need to resort to chromatographic methods of purification. The facility with which this disproportionation reaction occurs highlights the ability of **7** to function as a leaving group under these conditions. This pattern of chemical reactivity is consistent with the description of **6a** as a leaving group of comparable reactivity to *p*-nitrophenol[41] that has demonstrated practical utility in the context of amide bond forming reactions in peptide synthesis.[41,42] The yields of **7a,b** and **8a,b** prepared by these methods and their associated physical properties are reported in Table 1, entries 6–9, 21, and 22.

A characteristic feature of the ^1H NMR spectra of **7a** and **7b** is a 1 proton doublet, $J = 7.5$ Hz, at δ 7.69 and 7.77, respectively, that resonates approximately 0.5 ppm downfield of the remaining aromatic protons. This downfield signal is assigned to the proton *ortho* to the NCO_2R moiety, which is presumably deshielded by the anisotropic carbonyl functionality.[43] Since manifestation of this effect is dependent on close spatial proximity, it also indicates that the alkoxycarbonyl moiety of **7** resides on nitrogen rather than oxygen.

The relative stabilities of the EtO_2C and t-BuO_2C protecting groups of **7a** and **7b** were examined under a variety of conditions in an effort to define the limits of their chemical reactivity and establish efficient protocols for their removal. Both alkoxycarbonyl groups were sensitive to alkaline conditions, and **7a** and **7b** were efficiently hydrolyzed to **6a** when treated with either catalytic amounts or an excess of hydroxide or alkoxide in alcohol at room temperature or reflux. However, the two groups could readily be distinguished by their reactivity under acidic conditions. While the t-BuO_2C moiety of **7b** was rapidly degraded in the presence of acid (CF_3CO_2H or HCl in EtOH), **7a** demonstrated excellent stability under these conditions. When dissolved in 10% HCl in EtOH at room temperature, the EtO_2C group of **7a** remained intact for extended periods (18 h), and even heating **7a** at reflux in 30% HBr in AcOH resulted in little degradation over a period of 30 minutes. However, significant amounts of **6a** were detected by TLC analysis after **7a** was exposed to the latter conditions for 1 h. While these experiments firmly established that the EtO_2C and t-BuO_2C groups of **7** could be effectively discriminated under acidic conditions,[31] they could also be distinguished in a complementary fashion by their sensitivity toward to primary amines.[41,42] The EtO_2C group was completely removed from **7a** upon stirring with an excess of i-$PrNH_2$ in CH_3CN for 3 h, with significant decomposition evident by TLC after 20 min. In contrast, the t-BuO_2C moiety of **7b** was considerably more robust since minimal degradation was apparent by TLC after 7 h of exposure to excess i-$PrNH_2$ in a mixture of CH_3CN and THF. However, the stability of **7b** under these conditions is not absolute since significant amounts of **6a** were present in the reaction mixture after 24 h. The discriminatory power of i-$PrNH_2$ is clearly dependent on steric factors since the sterically less encumbered *n*-propylamine degraded **7b** far more rapidly, effecting almost complete conversion to **6a** over a 7 h period.

Another property that distinguishes the EtO_2C and t-BuO_2C groups of **7a** and **7b** is their relative thermal instability, although this aspect of chemical reactivity has not been investigated as a preparative procedure for protecting group removal. The thermal fragility of *tert*-butyl carbamates is well documented, and three mechanistically distinct decomposition pathways have been identified that are generally promoted by electron-withdrawing substituents on the carbamate nitrogen atom.[44,45] Presumably because of the electron deficient nature of the carbamate nitrogen atom, the t-BuO_2C group of **7b** and related benzimidazol-2-one derivatives appears to be quite sensitive to thermal degradation. This is reflected in the melting point data reported for **7b** in Table 1 (entry 8) and those of several other t-BuO_2C derivatives, which are considerably higher than would be anticipated based on the melting points of similarly substituted N-ethoxycarbonylated benzimidazol-2-ones. In fact, the melting point reported for **7b** is essentially identical to that of the parent compound **6a**, suggesting a facile but subtle degradation in the melting point tube. While stable up to temperatures of 150 °C, **7b** cleanly decomposes to **6a** between 160 and 200 °C. Mass spectral fragmentation patterns of **7a** and **7b** and homologous compounds are also consistent with markedly differing thermal stabilities. While the mass spectra of **7a** and related EtO_2C-substituted benzimidazol-2-one derivatives invariably show the molecular ion as the base peak, **7b** and other t-BuO_2C-substituted compounds exhibit very weak molecular ions, even under the mild conditions associated with ionization by FAB. The base peak for these compounds is generally that of the compounds lacking either the t-BuO_2C moiety or isobutylene. While we have made no attempt to develop the practical applicability of this method for removing the t-BuO_2C protecting group from benzimidazol-2-one derivatives and related cyclic ureas, the thermal decomposition of t-BuO_2C derivatives has proven to be an effective and advantageous method for unmasking this protecting functionality under certain circumstances.[46]

(ii) Alkoxycarbonylation of 1,3-Dihydro-2*H*-benzimidazol-2-one Derivatives Substituted in the Aromatic Ring. The effect of electronic and steric factors on the regiochemistry of introduction of the alkoxycarbonyl moiety was probed using several 1,3-dihydro-2*H*-benzimidazol-2-one derivatives (**6b–e**, Table 1, entries 2–5) that incorporated substituents in the benzene ring of the heterocycle. The results of these studies are summarized in Table 1, entries 10–14. As an example of a substrate substituted with a remote electron-

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withdrawing group,[47] derivatization of 5-(trifluoromethyl)-1,3-dihydro-2*H*-benzimidazol-2-one (**6b**) was examined. Compound **6b**, prepared from the corresponding diamine using carbonyldiimidazole[48,49] to effect ring closure, was treated with an excess of $(t\text{-}BuCO_2)_2O$ in THF in the presence of a catalytic quantity of DMAP to provide the bis-substituted compound **8d** in quantitative yield (Table 1, entry 24). Heating this material with an additional 1 equiv of **6b** afforded an equal mixture of the two isomeric monoprotected compounds **7c** and **7d**, which were separated by careful column chromatography. A similar result was obtained when **6b** was derivatized with $(t\text{-}BuCO_2)_2O$ using NaH in DMF, which gave a mixture of **7c** and **7d** directly. The structures of **7c** and **7d** were established from an analysis of the pattern of spin coupling and chemical shifts associated with the aromatic protons in the ^1H NMR spectra. The more polar material was identified as **7d** based on the fact that the proton deshielded by the $t\text{-}BuO_2C$ moiety resonated as a doublet, $J = 0.9$ Hz, at δ 7.89 while the proton *ortho* to the $t\text{-}BuO_2C$ group of the isomer **7c** resonated as a doublet, $J = 8.4$ Hz, at δ 7.79. Thus, in addition to functioning as a protecting group, the alkoxycarbonyl moiety also fulfills a useful diagnostic role in the elucidation of substitution patterns, which may be of broader application.[28]

The presence of an electron-donating group[47] in the aromatic ring also failed to significantly influence the regiochemistry of alkoxycarbonylation. Treatment of 5-methoxy-1,3-dihydro-2*H*-benzimidazol-2-one (**6c**) with ethyl 2-pyridyl carbonate[36] afforded an equal mixture of regioisomers, as determined by analysis of the ^1H NMR spectrum of the crude mixture. However, separation of these isomers and individual functionalization were not pursued further.

It is apparent from these results that the remote electronic effects associated with the CF_3 and MeO substituents of **6b** and **6c** exert little influence on the regiochemistry of introduction of the alkoxycarbonyl moiety. However, this reaction is sensitive to steric factors, an aspect that was examined using two dichlorobenzimidazol-2-one derivatives that exhibit complementary substitution patterns, **6d** and **6e** (Table 1, entries 4 and 5). The symmetrically substituted 5,6-dichloro-1,3-dihydro-2*H*-benzimidazol-2-one (**6d**),[50] prepared from **6a** by treatment with 2 equiv of SO_2Cl_2 in AcOH at room temperature, behaved in the standard fashion, as summarized in Table 1, entries 12 and 25. The monoprotected compound **7e** could be prepared through the intermediacy of the bis-protected derivative **8e** or directly from **7e** by using ethyl 2-pyridyl carbonate. In contrast, the 4,6-dichloro-substituted benzimidazol-2-one[50,51] **6e** behaved quite differently, demonstrating a pattern of reactivity that provides some insight into the steric demands of the alkoxycarbonylation reaction. Reaction of **6e**, prepared from commercially-available 2-amino-3,5-dichlorobenzoic acid by a Curtius reaction using DPPA[52] in toluene at reflux, with ethyl 2-pyridyl carbonate or diethyl pyrocarbonate provided a single product, Table 1, entry 13. This material was identified as **7f** based on the marked downfield shift of one of the two aromatic protons in the ^1H NMR spectrum when compared to **6e**. The identical result was obtained even when **6e** was exposed to a large excess of diethyl pyrocarbonate in THF at reflux for long periods. Similarly, the $t\text{-}BuO_2C$ derivative **7g** (Table 1, entry 14) was isolated after treatment of **6e** with $(t\text{-}BuO_2C)_2O$ in the presence of a catalytic amount of DMAP. In fact, attempts to introduce a second alkoxycarbonyl moiety to either **7f** or **7g** were not successful using pyrocarbonate derivatives, even under forcing conditions. The installation of this type of protecting group is thus quite sensitive to the steric environment in the immediate vicinity of the NH. That **7f** and **7g** were the sole products and could not be further alkoxycarbonylated is presumably reflective of the electronic demands of the RO_2C moiety. These are most effectively satisfied when the RO_2C group assumes a conformation in which the carbonyl moiety is coplanar with the heterocycle, thereby maximizing orbital overlap with the nitrogen lone pair.[43,53,54] However, this conformational arrangement is compromised by the severe steric interactions that would develop between the RO_2C group and the adjacent chlorine substituent in the isomers of **7f** and **7g**. As a consequence, **7f** and **7g** are a manifestation of thermodynamic rather than kinetic control due to the preferential degradation of the more sterically-congested and chemically reactive carbamate. Interestingly, the isopropenyl protecting group strategy may offer a superior synthetic approach to the preparation of functionalized derivatives of **6e** since both isomers are reported to be formed from the reaction of the appropriately substituted phenylene diamine derivative with ethyl acetoacetate,[55] although this has not been confirmed.[28]

(iii) Functionalization of the Aromatic Ring of Ethyl 2,3-Dihydro-2-oxo-1*H*-benzimidazole-1-carboxylate (7a). Although the two unsymmetrically-substituted benzimidazol-2-one derivatives examined, **6b** and **6c**, produced mixtures of isomeric alkoxycarbonylated products **7**, a regioselective approach to this topological pattern of substitution was developed that took advantage of the electronic properties of the alkoxycarbonyl protecting group of **7a**. The aromatic ring of **6a** can be acylated under Friedel–Crafts type conditions[56] and nitrated,[57] with the extent of nitration effectively controlled by modulating the reaction conditions. In contrast, the selective introduction of halogen atoms to **6a** has proven to be a more difficult challenge, with both the regiospecificity and the extent of halogenation difficult to control.[13,58] As a consequence of its electron-withdrawing nature, the alkoxycarbonyl moiety would be expected to influence both the regiochemical course and extent of electrophilic substitution of the aromatic ring of **7a** and **7b**. In reality, this proposal proved to be

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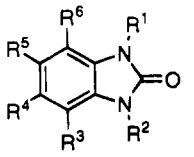
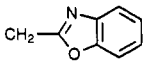
Table 1. Preparative Conditions, Yields, and Physical Properties Associated with Substituted Benzimidazol-2-one Derivatives



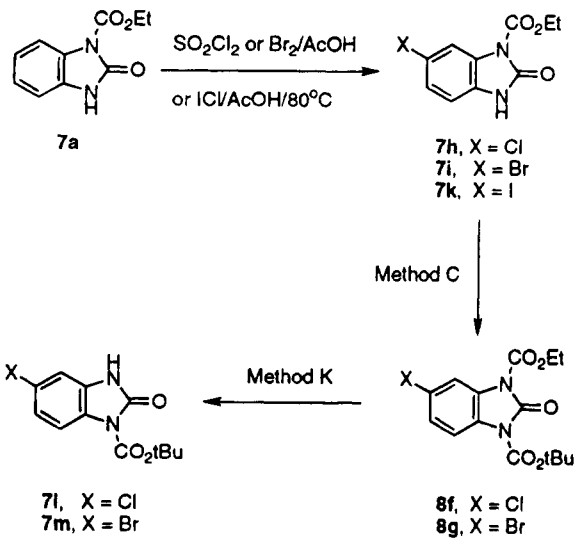
entry no.	compd no.	R^1	R^2	R^3	R^4	R^5	R^6	synthetic method[a]	% yield	mp, °C	molecular formula[b]
1	**6a**	H	H	H	H	H	H				
2	**6b**	H	H	H	H	CF_3	H		89	284–285	$C_8H_5F_3N_2O$
3	**6c**	H	H	H	H	MeO	H				
4	**6d**	H	H	H	Cl	Cl	H	**6a**, SO_2Cl_2, AcOH	98	>360	$C_7H_4Cl_2N_2O$
5	**6e**	H	H	Cl	H	Cl	H	Acid,[c] DPPA, Et_3N/Δ	75	360–361	$C_7H_4Cl_2N_2O$
6	**7a**	CO_2Et	H	H	H	H	H	A	94	149–151	$C_{10}H_{10}N_2O_3$
7	**7a**	CO_2Et	H	H	H	H	H	D	90		
8	**7b**	$CO_2{}^tBu$	H	H	H	H	H	B	76	313–315	$C_{12}H_{14}N_2O_3$
9	**7b**	$CO_2{}^tBu$	H	H	H	H	H	D	96		
10	**7c**	H	$CO_2{}^tBu$	H	H	CF_3	H	B	30	157–159	$C_{13}H_{13}F_3N_2O_3$
11	**7d**	$CO_2{}^tBu$	H	H	H	CF_3	H	B	55	284–286	$C_{13}H_{13}F_3N_2O_3$
12	**7e**	CO_2Et	H	H	Cl	Cl	H	A	90	191–193	$C_{10}H_8Cl_2N_2O_3{\cdot}0.1H_2O$
13	**7f**	CO_2Et	H	Cl	H	Cl	H	A	88	224–227	$C_{10}H_8Cl_2N_2O_3$
14	**7g**	$CO_2{}^tBu$	H	Cl	H	Cl	H	C	93	358–360	$C_{12}H_{12}Cl_2N_2O_3$
15	**7h**	CO_2Et	H	H	H	Cl	H	**7a**, SO_2Cl_2, AcOH	99	204–206	$C_{10}H_9ClN_2O_3$
16	**7i**	CO_2Et	H	H	H	Br	H	**7a**, Br_2, AcOH	94	210–215	$C_{10}H_9BrN_2O_3$
17	**7j**	$CO_2{}^tBu$	H	H	H	Br	H	**7b**, Br_2, AcOH, NaOAc	71	324–326	$C_{12}H_{13}BrN_2O_3$
18	**7k**	CO_2Et	H	H	H	I	H	**7a**, ICl, AcOH, 80 °C	91	180–182	$C_{10}H_9IN_2O_3{\cdot}0.1H_2O$
19	**7l**	H	$CO_2{}^tBu$	H	H	Cl	H	K	74	313–316	$C_{12}H_{13}ClN_2O_3$
20	**7m**	H	$CO_2{}^tBu$	H	H	Br	H	1. C; 2. K	85	327–329	$C_{12}H_{13}BrN_2O_3$
21	**8a**	CO_2Et	CO_2Et	H	H	H	H	C	95	120–122	$C_{13}H_{14}N_2O_5$
22	**8b**	$CO_2{}^tBu$	$CO_2{}^tBu$	H	H	H	H	C	98	141–143 dec	$C_{17}H_{22}N_2O_5$
23	**8c**	CO_2Et	$CO_2{}^tBu$	H	H	H	H	C	100	78–80	$C_{15}H_{18}N_2O_5$
24	**8d**	$CO_2{}^tBu$	$CO_2{}^tBu$	H	H	CF_3	H	C	100	127–128	$C_{18}H_{21}F_3N_2O_5$
25	**8e**	CO_2Et	CO_2Et	H	Cl	Cl	H	C	78	102–105	$C_{13}H_{12}Cl_2N_2O_5$
26	**8f**	CO_2Et	$CO_2{}^tBu$	H	H	Cl	H	C	75	104–107	$C_{15}H_{17}ClN_2O_5$
27	**9a**	CO_2Et	CH_2Ph	H	H	H	H	E	91	78–80	$C_{17}H_{16}N_2O_3$
28	**9a**	CO_2Et	CH_2Ph	H	H	H	H	G[d]	79		
29	**9a**	CO_2Et	CH_2Ph	H	H	H	H	G	97		
30	**9b**	CO_2Et	CH_2-3-$CF_3C_6H_4$	H	H	H	H	E	100	108–110	$C_{18}H_{15}F_3N_2O_3$
31	**9c**	CO_2Et	CH_2-3,5-$F_2C_6H_3$	H	H	H	H	E	100	139–141	$C_{17}H_{14}F_2N_2O_3$
32	**9d**	$CO_2{}^tBu$	CH_2Ph	H	H	CF_3	H	E	100	foam	$C_{20}H_{19}F_3N_2O_3$
33	**9e**	CH_2Ph	$CO_2{}^tBu$	H	H	CF_3	H	E	92	foam	$C_{20}H_{19}F_3N_2O_3{\cdot}0.2H_2O$
34	**9f**	CO_2Et	CH_2Ph	H	Cl	Cl	H	E	100	135–136	$C_{17}H_{14}Cl_2N_2O_3$
35	**9g**	CO_2Et	CH_2Ph	Cl	H	Cl	H	E	83	103–105	$C_{17}H_{16}Cl_2N_2O_3$
36	**9h**	CO_2Et	CH_2Ph	H	H	Cl	H	E	78	118–120	$C_{17}H_{15}ClN_2O_3$
37	**9i**	CO_2Et	CH_2Ph	H	H	Br	H	E	76	110–113	$C_{17}H_{15}BrN_2O_3$
38	**9j**	CO_2Et	$CH_2CO_2CH_3$	H	H	H	H	E	99	112–114	$C_{13}H_{14}N_2O_5$
39	**9k**	CO_2Et	$CH(Ph)CO_2Et$	H	H	H	H	E	92	109–111	$C_{20}H_{20}N_2O_5$
40	**9l**	CO_2Et	CH_2COPh	H	H	H	H	E	86	124–127	$C_{18}H_{16}N_2O_4$
41	**9m**	CO_2Et	CH_2COCH_3	H	H	H	H	E	87	149–151	$C_{13}H_{14}N_2O_4$
42	**9n**	CO_2Et	CH_2CN	H	H	H	H	E	100	133–135	$C_{12}H_{11}N_3O_3$
43	**9o**	$CO_2{}^tBu$	CH_2-2-C_5H_4N	H	H	H	H	1. B; 2. E[e]	92	122–125	$C_{18}H_{19}N_3O_3$
44	**9p**	CO_2Et	SO_2CH_3	H	H	H	H	H	91	124–126	$C_{11}H_{12}N_2O_5S$[f]
45	**9q**	CO_2Et	SO_2-4-$CH_3C_6H_4$	H	H	H	H	H	89	157–159	$C_{17}H_{16}N_2O_5S$
46	**9r**	CO_2Et	CH_2CH_2OAc	H	H	H	H	F	100	99–102	$C_{14}H_{16}N_2O_5$
47	**9s**	CO_2Et	CH_2-c-C_6H_{11}	H	H	Cl	H	G	92	oil	
48	**9t**	CH_2-c-C_6H_{11}	$CO_2{}^tBu$	H	H	Cl	H	G	80[g]		
49	**9u**	CO_2Et	CH_2-2-THP	H	H	H	H	F	92	71–73	$C_{16}H_{20}N_2O_4$
50	**10a**	H	CH_2Ph	H	H	H	H	I	72	198–200	$C_{14}H_{12}N_2O$
51	**10b**	H	CH_2-2-FC_6H_4	H	H	H	H	1. E; 2. I	92	179–182	$C_{14}H_{11}FN_2O$
52	**10c**	H	CH_2-2-ClC_6H_4	H	H	H	H	1. E; 2. I	91	169–171	$C_{14}H_{11}ClN_2O$
53	**10d**	H	CH_2-3-FC_6H_4	H	H	H	H	1. E; 2. I	72	165–167	$C_{14}H_{11}FN_2O$
54	**10e**	H	CH_2-3-ClC_6H_4	H	H	H	H	1. E; 2. I	77	163–165	$C_{14}H_{11}ClN_2O$
55	**10f**	H	CH_2-3-$CF_3C_6H_4$	H	H	H	H	I	75	165–167	$C_{15}H_{11}F_3N_2O_3{\cdot}0.4H_2O$
56	**10g**	H	CH_2-3,5-$F_2C_6H_3$	H	H	H	H	I	82	173–175	$C_{14}H_{10}F_2N_2O{\cdot}0.1H_2O$
57	**10h**	H	CH_2-3-$CH_3OC_6H_4$	H	H	H	H	1. E; 2. I	94	145–147	$C_{15}H_{14}N_2O_2$
58	**10i**	H	CH_2-4-$CH_3OC_6H_4$	H	H	H	H	1. E; 2. I	96	183–186	$C_{15}H_{14}N_2O_2{\cdot}0.2H_2O$
59	**10j**	H	CH_2Ph	H	H	CF_3	H	N	92	172–173	$C_{15}H_{11}F_3N_2O$
60	**10k**	CH_2Ph	H	H	H	CF_3	H	N	77	168–170	$C_{15}H_{11}F_3N_2O$
61	**10l**	H	CH_2Ph	H	Cl	Cl	H	I	89	230–233	$C_{14}H_{10}Cl_2N_2O{\cdot}0.2H_2O$
62	**10m**	H	CH_2Ph	Cl	H	Cl	H	I	94	indistinct	$C_{14}H_{10}Cl_2N_2O{\cdot}H_2O$[h]
63	**10n**	H	CH_2Ph	H	H	Cl	H	I	81	165–168	$C_{14}H_{11}ClN_2O$
64	**10o**	H	CH_2Ph	H	H	Br	H	I	80	215–217	$C_{14}H_{11}BrN_2O{\cdot}0.1H_2O$
65	**10p**	H	CH_2Ph	H	H	I	H	1. E; 2. I	100	228–232	$C_{14}H_{11}IN_2O$
66	**10q**	CH_2Ph	H	H	H	Cl	H	1. E; 2. L	93	241–248	$C_{14}H_{11}ClN_2O$
67	**10r**	CH_2Ph	H	H	H	Br	H	1. E; 2. I	61	258–260	$C_{14}H_{11}BrN_2O{\cdot}0.1H_2O$
68	**10s**	H	$CH_2CH{=}CH_2$	H	H	H	H	1. E; 2. J	78	88–90	$C_{10}H_{10}N_2O$

Table 1 (Continued)

entry no.	compd no.	R^1	R^2	R^3	R^4	R^5	R^6	synthetic method[a]	% yield	mp, °C	molecular formula[b]
69	**10t**	H	$CH_2CO_2CH_3$	H	H	H	H	J	100	136–138	$C_{10}H_{10}N_2O_3$
70	**10u**	H	$CH(Ph)CO_2Et$	H	H	H	H	J	82	97–100	$C_{17}H_{16}N_2O_3$
71	**10v**	H	CH_2COPh	H	H	H	H	I	93	233–235	$C_{15}H_{12}N_2O_2$
72	**10w**	H	CH_2COCH_3	H	H	H	H	J	75	175–177	$C_{10}H_{10}N_2O_2 \cdot 0.2H_2O$
73	**10x**	H	CH_2CN	H	H	H	H	K	70	165–167	$C_9H_7N_3O \cdot 0.5H_2O$
74	**10y**	H	CH_2-2-C_5H_4N	H	H	H	H	M	90	188–190	$C_{13}H_{11}N_3O \cdot TsOH$
75	**10z**	H		H	H	H	H	1. E; 2. M	57	220–232	$C_{15}H_{11}N_3O_2$
76	**10aa**	H	SO_2CH_3	H	H	H	H	K	67	179–181	$C_8H_8N_2O_3S$
77	**10ab**	H	SO_2-4-$CH_3C_6H_4$	H	H	H	H	K	95	198–200	$C_{14}H_{12}N_2O_3S$
78	**10ac**	H	$CH_2CH_2CH_3$	H	H	H	H	1. F; 2. I	78	95–97	$C_{10}H_{12}N_2O$
79	**10ad**	H	CH_2CH_2OH	H	H	H	H	I	72	136–138	$C_9H_{10}N_2O_2$
80	**10ae**	H	CH_2-c-C_6H_{11}	H	H	H	H	1. F; 2. I	89	179–181	$C_{14}H_{18}N_2O \cdot 0.1H_2O$
81	**10af**	H	CH_2-c-C_6H_{11}	H	Cl	Cl	H	1. F; 2. I	56	242–245	$C_{14}H_{16}Cl_2N_2O \cdot 0.1H_2O$
82	**10ag**	H	CH_2-c-C_6H_{11}	Cl	H	Cl	H	1. G; 2. I	54	202–205	$C_{14}H_{16}Cl_2N_2O$
83	**10ah**	H	CH_2-c-C_5H_9	H	H	Cl	H	1. G; 2. I	86	162–165	$C_{13}H_{15}ClN_2O$
84	**10ai**	H	CH_2-c-C_6H_{11}	H	H	Cl	H	I	77	194–197	$C_{14}H_{17}ClN_2O$
85	**10aj**	H	CH_2-c-C_6H_{11}	H	H	Br	H	1. G; 2. I	64	232–234	$C_{14}H_{17}BrN_2O \cdot 0.25H_2O$
86	**10ak**	CH_2-c-C_6H_{11}	H	H	H	Cl	H	I	54	174–176	$C_{14}H_{17}ClN_2O \cdot 0.2H_2O$
87	**10al**	CH_2-c-C_6H_{11}	H	H	H	Br	H	1. G; 2. L	66	184–185	$C_{14}H_{17}BrN_2O$
88	**10am**	H	CH_2-2-THP	H	H	H	H	I	64	138–140	$C_{13}H_{16}N_2O_2 \cdot 0.1H_2O$
89	**10an**	H	$(CH_2)_3CO_2Et$	H	H	H	H	1. F; 2. J	88	86–88	$C_{13}H_{16}N_2O_3$

[a] Synthetic methods: method A: EtO_2CO-2-pyridyl/K_2CO_3/CH_3CN/reflux; method B: $(RO_2C)_2O$/NaH/DMF; method C: $(RO_2C)_2O$/cat. DMAP/THF; method D: **6**/K_2CO_3/CH_3CN/reflux; method E: activated halide/K_2CO_3/CH_3CN/reflux; method F: unactivated halide/K_2CO_3/DMF/110 °C; method G: R^1OH/DEAD/PPh_3/THF; method H: sulfonyl chloride/Et_3N/cat. DMAP/THF; method I: 5 N NaOH/ROH; method J: cat. NaOR/ROH; method K: i-$PrNH_2$/THF; method L: CF_3CO_2H; method M: TsOH·H_2O/CH_3CN; method N: gaseous HCl in EtOAc, CH_3CN/Et_2O, or MeOH. [b] Elemental analyses for C, H, and N are within ±0.4 of the theoretical values. [c] Prepared from 2-amino-3,5-dichlorobenzoic acid available from Aldrich Chemical Co. [d] Reagents employed were 1,1'-(azodicarbonyl)dipiperidine and Bu_3P. [e] NaH-mediated N-*tert*-butoxycarbonylation of **6a** and subsequent K_2CO_3-mediated alkylation performed in a single vessel using DMF as solvent. [f] H: calcd, 4.25; found, 4.70. [g] O-alkylated isomer, mp 77–79 °C, isolated in 16% yield after chromatography. [h] H: Calcd, 3.89; found, 3.40.

Scheme 3



correct since treatment of **7a** with a slight excess of SO_2Cl_2 or Br_2 in AcOH at room temperature or 80 °C cleanly afforded the monochloro and monobromo derivatives **7h** and **7i**, respectively, in high yield, as depicted in Scheme 3. More vigorous conditions were essential in order to smoothly and completely effect iodination of **7a** which required heating in AcOH at 80 °C with 2 equiv of iodine monochloride to deliver **7k** in excellent yield. In these procedures, the EtO_2C protecting group offered a significant advantage over the t-BuO_2C because of its markedly enhanced stability under acidic conditions. The acid-sensitive nature of the t-BuO_2C moiety precluded the satisfactory chlorination of **7b** with complete preservation of the protecting group, even under buffered conditions. However, bromination of **7b** to afford **7j** could be accomplished efficiently by briefly stirring with Br_2 in AcOH at room temperature in the presence of a slight excess of NaOAc to neutralize the HBr produced. The yields for these halogenation processes are listed in Table 1, entries 15–18. The deactivating effect of the EtO_2C moiety on the aromatic ring of **7a** proved to be quite powerful since it was remarkably resistant to further halogenation, even under vigorous conditions. Heating either **7a** or **7h** with a large excess of SO_2Cl_2 in AcOH at 80 °C for periods of up to 18 h failed to effect introduction of a second chlorine atom, which contrasts strikingly with the behavior of the unmodified parent compound **6a**.[58]

The site of halogenation of **7a** was readily established by examination of the ^1H NMR spectra of **7h–k** in which the aromatic ring protons display a distinctive pattern of chemical shift and spin coupling consistent with the assigned structures. The low field signals, aromatic protons deshielded by the NCO_2Et substituent,[43] resonate as doublets between δ 7.60 and 8.00 and display a small coupling constant of 1.5 to 2 Hz, indicative of *meta* coupling.

The predictable and regiospecific introduction of halogens to the aromatic ring of **7a** provides additional opportunity for synthetic manipulation and structural modification based on the well-developed capacity of aryl bromides and iodides to participate in metal-catalyzed reactions, particularly Pd-catalyzed functionalization,[59] lithium–halogen exchange,[60] and as precursors to Grignard reagents.[61]

(59) (a) Heck, R. F. *Acct. Chem. Res.* **1979**, *12*, 146. (b) Heck, R. F. *Org. React.* **1982**, *27*, 345. (c) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985. (d) Daves, G. D.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433. (e) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508. (f) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *Synthesis* **1981**, 56.

(60) (a) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon Press: Oxford, 1974. (b) Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1985.

(iv) The Development of a Protecting Group Interchange Strategy. In order to further extend the flexibility of these strategies for heterocycle functionalization, a protecting group interchange protocol was sought that would provide access to compounds with a substitution topology complementary to that in **7h–k**. After examining several established amide protecting groups,[31,62] a solution was devised that combined elements of the chemistry used to prepare **7** with the differential sensitivity of the EtO_2C and t-BuO_2C moieties toward i-$PrNH_2$ (*vide supra*). This strategy, which was explored initially using **7a** as the substrate, is summarized in Scheme 3. Treatment of **7a** with (t-$BuCO_2)_2O$ and a catalytic amount of DMAP[40] afforded the mixed bis-alkoxycarbonyl derivative **8c** (Table 1, entry 23), which could be selectively deprotected, dependent upon the reaction conditions. While dissolution of **8c** in CF_3CO_2H rapidly regenerated **7a** in 82% yield, treatment of **8c** with a slight excess of i-$PrNH_2$ selectively removed the EtO_2C moiety, providing **7b** efficiently and quickly. From a practical perspective, this procedure was most conveniently performed in a single operation. Thus, after derivatization of **7a** with (t-$BuCO_2)_2O$, a slight excess of i-$PrNH_2$ was added to the reaction mixture and stirring continued until deprotection was complete according to TLC. This process was quite rapid and **7b** was isolated by simply evaporating the solvent and recrystallizing the residual solid.

Implementation of this synthetic protocol using the chloro-substituted compound **7h** as the substrate smoothly afforded **7l** (Table 1, entry 19), through the intermediacy of **8f** (Table 1, entry 26), as summarized in Scheme 3. The bromo-substituted compound **7i** behaved in a similar fashion, providing **7m** in excellent overall yield without isolation of the intermediate **8g** (Table 1, entry 20). The ^1H NMR spectra of **7l** and **7m** complement those of **7h–k** since the deshielded aromatic protons resonate as doublets, J = 8.5 Hz, indicative of *ortho* coupling and consistent with the assigned structures.

(v) Alkylation of Monoprotected Benzimidazolones. The selective introduction of a single alkoxycarbonyl moiety to **6** not only masks one the reactive NH's but, by virtue of its electron-withdrawing properties, enhances the acidity[41] of the remaining NH of **7**. This, in turn, would be expected to facilitate the base-mediated functionalization of **7**, which indeed proved to be the case. Alkylation of **7** with activated alkyl halides was readily accomplished under mild conditions and generally in excellent yield. Heating **7a** and **7b** with an activated halide at reflux in CH_3CN in the presence of powdered K_2CO_3 as the base (method E) rapidly provided the N-alkylated compounds **9**, as summarized in Scheme 2. From a practical perspective, this procedure is both straightforward and convenient, generally producing product of high purity after simply filtering the hot reaction mixture and evaporating the solvent. The halides selected to demonstrate the synthetic utility of this process using **7a** or **7b** as the substrate included benzyl halides, α-bromoacetates, allyl bromide, α-bromo ketone derivatives, and bromoacetonitrile. For the aromatic ring-substituted derivatives **7c–m**, benzyl bromide was selected as typical of an activated halide and alkylation generally proceeded rapidly and efficiently without complication. The yields for a series of representative examples where the immediate alkylated product was isolated and fully characterized are summarized in Table 1, entries 27, 30–42. In the case of the t-BuO_2C derivative **7b**, a one-pot procedure was developed that allowed the preparation of monosubstituted benzimidazol-2-one derivatives directly from **6a**. Thus, treating **6a** with a slight excess of NaH and (t-$BuO_2C)_2O$ in DMF furnished a solution of **7b** which was further derivatized *in situ* by adding an activated alkyl halide and excess K_2CO_3. The practicality of this protocol was illustrated using 2-(chloromethyl)pyridine as the electrophile, and **9o** was isolated in 92% overall yield from **6a** under these conditions (Table 1, entry 43).

Sulfonyl halides were also examined as electrophiles and found to efficiently functionalize the nitrogen atom of **7a** in the presence of Et_3N as the base (Scheme 2, method H), as summarized in Table 1, entries 44 and 45.

The mild conditions under which alkylation of **7a** and **7b** with activated halides proceeded were not effective when unactivated alkyl halides were employed as reaction partners, since little or no reaction occurred at reflux in CH_3CN, even over prolonged periods. In order to successfully couple **7a** and **7b** with simple alkyl halides, it was essential to conduct the reaction in a dipolar aprotic solvent, preferably DMF. Thus, heating **7a** and **7b** with an alkyl halide and K_2CO_3 in DMF at 110 °C for 30–60 min (Scheme 2, method F) generally provided the alkylated products **9** rapidly, cleanly and in high yield. Two representative examples that illustrate the efficiency of this process are presented in Table 1 as entries 46 and 47.

In contrast, alkylation of **7h** with cyclohexylmethyl bromide, which was selected as a somewhat sterically demanding representative of unactivated alkyl halides, using K_2CO_3 as the base in DMF at 110 °C proved to be problematic. After deprotection of the crude intermediate, the ^1H NMR spectrum of the alkylated material indicated that it consisted of a mixture of regioisomeric compounds. Evidently, under the reaction conditions, equilibration of the EtO_2C moiety of **7h** had occurred more rapidly than alkylation, leading to the production of a mixture of the two possible N-alkylated products. The lability of the EtO_2C group under these conditions was confirmed by heating a sample of **7h** in DMF at 110 °C in the presence of 25% mol equiv of K_2CO_3 for 45 min. The material isolated after cooling and acidification of the reaction mixture (73% recovery) was judged to be a 1:2 mixture of **7h** and its isomer based on the pattern and integration of the aromatic ring protons in the ^1H NMR spectrum.

In an effort to identify milder conditions for alkylation that would allow complete preservation of the regiochemical relationships between the chlorine atom and the N substituents in **7h–m**, the use of CH_3CN as the solvent was explored. However, as with the unsubstituted progenitor **7a**, **7h** could not be alkylated with unactivated halides in CH_3CN at reflux, prompting an examination of the applicability of the Mitsunobu[63] reaction. The pK_a of the parent benzimidazolone **6a** has been reported to range from 11.6 to 12.5,[64] a figure that places it just outside the pK_a window defined as optimal by the reactivity of the Mitsunobu reagents.[63] However, the NH

(61) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985; Chapter 16, pp 816–812.

(62) Greene, T. *Protective Groups in Organic Synthesis*, 1st ed.; John Wiley and Sons, New York, 1981.

(63) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L *Org. React.* **1992**, *42*, 335.

(64) (a) Brown, D. J.; *J. Chem. Soc.* **1958**, 1974. (b) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworth: London, 1965; p 265.

of a mono-N-acylated benzimidazol-2-one is considerably more acidic with a pK_a that has been reported to be 9.8.[41] Consideration of these data suggested that the EtO_2C moiety of **7a** and **7h** should enhance the acidity of the remaining NH to the point where these compounds would be capable of participating as the acidic partner in a Mitsunobu reaction. In order to establish the viability of this hypothesis, the reaction of **7a** with benzyl alcohol was studied, since this would provide a well characterized compound. Although a more powerful combination of phosphine and azodicarboxylate reagents[65] was initially selected and proved to be successful, these were not crucial since **7a** was readily derivatized in high yield under the standard conditions of stirring with diethyl azodicarboxylate (DEAD), Ph_3P, and benzyl alcohol in THF at room temperature. The products were isolated after chromatographic purification, and the yields for these procedures are reported in Table 1, entries 28 and 29. The chloro-substituted compound **7h** behaved similarly, providing the *N*-benzyl compound **9h** in 84% yield after chromatography (Table 1, entry 36). Treatment of **7h** with DEAD, Ph_3P, and cyclohexylmethanol produced **9s**, which was purified by column chromatography and isolated as an oil in 92% yield (Table 1, entry 47). A small amount of a chromatographically more mobile material was also present in the crude reaction mixture according to TLC and was tentatively identified as the O-alkylated isomer.[66,67] When **7l** was subjected to the same reaction conditions, the O-alkylated isomer was isolated and characterized (Table 1, entry 48). Mitsunobu conditions were subsequently employed to couple all substituted derivatives of **7** with unactivated halides when preservation of regiochemical integrity was an issue.

After alkylation of **7**, the EtO_2C and t-BuO_2C protecting groups were removed from the products **9** under a variety of conditions that depended upon the nature and sensitivity of the functionality present in the N substituent R^1 (Scheme 2). For robust substrates, stirring at room temperature or briefly heating **9** with either catalytic amounts or an excess of aqueous hydroxide in an alcohol as solvent (Scheme 2, method I) was most convenient, providing **10** in good yield. For those substrates containing an ester functionality in R^1, catalytic amounts of the appropriate alkoxide in the alcohol (Scheme 2, method J) was employed in order to preserve the ester moiety (Table 1, entries 69, 70, and 89). An exception to this is the acetoxy derivative reported in Table 1, entry 46, where the ester moiety was cleaved under these conditions, as shown by the product isolated in Table 1, entry 79. Although not specifically examined, the use of the t-BuO_2C protecting group rather than the EtO_2C would presumably allow preservation of this kind of functional group. For the N-sulfonylated benzimidazolones **9p** and **9q**,[47] the EtO_2C group was removed by exposing the substrates to an excess of i-$PrNH_2$ in THF (Scheme 2, method K) to give the products **10aa** and **10ab** (Table 1, entries 76 and 77). The t-BuO_2C moiety could also be removed from derivatives of **9** under alkaline conditions but was more frequently cleaved by treatment with acid. This was accomplished by several methods including dissolution of substrates in CF_3CO_2H (Scheme 2, method L), stirring or heating with *p*-TsOH in CH_3CN (Scheme 2, method M) or, alternatively, bubbling gaseous HCl into a solution of **9** in CH_3CN/Et_2O, EtOAc, or MeOH (Scheme 2, method N).

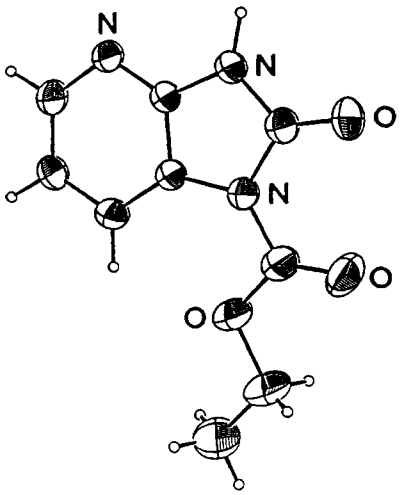


Figure 1. An ORTEP plot depicting the solid state conformation of **12**.

From a practical perspective, the intermediates **9** were generally not purified and the crude material was directly subjected to deprotection conditions to afford the target compounds **10a–an** in good to excellent overall yield (Table 1, entries 50–89). It should be emphasized that the yields reported in Table 1 represent the results of single experiments and no effort has been made to optimize the individual reaction conditions. Particularly notable is the fact that while alkoxycarbonylation of **7f** or **7g** was not successful, alkylation of **7f** with benzyl bromide or derivatization with cyclohexylmethanol under Mitsunobu conditions proceeded smoothly to furnish the alkylated products **10m** and **10ag** (Table 1, entries 62 and 82, respectively) after removal of the protecting group. This procedure therefore provides a convenient method for the selective alkylation of the sterically more hindered ureido nitrogen atom of **6e**.

(vi) Application to 1,3-Dihydro-2*H*-imidazo[4,5-*b*]-pyridin-2-one, 1,3-Dihydro-2*H*-imidazo[4,5-*b*]quinolin-2-one, and 1,3-Dihydro-2*H*-imidazo[4,5-*c*]pyridin-2-one Derivatives. Monoprotection of 1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one[68] (**11**), obtained from the corresponding diamine by treatment with carbonyldiimidazole,[48,49] was accomplished by heating with ethyl 2-pyridyl carbonate and K_2CO_3 in CH_3CN, as shown in Scheme 4. This procedure cleanly afforded a single product in 90% yield, identified as **12**[69] based on the downfield shift of the C-7 proton (proton *para* to N) when compared to the chemical shift of the C-7 proton in the ^1H NMR spectrum of **11**. The structural assignment was confirmed by single crystal X-ray analysis of a sample of **12** that crystallized from water.[82] An ORTEP plot of the solved structure is presented in Figure 1 and reveals that the carbonyl of the EtO_2C group is virtually coplanar with the urea carbonyl and the aromatic ring since the measured torsion angles are less than 4°. Interestingly, in the solid state the two carbonyl groups of **12** adopt the less thermodynamically stable conformation in which

(65) (a) Tsunoda, T.; Yamamiya, Y.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 1639. (b) Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Itô, S. *Chem. Lett.* **1994**, 539.

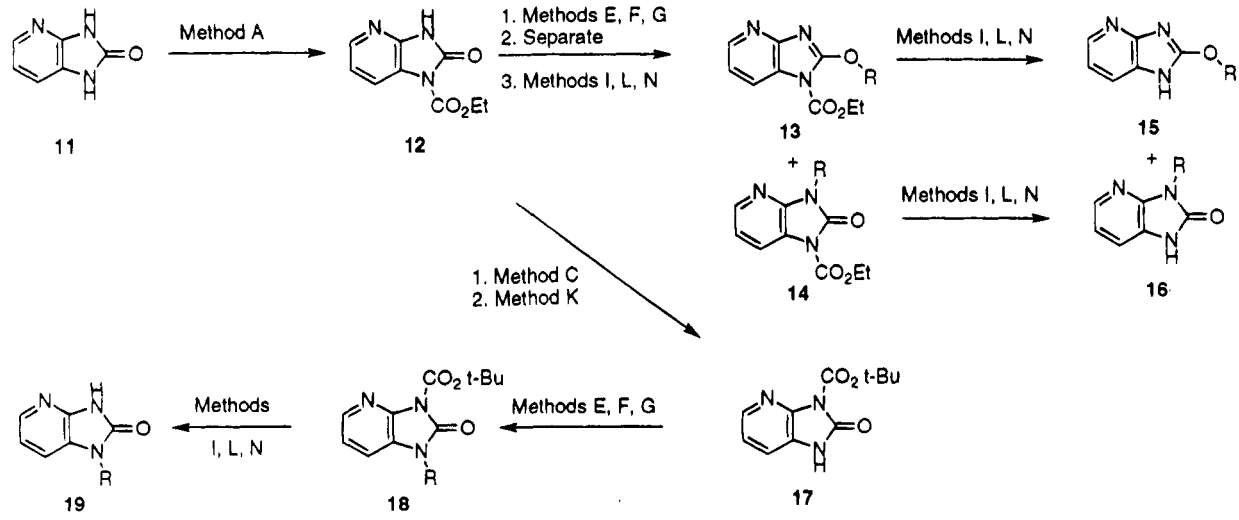
(66) Comins, D. L.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 2819.

(67) Mitsunobu, O.; Takizawa, S.; Morimato, H. *J. Am. Chem. Soc.* **1976**, *98*, 7858.

(68) (a) Hershenson, F. M.; Bauer, L.; King, K. F. *J. Org. Chem.* **1968**, *33*, 2543. (b) Takeda, K.; Ogura, H. *Synth. Commun.* **1982**, *12*, 213. (c) Zecchini, G. P.; Torrini, I.; Paradisi, M. P. *J. Heterocycl. Chem.* **1985**, *22*, 313.

(69) Zecchini, G. P.; Torrini, I.; Paradisi, M. P. *J. Heterocycl. Chem.* **1985**, *22*, 1061.

Scheme 4



their dipoles are aligned in a parallel fashion.[70] While this is not without precedence,[54a,b,d] in a previous example[54a] both carbonyl groups were found to be engaged in a bifurcated intermolecular hydrogen bonding interaction with the same proton. However, the only intermolecular interactions apparent in the crystal lattice of **12** are two identical and complementary hydrogen bonds that are formed between the NH and pyridine nitrogen atoms of adjacent molecules which are, consequently, related by a center of symmetry (see supplemental material).

That **12** is produced as the sole product is consistent with the results of previous studies of the alkoxycarbonylation or acylation of **11**.[69,71] and appears to reflect differences in the relative acidity of the two NH protons of **11.** While ethoxycarbonylation of the 3-NH (*ortho* to the pyridine N atom) would be expected to occur first based on the kinetic acidity of this proton,[34] the product **12** presumably represents the thermodynamically more stable isomer.

Alkylation of **12** with benzyl bromide, using K_2CO_3 as the base in CH_3CN at reflux, afforded a 1:2 mixture of the O- and N-alkylated products, **13a** and **14a**, respectively, which were readily separated by column chromatography. Subsequent deprotection afforded the O-benzylated isomer **15a**, and the N-alkylated material **16a**. However, when **12** was alkylated with cyclohexylmethyl bromide in DMF at 110 °C, the N-substituted isomer was the sole product and this was deprotected to afford **16b**.

Implementation of the protecting group interchange strategy developed for functionalized benzimidazol-2-one derivatives provided access to the isomerically substituted compounds **19**, through the intermediacy of **17** and **18** (Scheme 4). Of particular concern in the K_2CO_3-mediated alkylation of **17** reaction was the potential for the t-BuO_2C group to equilibrate prior to benzylation. However, the ^1H NMR spectrum of **18a** did not exhibit the low field doublet characteristic of the C-7 proton in the isomeric series derived from **12**, confirming that the regiochemical integrity of the protecting group of **17** was maintained under these reaction conditions. The importance of this spectral data was underscored by the fact that the ^1H NMR spectra of the isomeric N-benzylated imidazo[4,5-*b*]pyridin-2-ones **16a** and **19a** are virtually superimposable and the two compounds can only be reliably distinguished by NOE difference spectra.[72]

The representative examples of imidazo[4,5-*b*]pyridin-2-ones prepared by the procedures depicted in Scheme 4 are presented in Table 2, entries 1−10.

The homologous 1,3-dihydro-2*H*-imidazo[4,5-*b*]quinolin-2-one heterocycle[8] behaved similarly, as summarized in Scheme 5. The regiochemistry of ethoxycarbonylation of **20**, introduced using ethyl 4-nitrophenyl carbonate and either K_2CO_3 or NaH in DMF, was determined to be the 1-position as shown in **21** based on the ~0.5 ppm downfield shift of the singlets attributable to the C-9 protons (*para* to N) when compared to the parent molecules **20**. Although alkylation reactions of **21** were not specifically explored, the pattern of N-substitution potentially accessible by this approach is the same as that in the chromophoric element of azotobactin.[10]

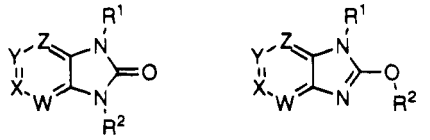
As depicted in Scheme 6, 1,3-dihydro-2*H*-imidazo[4,5-*c*]pyridin-2-one[73] (**22**) also provided a single product **23** when treated with NaH and $(t\text{-}BuO_2C)_2O$ in DMF. The identity of **23** was readily determined from ^1H NMR spectral data since the C-4 proton of **23**, a singlet at δ 8.66, resonates 0.53 ppm downfield of the C-4 proton of **22**, a result of the deshielding effect of the adjacent t-BuO_2C moiety. In contrast, the C-7 protons (*meta* to the ring N atom) of **22** and **23** display similar chemical shifts. The selective formation of **23** from **22** can be attributed to the same arguments based on the different acidities of the NH's of **22**[34,74] that was presented above to rationalize the production of a single isomer **12** from the isomeric heterocycle **11**.

Derivatization of **23** under Mitsunobu conditions afforded mixtures of the O- and N-alkylated products **24** and **25**, respectively, based on an examination of the ^1H NMR spectra of the crude products. The O-alkylated isomers amounted to only a small percentage of the yield

(70) Atkins, P. W. *Physical Chemistry*; W. H. Freeman and Co.: San Francisco, 1978; Chapter 23, pp 760−761.
(71) Harrison, D.; Smith, A. C. B. *J. Chem. Soc.* **1959**, 3157.

(72) For the 1-benzyl derivative **17a**, irradiation of the NH proton produced no signal enhancement whereas irradition of the benzylic protons resulted in the enhancement of a doublet, J = 8 Hz, assigned to the C-7 proton, and a doublet J = 5 Hz, assigned to the *ortho* protons of the phenyl ring. In contrast, irradiation of the benzylic protons of **16a** enhanced only the doublet associated with the adjacent *ortho* protons of the phenyl ring while irradiation of the NH proton led to enhancement of the doublet, J = 8 Hz assigned to the C-7 proton of the heterocyclic ring.
(73) (a) Debeljak-Sustar, M.; Stanovnik, B.; Tisler, M.; Zrimsek, Z. *J. Org. Chem.* **1978**, *43*, 393. (b) Tomazic, A.; Tisler, M.; Stanovnik, B. *J. Heterocycl. Chem.* **1979**, *16*, 861.
(74) Barlin, G. B. *J. Chem. Soc. (B)* **1966**, 285.

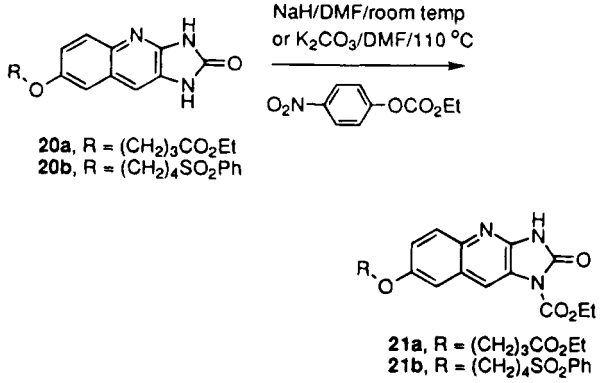
Table 2. Preparative Conditions, Yields, and Physical Properties Associated with Imidazo[4,5-*b*]pyridin-2-one and Imidazo[4,5-*c*]pyridin-2-one Derivatives



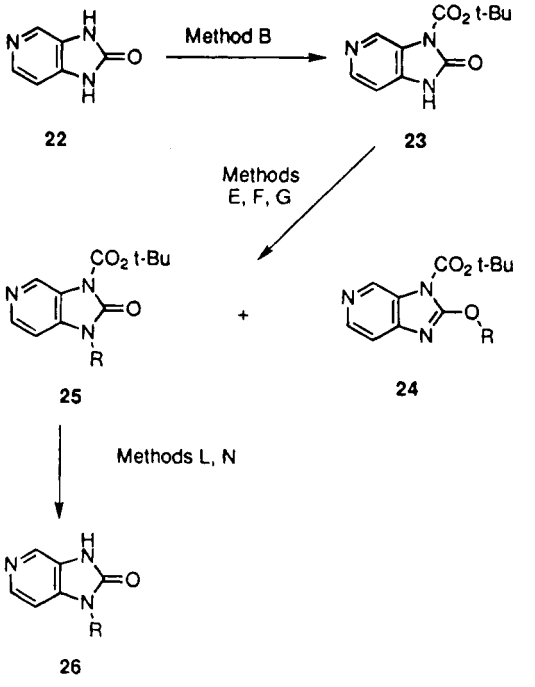
entry no.	compd no.	R^1	R^2	W	X	Y	Z	site of R^2: N,O	synthetic method[a]	% yield	mp, °C	molecular formula[b]
1	**12**	CO_2Et	H	N	CH	CH	CH	N	A	90	204–206	$C_9H_9N_3O_3$
2	**13a**	CO_2Et	CH_2Ph	N	CH	CH	CH	O	E	29[c]		
3	**14a**	CO_2Et	CH_2Ph	N	CH	CH	CH	N	E	59	74–76	$C_{16}H_{15}N_3O_3$
4	**14b**	CO_2Et	CH_2-c-C_6H_{11}	N	CH	CH	CH	N	F	75	94–96	$C_{16}H_{21}N_3O_3$
5	**15a**	H	CH_2Ph	N	CH	CH	CH	O	MeOH	62	245–247	$C_{13}H_{11}N_3O$
6	**16a**	H	CH_2Ph	N	CH	CH	CH	N	I	91	171–173	$C_{13}H_{11}N_3O{\cdot}0.1H_2O$
7	**16b**	H	CH_2-c-C_6H_{11}	N	CH	CH	CH	N	I	80	206–208	$C_{13}H_{17}N_3O{\cdot}0.2H_2O$
8	**17**	H	$CO_2{}^tBu$	N	CH	CH	CH	N	C	74	262–263 dec	$C_{11}H_{13}N_3O_3{\cdot}0.1H_2O$
9	**19a**	CH_2Ph	H	N	CH	CH	CH	N	1. E; 2. L	74	166–168	$C_{13}H_{11}N_3O{\cdot}0.25H_2O$[d]
10	**19b**	CH_2-cC_6H_{11}	H	N	CH	CH	CH	N	1. G 2. I	63	137–140	$C_{13}H_{17}N_3O{\cdot}0.5H_2O$
11	**23**	H	$CO_2{}^tBu$	CH	N	CH	CH	N	C	50	158–160	$C_{11}H_{13}N_3O_3$
12	**25a**	CH_2Ph	$CO_2{}^tBu$	CH	N	CH	CH	N[e]	G	70	123–125	$C_{18}H_{19}N_3O_3$
13	**25b**	$CO_2{}^tBu$	CH_2-c-C_6H_{11}	CH	CH	N	CH	N[f]	G	79	142–143	$C_{18}H_{25}N_3O_3$
14	**25c**	CH_2CH_2OMe	$CO_2{}^tBu$	CH	N	CH	CH	N[g]	G	75		
15	**26a**	CH_2Ph	H	CH	N	CH	CH	N	N[h]	87	267–269	$C_{13}H_{11}N_3O{\cdot}HCl{\cdot}0.1H_2O$
16	**26b**	H	CH_2-c-C_6H_{11}	CH	CH	N	CH	N	N[h]	100	265–267	$C_{13}H_{17}N_3O{\cdot}HCl$
17	**26c**	CH_2CH_2OMe	H	CH	N	CH	CH	N	N[h]	94	201–203	$C_9H_{11}N_3O_2{\cdot}HCl{\cdot}0.1H_2O$

[a] Synthetic methods are as described in the footnote to Table 1. [b] Elemental analyses for C, H, and N are within ±0.4 of the theoretical values. [c] Compound decomposed in MeOH during recrystallization with loss of the CO_2Et moiety. See entry 5 for the product. [d] C: Calcd, 67.96, found, 68.38; N: calcd, 18.29; found, 17.64. [e] The ^1H NMR spectrum of the crude product indicated the presence of a small amount of the O-alkylated isomer. [f] The ^1H NMR spectrum of the crude product indicated the presence of approximately 10% of the O-alkylated isomer. [g] The ^1H NMR spectrum of the crude product indicated the presence of approximately 3% of the O-alkylated isomer and ^1H NMR spectrum of the purified material indicated the presence of approximately 14% of $Ph_3P{=}O$. [h] Gaseous HCl in MeOH was employed.

Scheme 5



Scheme 6



and were not isolated. After purification by chromatography, deprotection of **25** gave **26**. The compounds prepared as part of this study are listed in Table 2, entries 11–17.

(vii) Application to 4-Phenyl-1,3-dihydro-2*H*-imidazol-2-one. As depicted in Scheme 7, heating 4-phenyl-1,3-dihydro-2*H*-imidazol-2-one[75] (**27**) with ethyl 2-pyridyl carbonate and K_2CO_3 in DMF[76] at 75 °C afforded a single ethoxycarbonyl derivative, identified as **28** after inspection of ^1H NMR spectral data.[77] The heterocyclic ring proton of **28**, which resonates at δ 7.26, is deshielded by the adjacent EtO_2C moiety[38] and is thus shifted 0.38 ppm downfield relative to the same proton in **27**, a triplet, J = 2 Hz, at δ 6.88. Although we were unable to obtain crystals of **28** suitable for structure determination by X-ray crystallographic analysis, the solid state structures of derivatives of **28** subsequently confirmed its identity (*vide infra*). That the single isomer **28** was produced as the sole product from the alkoxycarbonylation of **27** is consistent with the earlier observations concerning the sensitivity of the stability of the reaction products to steric factors.

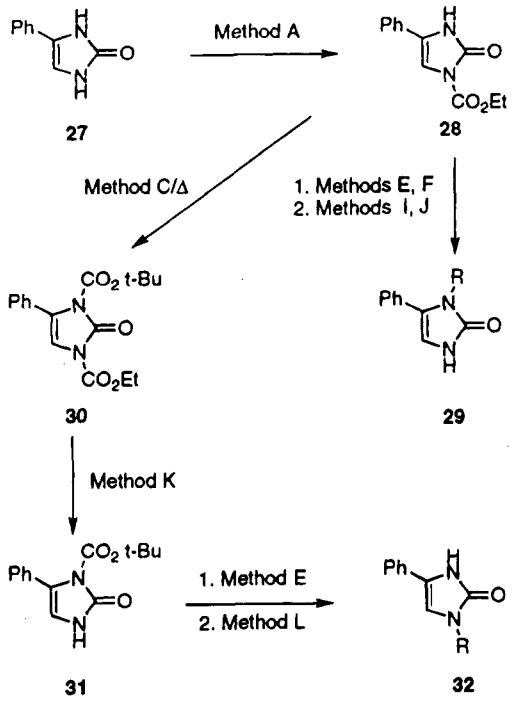
Alkylation of **28** and subsequent deprotection afforded the imidazol-2-ones **29**, derivatives of **27** in which substitution has been selectively introduced at the sterically more congested ureido nitrogen atom. Alkylation of **28** could be accomplished readily with both activated and unactivated halides and was most effectively achieved

(75) Calis, Ü.; Dalkara, S.; Ertan, M. *Arzneim. Forsch.* **1992**, *42*, 592.

(76) The use of DMF as the solvent was essential for the success of this reaction since it did not progress to completion in CH_3CN at reflux.

(77) Taguchi, T.; Sato, Y.; Watanabe, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 401.

Scheme 7



by heating in DMF at 110 °C in the presence of K_2CO_3 as the base. The compounds prepared to demonstrate the synthetic viability of this protocol are compiled in Table 3, entries 2–5.

The protecting group interchange strategy developed for the benzimidazol-2-one series proved to be an effective method of gaining access to the isomerically substituted compounds **32**. Treating **28** with excess $(t\text{-}BuO_2C)_2O$ and a catalytic amount of DMAP in THF afforded the bis-substituted compound **30**, although heating the reaction mixture at reflux was necessary in order to effect the complete conversion of **28** to **30**. This presumably reflects the unfavorable steric demands imposed by the proximity of the bulky $t\text{-}BuO_2C$ group and the adjacent phenyl ring in **30**. Nevertheless, selective deprotection of the sterically less encumbered EtO_2C group by exposure to $i\text{-}PrNH_2$ in THF was successful and provided the imidazol-2-one **31**, which complements **28**, in good yield. The ^1H NMR spectra of **30** and **31** provided some insight into aspects of the conformation of the substituents appended to the heterocyclic ring. The heterocyclic ring proton of **30** resonates as a singlet at δ 6.99, which is 0.27 ppm upfield of the same proton in **28**. For **31**, the same proton resonates as a doublet, J = 2.45 Hz, at δ 6.61, which is 0.27 ppm upfield of the same proton in **27**. Taken together, these observations indicate that the imidazol-2-one ring proton of **30** and **31** experiences reduced deshielding by the adjacent aromatic ring and suggests that the phenyl ring in these molecules is significantly distorted from coplanarity[78] with the imidazol-2-one ring. These conformational constraints are presumably a consequence of distortions induced by steric interactions between the phenyl ring and the adjacent bulky $t\text{-}BuO_2C$ moiety. The results of single crystal X-ray structural analyses[82] of **30** and **31**, depicted in Figures 2 and 3 as ORTEP plots, reflect the conclusions reached after examination of ^1H NMR spectral data.[78] In the solid state, the phenyl ring of **30** is twisted approximately 44° out of the plane of the imidazolone ring (Figure 2) while for **31** the plane of the phenyl ring deviates from that of the heterocycle by approximately 45° (Figure 3). Steric interference with the phenyl ring also forces the $t\text{-}BuO_2C$ carbonyl moiety out of the plane of the heterocyclic ring by 55° for **30** and 38° for **31**. In addition, the carbonyl groups of the $t\text{-}BuO_2C$ groups of both **30** and **31** are aligned in the thermodynamically more stable antiparallel arrangement with the ureido carbonyl.[70] In contrast, the carbonyl group of the EtO_2C moiety of **30** is twisted from planarity only by approximately 12°, although it is aligned in the thermodynamically less favorable arrangement in which the dipole is parallel with the ring carbonyl. However, in this case, the parallel orientation of the carbonyl oxygen atoms is stabilized by virtue of their participation in a bifurcated intermolecular hydrogen bonding interaction with the NH of an adjacent molecule in the crystal lattice (see supplemental material). Taken together with ^1H NMR spectral data, these observations suggest that in solution the phenyl rings of **27** and **28** adopt conformations in which they are aligned in a more coplanar arrangement with the heterocycle, consistent with the results of studies conducted with structurally-related compounds.[79]

Alkylation of **31** was explored using benzyl bromide as the alkylating agent and K_2CO_3 as the base in CH_3CN at reflux. Subsequent deprotection provided the N-1 benzyl derivative **32a** (Table 3, entry 8) in good overall yield. Comparison of spectral data for **29a** and **32a** demonstrated that alkylation of **31** under these conditions occurred without prior equilibration of the $t\text{-}BuO_2C$ moiety. The imidazolone **31** could not be alkylated under Mitsunobu conditions and alkylation of **31** with unactivated halides using K_2CO_3 in hot DMF was not examined due to the propensity for alkoxycarbonyl moiety migration observed with the benzimidazol-2-one series and in structurally related compounds.[80]

Conclusion

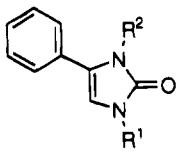
In summary, we have described preparative procedures that allow the selective derivatization of a single nitrogen atom of cyclic urea derivatives with EtO_2C or $t\text{-}BuO_2C$ protecting group moieties in high yield. These protecting groups facilitate functionalization of the remaining nitrogen atom under mild conditions and are then readily removed under a variety of conditions, dependent upon the identity of the protecting group. Moreover, when installed on the benzimidazol-2-one heterocycle, the ethoxycarbonyl moiety controls the regiospecificity and extent of halogenation of the aromatic ring. The synthetic versatility of this protecting group strategy is further enhanced by a protecting group interchange protocol based on the EtO_2C and $t\text{-}BuO_2C$ groups that takes advantage of subtle differences in their chemical reactivity and provides access to a series of benzimidazol-2-one derivatives substituted in a topologically complementary fashion. Overall, these preparative procedures represent convenient and efficient strategic approaches to the preparation of functionalized cyclic urea derivatives.

(78) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; 2nd ed., Pergamon Press: Oxford, 1969; Part 2, pp 94–98.

(79) (a) Hallows, W. A.; Carpenter, G. B.; Pevear, K. A.; Sweigart, D. A. *J. Heterocycl. Chem.* **1994**, *31*, 899. (b) Nalini, V.; Desiraju, G. R. *Acta Crystallogr. C (Cr. Str. Commun.)* **1989**, *45*, 1525. (c) Nalini, V.; Desiraju, G. R. *Acta Crystallogr. C (Cr. Str. Commun.)* **1989**, *45*, 1528. (d) Soriano-Garcia, M.; Serrano, J. S. X.; Jiminez, F. G.; Toscano, R. A. *Acta Crystallogr. C (Cr. Str. Commun.)* **1986**, *42*, 1828. (e) Heinisch, G.; Holzer, W.; Vollenkle, H. *Monatsh. Chem.* **1987**, *118*, 409.

(80) (a) Sayo, S.; Wada, M.; Himizu, J-i.; Ishida, A. *Chem. Pharm. Bull.* **1980**, *28*, 1459. (b) Hayashi, K.; Nunami, K-i.; Kato, J.; Yoneda, N.; Kubo, M.; Ochiai, T.; Ishida, R. *J. Med. Chem.* **1989**, *32*, 289.

Table 3. Preparative Conditions, Yields, and Physical Properties Associated with N-Substituted, 4-Phenylimidazol-2-one Derivatives



entry no.	compd no.	R^1	R^2	synthetic method[a]	% yield	mp, °C	molecular formula[b]
1	**28**	CO_2Et	H	A[c]	95	211–214	$C_{12}H_{12}N_2O_3$
2	**29a**	H	CH_2Ph	1. F; 2. I	53	143–146	$C_{16}H_{14}N_2O{\cdot}0.2H_2O$
3	**29b**	H	$CH_2CO_2CH_3$	1. E; 2. J	83	128–130	$C_{12}H_{12}N_2O_3$
4	**29c**	H	$CH_2CH_2CH_3$	1. F; 2. I	37	91–93	$C_{12}H_{14}N_2O$
5	**29d**	H	$(CH_2)_3CO_2Et$	1. F; 2. J	84	126–128	$C_{15}H_{18}N_2O_3{\cdot}0.2H_2O$
6	**30**	CO_2Et	$CO_2{}^tBu$	C	80	95–97	$C_{17}H_{20}N_2O_5{\cdot}0.1H_2O$
7	**31**	H	$CO_2{}^tBu$	K	71	152–155 dec	$C_{14}H_{16}N_2O_3{\cdot}0.1H_2O$
8	**32a**	CH_2Ph	H	1. F; 2. L	57	253–255	$C_{16}H_{14}N_2O{\cdot}0.2H_2O$

[a] Synthetic methods are as described at the foot of Table 1. [b] Elemental analyses for C, H, and N are within ±0.4 of the theoretical values. [c] DMF used as the solvent rather than CH_3CN.

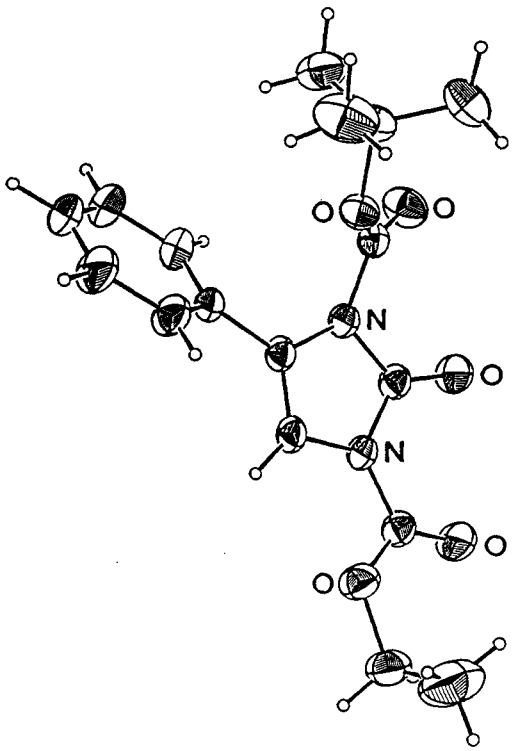


Figure 2. An ORTEP plot depicting the solid state conformation of **30**.

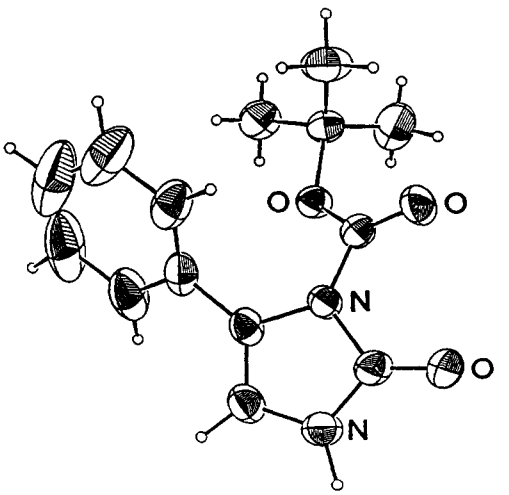


Figure 3. An ORTEP plot depicting the solid state conformation of **31**.

Experimental Section

Melting points were recorded on a Thomas-Hoover capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Bruker AM 300 or Varian Gemini 300 FT spectrometers operating at 300 MHz for ^1H and 75 MHz for ^{13}C. All chemical shifts are reported in ppm downfield relative to TMS, and spectra were recorded using either TMS or the residual solvent ($CHCl_3$ or DMSO) as internal standards. Signal multiplicity was designated according to the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet. Infrared (IR) spectra were obtained using a Perkin Elmer 1800 FT IR, scanning from 4000 to 400 cm^{-1} and calibrated to the 1601 cm^{-1} absorption of a polystyrene film. Mass spectral data were obtained on a Finnigan Model 4500 GC/MS using electrical or chemical ionization (isobutane) procedures. Fast atom bombardment (FAB) mass spectra were obtained on a Kratos MS 25 spectrometer using *m*-nitrobenzyl alcohol (NOBA) as the matrix. Analytical samples were dried *in vacuo* at 78 °C or in the presence of P_2O_5 at room temperature for at least 12 h. Elemental analyses were provided by Bristol-Myers Squibb's Analytical Chemistry Department or Oneida Research Services, Whitesboro, N.Y. Unless otherwise stated, an extractive workup procedure comprised extraction of the aqueous layer with solvent (three times), washing the combined extracts with H_2O (usually a single time except where DMF or AcOH was present when the organic phase was washed three times), and drying over Na_2SO_4 or $MgSO_4$ prior to evaporation of the solvent *in vacuo*.

Ethyl 2,3-Dihydro-2-oxo-1*H*-benzimidazole-1-carboxylate (7a) (Method A). A mixture of **6a** (89.90 g, 0.67 mol), ethyl 2-pyridyl carbonate[36] (131.82 g, 0.79 mol), K_2CO_3 (108.90 g, 0.79 mol), and CH_3CN (2 L) was stirred at reflux for 30 min. The mixture was concentrated *in vacuo* and the residue diluted with H_2O and 2 N HCl solution until pH = 1. The solid was filtered off, washed with H_2O, and dried in air to afford **7a** (131.19 g, 94%). An analytical sample recrystallized from a mixture of CH_2Cl_2 and hexane had mp 149–151 °C (lit. mp 158–160 °C[30] (EtOH) and 155.5–156.5 °C[16]). IR (KBr) 3270, 1780, 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (3H, t, J = 7 Hz), 4.53 (2H, q, J = 7 Hz), 7.05 to 7.20 (3H, m), 7.77 (1H, d, J = 7.5 Hz), 10.27 (1H, s, N*H*); MS *m/z* 207 (MH^+).

2,3-Dihydro-2-oxo-1*H*-benzimidazole-1-carboxylic acid, 1,1-Dimethylethyl Ester (7b) (Method B). NaH (16.40 g, 0.41 mol, 60% in mineral oil) was added portionwise to a stirred solution of **6a** (50.00 g, 0.37 mol) in dry DMF (1 L) maintained under an atmosphere of N_2. After 75 min, a solution of di-*tert*-butyl dicarbonate (81.35 g, 0.37 mol) in dry DMF (200 mL) was added dropwise and the mixture stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the residue diluted with saturated NH_4Cl solution

and extracted with EtOAc. The residue was chromatographed on a column of silica gel using a mixture of hexane and EtOAc (7:3) as eluant to furnish **7b** (66.70 g, 76%), mp 313–315 °C. IR (KBr) 1785, 1770, 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (9H, s), 7.06–7.18 (3H, m), 7.69 (1H, d, J = 7.5 Hz), 10.44 (1H, s); ^{13}C NMR δ 28.14, 85.08, 110.02, 114.51, 122.12, 124.22, 126.87, 127.74, 148.63, 153.47; MS m/z 235 (MH^+), 178 ($MH^+ - CH_2{=}C(CH_3)_2$, 134 ($MH^+ - CO_2tBu$). Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.53; H, 6.12; N, 11.90.

Diethyl 2,3-Dihydro-2-oxo-1*H*-benzimidazole-1,3-dicarboxylate (8a) (Method C). Diethyl pyrocarbonate (15.11 g, 13.75 mL, 93 mmol) was added dropwise to a stirred suspension of **6a** (5.00 g, 37 mmol) and DMAP (catalytic quantity) in dry THF (100 mL). The mixture was stirred for 30 min to afford a solution, the solvent evaporated, and the residual solid triturated with hexane to give **8a** (9.85 g, 95%). An analytical sample recrystallized from EtOH had mp 120–122 °C. IR (KBr) 1800, 1740, 1730, 1480, 1470 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.35 (6H, t, J = 7 Hz), 4.41 (2H, q, J = 7 Hz), 7.25 (2H, m), 7.80 (2H, m); MS m/z 279 (MH^+). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 55.93; H, 5.07; N, 10.03.

2,3-Dihydro-2-oxo-1*H*-benzimidazole-1,3-(2*H*)-dicarboxylic acid, Bis(1,1-dimethylethyl ester) (8b) (Method C). Di-*tert*-butyl dicarbonate (191.80 g, 0.88 mol) was added portionwise to a stirred suspension of **6a** (53.60 g, 0.40 mol) and DMAP (5.00 g, 40 mmol) in dry THF (1500 mL). The mixture was stirred at reflux for 1 h to afford a solution and cooled and the solvent evaporated. The residual solid was dissolved in EtOAc (1 L), washed with ice-cold 0.5 N HCl, and concentrated to afford **8a** (328.00 g, 98%), mp 141–143 °C dec. IR (KBr) 1780, 1735, 1480, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (18H, s), 7.20 (2H, m), 7.85 (2H, m); MS m/z 335 (MH^+), 279 ($MH^+ - CH_2{=}C(CH_3)_2$), 223 ($MH^+ - 2 \times CH_2{=}C(CH_3)_2$, base peak), 135 ($MH^+ - 2 \times CO_2tBu$). Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63; N, 8.38. Found: C, 60.98; H, 6.63; N, 8.33.

Ethyl 2,3-Dihydro-2-oxo-1*H*-benzimidazole-1-carboxylate (7a) (Method D). A mixture of **8a** (102.52 g, 368 mmol), **6a** (49.24 g, 367 mmol), K_2CO_3 (61.07 g, 443 mmol) and CH_3CN (1 L) was stirred vigorously at reflux for 2 h. The majority of the solvent was removed *in vacuo* and the residue diluted with 1 N HCl solution (3 L) and filtered to furnish **7a** (137.38 g, 90%).

2,3-Dihydro-2-oxo-5-(trifluoromethyl)-1*H*-benzimidazole-1-carboxylic acid, 1,1-Dimethylethyl Ester (7c) and 2,3-Dihydro-2-oxo-6-(trifluoromethyl)-1*H*-benzimidazole-1-carboxylic acid, 1,1-Dimethylethyl Ester (7d) (Method B). NaH (200 mg, 4.9 mmol, 60% in mineral oil) was added to a solution of **6b** (1.00 g, 4.9 mmol) in dry DMF (25 mL) stirred at ambient temperature under an atmosphere of N_2. After 75 min, a solution of di-*tert*-butyl dicarbonate (1.10 g, 4.9 mmol) in dry DMF (5 mL) was added dropwise and the mixture stirred for 24 h. The solvent was removed *in vacuo* and the residue was diluted with saturated NH_4Cl solution and extracted with EtOAc to give a solid which was chromatographed on a column of silica gel. Elution with a mixture of hexane and EtOAc (3:1) furnished **7c** (450 mg, 30%) as a white foam, mp 157–159 °C. IR (KBr) 3284, 2986, 2940, 1792, 1746, 1470 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.57 (9H, s), 7.19 (1H, d, J = 1.2 Hz), 7.41 (1H, d, J = 8.4, Hz, J' = 1.2 Hz), 7.79 (1H, d, J = 8.4 Hz), 11.55 (1H, bs, N*H*); ^{13}C NMR δ 150.54, 148.06, 129.79, 128.96, 126.09, 124.86, 124.44, 124.01, 122.49, 118.52, 118.47, 114.04, 105.46, 105.41, 84.34, 27.60; MS m/z 303 (MH^+), 247 ($MH^+ - CH_2{=}C(CH_3)_2$), 203 (MH^+ – Boc). Anal. Calcd for $C_{13}H_{13}F_3N_2O_3$: C, 51.66; H, 4.34; N, 9.27. Found: C, 51.55; H, 4.15; N, 9.32.

Further elution gave **7d** (830 mg, 55%), mp 284–286 °C. IR (KBr) 3270, 2986, 1794, 1778, 1510, 1465 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.57 (9H, s), 7.14 (1H, d, J = 8.2 Hz), 7.47 (1H, dd, J = 8.2 Hz, J' = 0.9 Hz), 7.89 (1H, d, J = 0.9 Hz), 11.93 (1H, bs, N*H*); ^{13}C NMR δ 150.58, 148.12, 131.86, 126.91, 126.41, 122.81, 122.26, 121.84, 121.42, 121.22, 121.18, 110.45, 110.40, 109.31, 84.32, 27.56; MS m/z 303 (MH^+), 247 ($MH^+ - CH_2{=}C(CH_3)_2$), 203 (MH^+ – Boc). Anal. Calcd for $C_{13}H_{13}F_3N_2O_3$: C, 51.66; H, 4.34; N, 9.27. Found: C, 51.60; H, 4.22; N, 9.31.

2-Oxo-5-(trifluoromethyl)-1*H*-benzimidazole-1,3(2*H*)-dicarboxylic Acid, Bis(1,1-dimethylethyl ester) (8d) (Method C). Di-*tert*-butyl dicarbonate (209.00 g, 0.96 mol) was added to a suspension of **6b** (88.00 g, 0.44 mol) and DMAP (10.60 g, 86 mmol) in dry THF (2 L). The mixture was stirred at room temperature for 30 min and at reflux for 18 h before the solvent was evaporated. The residue was dissolved in EtOAc, washed with cold 0.5 N HCl solution, 2% $NaHCO_3$ solution, H_2O, and brine and then dried and concentrated to afford **8d** (175.00 g, 100%). An analytical sample recrystallized from Et_2O/hexane had mp 127–128 °C. IR (KBr) 2995, 1805, 1740, 1460, 1330 1165 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.59 (18 H, s), 3.31 (4H, s), 7.61 (1H, dd, J = 7 Hz, J' = 1 Hz), 7.92 (1H, d, J = 7 Hz), 8.02 (1H, d, J = 1 Hz); MS m/z 403 (MH^+), 347 ($MH^+ - CH_2{=}C(CH_3)_2$), 291 ($MH^+ - 2 \times CH_2{=}C(CH_3)_2$, base peak). Anal. Calcd for $C_{18}H_{21}F_3N_2O_5$: C, 53.73; H, 5.26; N, 6.96. Found: C, 53.81; H, 5.25; N, 7.09.

5,6-Dichloro-2,3-dihydro-2-oxo-1*H*-benzimidazole-1-carboxylic Acid, Ethyl Ester (7e) (Method A). A mixture of **6d** (2.00 g, 9.8 mmol), ethyl 2-pyridyl carbonate[36] (1.81 g, 10.8 mmol), K_2CO_3 (1.50 g, 10.80, mmol), and CH_3CN (30 mL) was stirred at reflux for 3.5 h. The solvent was evaporated and the residue diluted with 1 N HCl solution and filtered to give **7e** (2.45 g, 90%). An analytical sample recrystallized from EtOAc/hexane had mp 191–193 °C. IR (KBr) 3270, 1790, 1480, 1340 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.33 (3H, t, J = 7 Hz), 4.38 (2H, q, J = 7 Hz), 7.14 (1H, s), 7.71 (1H, s); MS m/z 275, 277 (MH^+). Anal. Calcd for $C_{10}H_8Cl_2N_2O_3.0.1H_2O$: C, 43.38; H, 2.99; N, 10.12. Found: C, 43.13; H, 2.69; N, 10.20.

4,6-Dichloro-2,3-dihydro-2-oxo-1*H*-benzimidazole-1-carboxylic Acid, Ethyl Ester (7f) (Method A). A mixture of **6e** (13.00 g, 64 mmol), ethyl 2-pyridyl carbonate[36] (12.81 g, 77 mmol), K_2CO_3 (10.60 g, 77, mmol) and CH_3CN (250 mL) was stirred at reflux for 1 h. The solvent was evaporated and the residue diluted with 1 N HCl solution and filtered to give **7f** (15.65 g, 88%). An analytical sample recrystallized from EtOAc/hexane had mp 224–227 °C. IR (KBr) 3094, 1770, 1480, 1340, 1300, 1170, cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.33 (3H, t, J = 7 Hz), 4.38 (2H, q, J = 7 Hz), 7.35 (1H, d, J = 1.9 Hz), 7.61 (1H, d, J = 1.9 Hz), 11.98 (1H, bs, N*H*); MS m/z 275, 277 (MH^+). Anal. Calcd for $C_{10}H_8Cl_2N_2O_3$: C, 43.66; H, 2.93 N, 10.18 Found: C, 43.64; H, 2.90; N, 10.20.

Ethyl 6-Chloro-2,3-dihydro-2-oxo-1*H*-benzimidazole-1-carboxylate (7h). A mixture of **7a** (1.00 g, 4.8 mmol), SO_2Cl_2 (0.72 g, 0.43 mL, 5.3 mmol), and AcOH (15 mL) was stirred at 90 °C. After 1 h, the mixture was cooled, poured onto H_2O, and filtered to give **7h** (1.15 g, 99%). An analytical sample recrystallized from EtOAc and hexane had mp 204–206 °C. IR (KBr) 3280, 1795, 1775, 1480, 1340, 1130 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.33 (3H, t, J = 7 Hz), 4.38 (2H, q, J = 7 Hz), 6.99 (1H, d, J = 8 Hz), 7.18 (1H, dd, J = 8 Hz, J' = 2 Hz), 7.66 (1H, d, J = 2 Hz), 11.44 (1H, bs, N*H*); MS m/z 241, 243 (MH^+). Anal. Calcd for $C_{10}H_9ClN_2O_3$: C, 49.91; H, 3.77; N, 11.64. Found: C, 49.71; H, 3.74; N, 11.49.

Ethyl 6-Bromo-2,3-dihydro-2-oxo-1*H*-benzimidazole-1-carboxylate (7i). Br_2 (932 mg, 0.3 mL, 5.8 mmol) was added dropwise to a stirred solution of **7a** (1.00 g, 4.8 mmol) in AcOH (15 mL). After 45 min, a precipitate appeared and the mixture was heated to 80 °C for 1 h. The mixture was cooled and diluted with H_2O, and a yellow solid was filtered off and dried in air to give **7i** (1.30 g, 94%). An analytical sample, prepared by recrystallization from EtOAc containing a small amount of MeOH, had mp 210–215 °C. IR (KBr) 3250, 1790, 1480 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.33 (3H, t, J = 7 Hz), 4.38 (2H, q, J = 7 Hz), 6.94 (1H, d, J = 8.3 Hz), 7.30 (1H, dd, J = 8.3 Hz, J' = 1.6 Hz), 7.79 (1H, d, J = 1.6 Hz), 11.44 (1H, s, N*H*); MS m/z 285, 287 (MH^+). Anal. Calcd for $C_{10}H_9BrN_2O_3$: C, 42.13; H, 3.18; N, 9.83. Found: C, 41.91; H, 3.08; N, 9.82.

Ethyl 2,3-Dihydro-6-iodo-2-oxo-1*H*-benzimidazole-1-carboxylate (7k). A mixture of **7a** (6.00 g, 29 mmol), ICl (9.42 g, 58 mmol), and AcOH (90 mL) was stirred at room temperature for 5 min and then at 80 °C for 2.5 h. The mixture was cooled, poured onto H_2O, and filtered to give **7k** (8.80 g, 91%). An analytical sample recrystallized from THF and hexane had

mp 180–182 °C. IR (KBr) 3270, 1798, 1778, 1475, 1290, 1130 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.34 (3H, t, J = 7 Hz), 4.39 (2H, q, J = 7 Hz), 6.83 (1H, d, J = 8 Hz), 7.46 (1H, dd, J = 8 Hz, J' = 1.5 Hz), 7.98 (1H, d, J = 1.5 Hz), 11.43 (1H, s, N*H*); MS m/z 333 (MH^+). Anal. Calcd for $C_{10}H_9IN_2O_3 \cdot 0.1H_2O$: C, 35.97; H, 2.78; N, 8.39. Found: C, 35.66; H, 2.67; N, 8.19.

6-Chloro-1*H*-benzimidazole-1,3-(2*H*)-dicarboxylic acid, 1-Ethyl, 3-(1,1-Dimethylethyl) ester (8f) (Method C). Di-*tert*-butyl dicarbonate (2.18 g, 10 mmol) was added to a stirred suspension of **7h** (2.00 g, 8 mmol) and DMAP (catalytic quantity) in dry THF (30 mL). After 20 min, the solvent was evaporated and the residue diluted with hexane and filtered. The filtrate was concentrated *in vacuo* and the residue chromatographed on a column of silica gel. Elution with a mixture of hexane and Et_2O (4:1) afforded **8f** (2.15 g, 75%), mp 104–107 °C. IR (KBr) 2985, 1815, 1790, 1740, 1485 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (3H, t, J = 7 Hz), 1.63 (9H, s), 4.50 (2H, q, J = 7 Hz), 7.18 (1H, dd, J = 8.8 Hz, J' = 2.1 Hz), 7.80 (1H, d, J = 8.8 Hz), 7.92 (1H, d, J = 2.1 Hz); MS m/z 341, 343 (MH^+). Anal. Calcd for $C_{15}H_{17}ClN_2O_5$: C, 52.87; H, 5.03; N, 8.22. Found: C, 52.52; H, 4.96; N, 8.15.

5-Bromo-2,3-dihydro-2-oxo-1*H*-benzimidazole-1-carboxylic Acid, 1,1-Dimethylethyl Ester (7m) (Method C). Di-*tert*-butyl dicarbonate (7.34 g, 34 mmol) was added to a stirred suspension of **7i** (8.00 g, 28 mmol) and DMAP (catalytic quantity) in dry THF (150 mL). After 45 min, i-$PrNH_2$ (2.15 g, 3.12 mL, 36 mmol) was added to the solution and the mixture stirred for 25 min. The solvent was evaporated and the residue triturated with hexane and filtered to give **7m** (7.50 g, 85%). An analytical sample, prepared by chromatography over silica gel using a mixture of Et_2O and hexane (2:1) as eluant, had mp 327–329 °C. IR (KBr) 3260, 1780, 1480, 1340, 1160, 1130 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.56 (9H, s), 7.11 (1H, d, J = 2 Hz), 7.21 (1H, dd, J = 8.5 Hz, J' = 2 Hz), 7.54 (1H, d, J = 8.5 Hz), 11.38 (1H, bs, N*H*); MS m/z 313, 315 (MH^+). Anal. Calcd for $C_{12}H_{13}BrN_2O_3$: C, 46.02; H, 4.18; N, 8.95. Found: C, 46.05; H, 4.22; N, 8.79.

5-Chloro-2,3-dihydro-2-oxo-1*H*-benzimidazole-1-carboxylic Acid, 1,1-Dimethylethyl Ester (7l) (Method C). Di-*tert*-butyl dicarbonate (6.53 g, 30 mmol) was added to a stirred suspension of **7h** (6.00 g, 25 mmol) and DMAP (catalytic quantity) in dry THF (90 mL). After 25 min, i-$PrNH_2$ (1.91 g, 2.77 mL, 32 mmol) was added to the solution and the mixture stirred for 45 min. The solvent was evaporated and the residue triturated with Et_2O and filtered to give **7l** (5.00 g, 74%). An analytical sample recrystallized from CH_2Cl_2 and hexane had mp 313–316 °C. IR (KBr) 3260, 1790, 1480, 1340, 1160, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (9H, s), 7.05 (1H, dd, J = 8.5 Hz, J' = 2 Hz), 7.14 (1H, d, J = 2 Hz), 7.62 (1H, d, J = 8.5 Hz), 10.15 (1H, bs, N*H*); MS m/z 269 (MH^+). Anal. Calcd for $C_{12}H_{13}ClN_2O_3$: C, 53.64; H, 4.88; N, 10.43. Found: C, 53.47; H, 4.84; N, 10.36.

General Procedures for the Functionalization of Monoprotected Cyclic Urea Derivatives. Alkylation of monoprotected cyclic urea derivatives with activated halides was accomplished by stirring at room temperature or heating at reflux in CH_3CN with 1.1 equiv of the halide in the presence of 1.2 equiv of powdered K_2CO_3, frequently in the presence of a catalytic amount of KI (method E). After the reaction was complete according to TLC, the hot mixture was filtered and concentrated to afford the crude product. The same proportion of reagents was employed for unactivated alkyl halides, but the mixture was heated at 110 °C in DMF in the presence of a catalytic quantity of KI until the reaction was complete by TLC (method F). The product was isolated by diluting the cooled reaction mixture with H_2O or 1 N HCl and extracting with Et_2O. The products were purified by column chromatography or recrystallization.

Alkylation under Mitsunobu[63] conditions was performed by adding DEAD (1.2 equiv) to a stirred mixture of the substrate, Ph_3P (1.2 equiv) and alcohol (1.2 equiv) in dry THF at room temperature (method G). When the reaction was complete by TLC analysis, the solvent was evaporated and the residue chromatographed on a column of silica gel to afford the product.

The conditions employed to prepare the individual examples are reported in Tables 1–3.

General Conditions for Removal of the Alkoxycarbonyl Moieties. Both the ethoxycarbonyl and *tert*-butoxycarbonyl groups could be removed by stirring the substrate with catalytic amounts or an excess of 5 N NaOH solution in an alcohol solvent, either at room temperature or reflux (method I). The products were isolated by evaporating the solvent, acidifying the residue, and either filtering off the product or extracting with CH_2Cl_2 or EtOAc. Alternatively, substrates were added to an alcohol solvent in which a catalytic quantity of Na metal had been dissolved and the mixture stirred at room temperature or reflux (method J) prior to an identical workup protocol. Removal of the ethoxycarbonyl by exposure to isopropylamine (method K) was accomplished by stirring with the amine in THF at room temperature until the the reaction was complete. After evaporation of the solvent, the crude products were isolated as described above and purified by chromatography or recrystallization.

The *tert*-butoxycarbonyl groups could also be removed under acidic conditions, most conveniently by stirring the substrate in neat CF_3CO_2H until decomposition was complete (method L). The product was isolated by evaporating the CF_3CO_2H, diluting the residue with H_2O, and either filtering off the crude product or extracting with CH_2Cl_2 or EtOAc. Alternatively, stirring the substrates with a catalytic amount of $TsOH \cdot H_2O$ (or a slight excess when a basic group was present in the molecule) in CH_3CN, at room temperature or reflux (method M), or dissolving in EtOAc, Et_2O or MeOH containing excess gaseous HCl (method N) effected deprotection. Evaporation of the solvent afforded the products which were further purified by extraction, chromatography, or recrystallization.

The conditions under which the protecting groups were removed for the individual examples are compiled in Tables 1–3.

Ethyl 2,3-Dihydro-2-oxo-3-(phenylmethyl)-1*H*-benzimidazole-1-carboxylate (9a) (Method E). Alkylation of **7a** (2.00 g, 9.7 mmol) with benzyl bromide afforded **9a** (2.62 g, 91%), mp 78–80 °C, after chromatography on a column of silica gel using a mixture of Et_2O and hexane (1:1) as eluant. IR (KBr) 1760, 1725, 1500, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (3H, t, J = 7 Hz), 4.52 (2H, q, J = 7 Hz), 5.02 (2H, s), 6.86 (1H, m), 7.10 (2H, m), 7.20 to 7.35 (5H, m), 7.86 (1H, m); MS m/z 297 (MH^+). Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91 H, 5.44; N, 9.45. Found: C, 68.84; H, 5.34; N, 9.38.

2,3-Dihydro-2-oxo-3-(phenylmethyl)-6-(trifluoromethyl)-1*H*-benzimidazole-1-carboxylic Acid, 1,1-Dimethylethyl Ester (9d) (Method D). A sample of **7d** (1.50 g, 5 mmol) was alkylated with benzyl bromide (0.90 g, 5.3 mmol) to afford **9d** (1.95 g, 100%) as a foam. IR (KBr) 1795, 1755, 1625, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (9H, s), 5.05 (2H, s), 6.90 (1H, d, J = 8.2 Hz), 7.20–7.30 (5H, m), 7.36 (1H, dd, J = 8.2 Hz, J' = 1 Hz), 8.12 (1H, d, J = 1 Hz); MS (FAB) m/z 393 (MH^+), 337 ($MH^+ - (CH_3)_2C{=}CH_2$, base peak), 292 (MH^+ – Boc). Anal. Calcd for $C_{20}H_{19}F_3N_2O_3$: C, 61.22; H, 4.84; N, 7.14. Found: C, 61.26; H, 4.65; N, 7.03.

2,3-Dihydro-2-oxo-3-(phenylmethyl)-5-(trifluoromethyl)-1*H*-benzimidazole-1-carboxylic acid, 1,1-dimethylethyl ester (9e) (Method D). Alkylation of **7c** (1.50 g, 5 mmol) with benzyl bromide afforded **9e** (1.80 g, 92%) as a foam. IR (KBr) 1750, 1730, 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (9H, s), 5.26 (2H, s), 7.07 (1H, d, J = 1 Hz), 7.20–7.40 (6H, m), 7.92 (1H, d, J = 8.4 Hz); MS (FAB) m/z 393 (MH^+), 337 ($MH^+ - (CH_3)_2C{=}CH_2$, base peak), 292 (MH^+ – Boc). Anal. Calcd for $C_{20}H_{19}F_3N_2O_3 \cdot 0.2H_2O$: C, 60.67; H, 4.94; N, 7.08. Found: C, 60.68; H, 4.80; N, 6.77.

5,6-Dichloro-2,3-dihydro-2-oxo-3-(phenylmethyl)-1*H*-benzimidazole-1-carboxylic Acid, Ethyl Ester (9f) (Method E). A sample of **7e** (3.00 g, 10.9 mol) was alkylated with benzyl bromide to afford **9f** (3.98 g, 100%). An analytical sample recrystallized from CH_2Cl_2 and hexane had mp 135–136 °C. IR (KBr) 1795, 1720, 1495, cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.34 (3H, t, J = 7 Hz), 4.41 (2H, q, J = 7 Hz), 5.04 (2H, s), 7.20–7.40 (5H, m), 7.55 (1H, s), 7.86 (1H, s); MS m/z 365, 367 (MH^+). Anal. Calcd for $C_{17}H_{14}Cl_2N_2O_3$: C, 55.91; H, 3.86; N, 7.67. Found: C, 56.11; H, 3.89; N, 7.64.

2,3-Dihydro-2-oxo-3-[(2-pyridinyl)methyl]-1*H*-benzimidazole-1-carboxylic Acid, 1,1-Dimethylethyl Ester (9o) (Method B, Method F; in a single reaction vessel). NaH

(2.10 g of a 60% dispersion in mineral oil, 52 mmol) was added portionwise to a solution of **6a** (6.70 g, 50 mmol) in DMF (100 mL). After stirring at room temperature for 2 h, di-*tert*-butyl dicarbonate (12.00 g, 0.55 mmol) was added and the mixture stirred overnight. K_2CO_3 (14.50 g, 105 mmol) was added, the mixture stirred for 30 min, and 2-(chloromethyl)pyridine hydrochloride (9.02 g, 55 mmol) was added. After stirring for 6 h, the DMF was evaporated and the residue diluted with H_2O (100 mL) and extracted with CH_2Cl_2 to afford **9o** (15.00 g, 92%), mp 122–125 °C. IR (KBr) 1780, 1700, 1310, 1140 cm^{-1}; ^1H NMR (MeOD) δ 1.68 (9H, s), 5.18 (2H, s), 7.00 (1H, m), 7.12 (2H, m), 7.30 (2H, m), 7.78 (2H, m), 8.47 (1H, d, J = 7.5 Hz); MS *m/z* 326 (MH^+), 270 ($MH^+ - CH_2{=}C(CH_3)_2$), 226 (MH^+ – t-BuO_2C, base peak). Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.90. Found: C, 66.12; H, 5.90; N, 12.85.

2,3-Dihydro-3-(methanesulfonyl)-2-oxo-1*H*-benzimidazole-1-carboxylic Acid, Ethyl Ester (9p) (Method H). Methanesulfonyl chloride (667 mg, 0.45 mL, 5.8 mmol) was added dropwise to a stirred solution of **7a** (1.00 g, 4.8 mmol), Et_3N (588 mg, 0.80 mL, 5.8 mmol), and DMAP (catalytic quantity) in CH_2Cl_2 (20 mL). After 20 min, additional methanesulfonyl chloride (667 mg, 0.45 mL, 5.8 mmol) was added, the mixture stirred at room temperature for 45 min before diluting with 1 N HCl solution. The organic phase was separated, the aqueous layer was extracted with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4. Evaporation of the solvent left a white solid which was dissolved in CH_2Cl_2 and diluted with Et_2O to afford **9p** (1.25 g, 91%), mp 124–126 °C. IR (KBr) 1770, 1740, 1475, 1370, 1330, 1160 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.36 (3H, t, J = 7 Hz), 3.63 (3H, s), 4.42 (2H, q, J = 7 Hz), 7.28 (2H, m), 7.67 (1H, m), 7.85 (1H, m); MS *m/z* 285 (MH^+). Anal. Calcd for $C_{11}H_{12}N_2O_5S$: C, 46.47; H, 4.25; N, 9.85. Found: C, 46.50; H, 4.70; N, 9.67.

1,3-Dihydro-1-(phenylmethyl)-2*H*-benzimidazol-2-one (10a) (Method I). Deprotection of **9a** (1.50 g, 5 mmol) using 5 N NaOH (1 mL, 5 mmol) in EtOH (30 mL) gave **10a** (980 mg, 86%). An analytical sample recrystallized from EtOH had mp 198–200 °C. IR (KBr) 3200, 3150, 3080, 3040, 1700, 1490, 1400, 750 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.98 (2H, s), 6.85–7.05 (4H, m), 7.20–7.35 (5H, m); MS *m/z* 225 (MH^+). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.16; H, 5.53; N, 12.47.

1,3-Dihydro-1-(phenylmethyl)-5-(trifluoromethyl)-2*H*-benzimidazol-2-one (10j) (Method N). A mixture of **9d** (1.00 g, 2.6 mmol), CH_3CN (10 mL), and HCl in Et_2O (5 mL) was stirred at room temperature for 3 h, concentrated, and triturated with Et_2O to afford **10j** (0.69 g, 92%), mp 172–173 °C. IR (KBr) 1705, 1330, 1155, 1100 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.04 (2H, s), 7.10–7.40 (8H, m), 11.35 (1H, s, N*H*); MS (FAB) *m/z* 293 (MH^+). Anal. Calcd for $C_{15}H_{11}F_3N_2O$: C, 61.65; H, 3.79; N, 9.59. Found: C, 61.68; H, 3.63; N, 9.48.

1,3-Dihydro-1-(phenylmethyl)-6-(trifluoromethyl)-2*H*-benzimidazol-2-one (10k) (Method N). A mixture of **9e** (1.00 g, 2.6 mmol), CH_3CN (10 mL), and HCl in Et_2O (5 mL) was stirred at room temperature for 3 h, concentrated, and triturated with Et_2O to afford **10k** (0.58 g, 77%), mp 168–170 °C. IR (KBr) 1700, 1475, 1320 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.07 (2H, s), 7.14 (1H, d, J = 8 Hz), 7.18–7.35 (6H, m), 7.39 (1H, s), 11.42 (1H, s, N*H*); MS (FAB) *m/z* (293 (MH^+). Anal. Calcd for $C_{15}H_{11}F_3N_2O$: C, 61.65; H, 3.79; N, 9.59. Found: C, 61.25; H, 3.67; N, 9.26.

5,6-Dichloro-1,3-dihydro-1-(phenylmethyl)-2*H*-benzimidazol-2-one (10l) (Method I). A sample of **9f** (3.00 g, 8.2 mmol) was deprotected using 5 N NaOH solution (3 mL) and MeOH (100 mL) to give **10l** (2.15 g, 89%), mp 230–233 °C. IR (KBr) 1700, 1490, 710 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.99 (2H, s), 7.19 (1H, s), 7.20–7.40 (6H, m); MS *m/z* 293, 295 (MH^+). Anal. Calcd for $C_{14}H_{10}Cl_2N_2O{\cdot}0.2H_2O$: C, 56.67; H, 3.53; N, 9.44; Found: C, 56.28; H, 3.41; N, 9.37.

1,3-Dihydro-1-[(2-pyridinyl)methyl]-2*H*-benzimidazol-2-one, *p*-Toluenesulfonate Salt (10y) (Method M). A mixture of **9o** (1.63 g, 5 mmol), $TsOH{\cdot}H_2O$ (997 mg, 5.2 mmol), and CH_3CN (20 mL) was stirred at room temperature for 2 h. The solvent was evaporated and the residue triturated with Et_2O to afford **10y** (1.80 g, 90%), mp 188–190 °C. IR (KBr) 1710, 1490, 1170, 680, 560 cm^{-1}; ^1H NMR (MeOD) δ 2.33 (3H, s), 5,49 (2H, s), 7.00–7.15 (4H, m), 7.19 (2H, d, J = 8 Hz), 7.67 (2H, d, J = 8 Hz), 7.85 (1H, d, J = 8 Hz), 7.99 (1H, t, J = 7 Hz), 8.53 (1H, dt, J = 8 Hz, J' = 1.5 Hz), 8.80 (1H, dd, J = 6 Hz, J' = 1 Hz); MS *m/z* 226 (MH^+), 173 (MH^+ for TsOH). Anal. Calcd for $C_{13}H_{11}N_3O$. $C_7H_8O_3S$: C, 58.84; H, 4.90; N, 10.29. Found: C, 58.76; H, 4.85; N, 10.10.

1,3-Dihydro-1-(methylsulfonyl)-2*H*-benzimidazole-2-one (10aa) (Method K). Isopropylamine (1 mL) was added to a stirred solution of **9p** (0.90 g, 3 mmol) in THF (20 mL). After 5 min, the solvent was evaporated and the residue triturated with Et_2O and filtered to give **10aa** (450 mg, 67%). An analytical sample recrystallized from CH_2Cl_2/hexane had mp 179–181 °C. IR (KBr) 3300–2900, 1715, 1475, 1370, 1170 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.58 (3H, s), 7.07 (2H, m), 7.15 (1H, dt, J = 8.5 Hz, J' = 1.3 Hz), 7.56 (1H, dd, J = 8.5 Hz, J' = 1.3 Hz); MS *m/z* 213 (MH^+). Anal. Calcd for $C_8H_8N_2O_3S$: C, 45.28; H, 3.80; N, 13.20. Found: C, 45.10; H, 3.99; N, 13.05.

1,3-Dihydro-1-(cyclohexylmethyl)-2*H*-benzimidazol-2-one (10ae) (Method F). A sample of **7a** (2.00 g, 9.7 mmol) was alkylated with cyclohexylmethyl bromide (1.89 g, 1.45 mL, 10.7 mmol) in DMF (50 mL) at 110 °C and the crude product deprotected with 5 N NaOH in MeOH to afford **10ae** (2.00 g, 89%). An analytical sample recrystallized from THF/hexane had mp 179-181 °C. IR (KBr) 2930, 1700, 1480, 1395 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.90–1.20 (5H, m), 1.50–1.80 (6H, m), 3.58 (2H, d, J = 7.2 Hz), 6.95 (3H, m), 7.08 (1H, m); MS *m/z* 231 (MH^+). Anal. Calcd for $C_{14}H_{18}N_2O{\cdot}0.1H_2O$: C, 72.45; H, 7.90; N, 12.07. Found: C, 72.68; H, 7.99; N, 11.74.

5-Chloro-1-(cyclohexylmethyl)-1,3-dihydro-1*H*-benzimidazol-2-one (10ai) (Method G). A sample of **7h** (1.00 g, 4 mmol) was derivatized with cyclohexanemethanol (0.568 g, 0.63 mL, 5 mmol) under Mitsunobu conditions by stirring at room temperature overnight. Purification by column chromatography using hexane/Et_2O (7:3) as eluant afforded an oil (1.20 g) which was deprotected to give **10ai** (0.84 g, 77%). An analytical sample recrystallized from CH_2Cl_2 and hexane and had mp 194–197 °C. IR (KBr) 2915, 1710, 1490, 1395, 1140 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.85–1.20 (5H, m), 1.50–1.80 (6H, m), 3.58 (2H, d, J = 7.3 Hz), 6.90–7.10 (2H, m), 7.10 (1H, d, J = 8.4 Hz); MS *m/z* 265, 267 (MH^+). Anal. Calcd for $C_{14}H_{17}ClN_2O$: C, 63.51; H, 6.47; N, 10.58. Found: C, 63.50; H, 6.49; N, 10.54.

2,3-Dihydro-2-oxo-1*H*-imidazo[4,5-*b*]pyridine-1-carboxylic Acid, Ethyl Ester (12). A mixture of **11** (10.00 g, 74 mmol), ethyl 2-pyridyl carbonate[36] (16.60 g, 99 mmol), K_2CO_3 (13.70 g, 99 mmol), and CH_3CN (200 mL) was stirred at reflux for 90 min. The mixture was concentrated *in vacuo*, diluted with H_2O and 1 N HCl solution until pH = 1 and filtered to give **12** (12.15 g, 90%), mp 204–206 °C (EtOH). IR (KBr) 1770, 1725 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.33 (3H, t, J = 7 Hz), 4.36 (2H, q, J = 7 Hz), 7.04 (1H, ABq), 7.82 (1H, dd, J = 8 Hz, J' = 1.5 Hz), 8.01 (1H, dd, J = 5 Hz, J' = 1.5 Hz), 11.93 (1H, bs, N*H*); MS *m/z* 208 (MH^+). Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.05; H, 4.34; N, 20.20.

2-(Phenylmethoxy)-1*H*-imidazo[4,5-*b*]pyridine (13a) and 3-(phenylmethyl)-2,3-dihydro-2-oxo-1*H*-imidazo[4,5-*b*]-pyridine-1-carboxylic Acid, Ethyl Ester (14a). A sample of **12** (2.50 g, 12 mmol) was alkylated with benzyl bromide in CH_3CN (50 mL) at reflux for 30 min. The mixture was cooled, poured onto H_2O, and filtered to give a white solid (1.05 g, 29%) which was recrystallized from MeOH to afford **13a** (0.50 g, 62% based on 1.05 g of the ester), mp 245–247 °C. IR (KBr) 1680, 1655, 1590, 1580, 1515 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.45 (2H, s), 6.62 (1H, t, J = 7 Hz), 6.98 (1H, dd, J = 7 Hz, J' = 1 Hz), 7.25-7.45 (5H, m), 7.66 (1H, dd, J = 7 Hz, J' = 1 Hz) 10.66 (1H, bs, NH); MS *m/z* 226 (MH^+). Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.00; H, 4.86; N, 18.60.

The aqueous layer was extracted with Et_2O and the residual oil chromatographed on a column of silica gel using a mixture of Et_2O and hexane (1:1) as eluant to furnish **14a** (2.15 g, 59%), mp 74–76 °C. IR (KBr) 1795, 1755, 1610, 1595, 1480, 1460, 1380, 1280 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.34 (3H, t, J = 7 Hz), 4.39 (2H, q, J = 7 Hz), 5.01 (2H, s), 7.14 (1H, dd, J = 7.8 Hz, J' = 5 Hz), 7.17–7.40 (5H, m), 7.91 (1H, dd, J = 7.8 Hz, J' = 1.4 Hz), 8.09 (1H, dd, J = 5 Hz, J' = 1.4 Hz); MS *m/z* 298 (MH^+). Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.08; N, 14.13. Found: C, 64.76; H, 5.08; N, 13.92.

1,3-Dihydro-3-(phenylmethyl)-2*H*-imidazo[4,5-*b*]pyridin-2-one (16a). A sample of **14a** (1.50 g, 5 mmol) was deprotected using 5 N NaOH solution (2 mL) in MeOH (40 mL) to afford **16a** (1.05 g, 92%), mp 171–173 °C (CH_2Cl_2/MeOH/hexane). IR (KBr) 1730, 1700, 1465, 765, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.00 (2H, s), 6.99 (1H, ABq), 7.15–7.30 (6H, m), 7.91 (1H, dd, J = 7.8 Hz, J' = 1.25 Hz), 11.21 (1H, s, N*H*); MS *m/z* 226 (MH^+). Anal. Calcd for $C_{13}H_{11}N_3O{\cdot}0.1H_2O$: C, 68.77; H, 4.97; N, 18.51. Found: C, 68.64; H, 4.76; N, 18.14.

Ethyl 3-(Cyclohexylmethyl)-2,3-dihydro-2-oxo-1*H*-imidazo[4,5-*b*]pyridine-1-carboxylate (14b). A sample of **12** (2.50 g, 12 mmol) was alkylated with cyclohexymethyl bromide in DMF (50 mL) at 110 °C for 30 min to afford **14b** (2.74 g, 75%) after chromatography on a column of silica gel using hexane and Et_2O (3:2) as eluant, mp 94–96 °C. IR (KBr) 3010, 2960, 1790, 1760, 1730, 1615, 1600, 1480, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95–1.30 (5H, m), 1.46 (3H, t, J = 7 Hz), 1.50–1.70 (5H, m), 1.98 (1H, m), 3.77 (1H, d, J = 7.5 Hz), 4.49 (2H, q, J = 7 Hz), 7.03 (1H, ABq), 7.99 (1H, dd, J = 7.8 Hz, J' = 1.4 Hz), 8.11 (1H, dd, J = 5 Hz, J' = 1.4 Hz); MS *m/z* 304 (MH^+). Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C; 63.33; H, 7.04; N, 13.87.

3-(Cyclohexylmethyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridine-2-one (16b). A sample of **14b** (2.00 g, 6.6 mmol) was deprotected using 5 N NaOH solution in MeOH (40 mL) and H_2O (10 mL) to furnish **16b** (1.22 g, 80%), mp 206–208 °C. IR (KBr) 2930, 1730, 1490, 760 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.85–1.20 (5H, m), 1.50–1.70 (5H, m), 1.87 (1H, m), 3.63 (1H, d, J = 7.3 Hz), 6.96 (1H, ABq), 7.26 (1H, dd, J = 7.7 Hz, J' = 1.4 Hz), 7.90 (1H, dd, J = 5 Hz, J' = 1.4 Hz); MS *m/z* 232 (MH^+). Anal. Calcd for $C_{13}H_{17}N_3O{\cdot}0.2H_2O$: C, 66.47; H, 7.47; N, 17.89. Found: C, 66.54; H, 7.33; N, 17.82.

1,2-Dihydro-2-oxo-3*H*-imidazo[4,5-*b*]pyridine-3-carboxylic Acid, 1,1-Dimethylethyl Ester (17). DMAP (catalytic amount) was added to a stirred solution of **12** (5.00 g, 24 mmol) and di-*tert*-butyl dicarbonate (6.32 g, 29 mmol) in dry THF (75 mL). After 1 h, i-$PrNH_2$ (2.57 g, 3.75 mL, 29 mmol) was added and the mixture stirred for 20 min. The solvent was evaporated and the residual solid triturated with Et_2O to give **17** (4.20 g, 74%). An analytical sample recrystallized from CH_2Cl_2 and hexane had mp 262–263 °C (dec, shrank at 150–160 °C). IR (KBr) 3100, 1760, 1740, 1450, 1150 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.55 (9H, s), 7.12 (1H, dd, J = 7.8 Hz, J' = 5 Hz), 7.32 (1H, dd, J = 7.8 Hz, J' = 1.4 Hz), 7.99 (1H, dd, J = 5 Hz, J' = 1.4 Hz), 11.39 (1H, bs, N*H*); MS *m/z* 236 (MH^+), 136 ($MH^+ - CO_2{}^t$Bu, base peak). Anal. Calcd for $C_{11}H_{13}N_3O_3{\cdot}0.1H_2O$: C, 55.74; H, 5.61; N, 17.73. Found: C, 55.64; H, 5.51; N, 17.85.

1,3-Dihydro-1-(phenylmethyl)-2*H*-imidazo[4,5-*b*]pyridin-2-one (19a). A sample of **17** (350 mg, 1.5 mmol) was alkylated with benzyl bromide to give an oil: ^1H NMR ($CDCl_3$) δ 1.59 (9H, s), 5.10 (2H, s), 7.18 (1H, dd, J = 7.8 Hz, J' = 5 Hz), 7.24–7.40 (5H, m), 7.52 (1H, d, J = 7.8 Hz), 8.08 (1H, d, J = 5 Hz). This material was deprotected by dissolving in CF_3CO_2H (5 mL) to furnish **19a** (250 mg, 74%), mp 166–168 °C. IR (KBr) 3150–2900, 1700, 1625, 1605, 1450, 1150, 735 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.00 (2H, s), 6.95 (1H, dd, J = 7.4 Hz, J' = 5 Hz), 7.20–7.40 (6H, m), 7.88 (1H, dd, J = 5 Hz, J' = 1.3 Hz), 11.65 (1H, bs, N*H*); MS *m/z* 226 (MH^+). Anal. Calcd for $C_{13}H_{11}N_3O{\cdot}0.25H_2O$: C, 67.96; H, 5.05; N, 18.29. Found: C, 68.38; H, 5.09; N, 17.64.

1-(Cyclohexymethyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (19b). A sample of **17** (1.50 g, 6.3 mmol) was reacted with cyclohexylmethyl alcohol (873 mg, 7.6 mmol) in dry THF (30 mL) under Mitsunobu conditions for 17 h. The residue was chromatographed on a column of silica gel using a mixture of hexane and Et_2O (3:2) as eluant to give an oil which was deprotected using 5 N NaOH solution (2 mL) in MeOH (20 mL). Trituration of the resultant oil with Et_2O afforded **19b** (930 mg, 63%), mp 137–140 °C. IR (KBr) 3420, 2930, 1730, 1700, 1625, 1460, 1140 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.85–1.25 (5H, m), 1.50–1.90 (6H, m), 3.60 (2H, d, J = 7.2 Hz), 6.96 (1H, dd, J = 7.8 Hz, J' = 5 Hz), 7.41 (1H, dd, J = 7.8 Hz, J' = 1.3 Hz), 7.86 (1H, dd, J = 5 Hz, J' = 1.3 Hz), 11.49 (1H, bs, N*H*); MS *m/z* 232 (MH^+). Anal. Calcd for $C_{13}H_{17}N_3O{\cdot}0.5H_2O$: C, 64.98; H, 7.55; N, 17.49. Found: C, 65.13; H, 7.37; N, 17.47.

Ethyl 2,3-Dihydro-7-[(4-methoxy-4-oxobutyl)oxy]-2-oxo-1*H*-imidazo[4,5-*b*]quinoline-1-carboxylate (21a). A mixture of **20a** (1.00 g, 3 mmol), ethyl 4-nitrophenyl carbonate (0.84 g, 5 mmol), K_2CO_3 (0.96 g, 7 mmol), and DMF (15 mL) was stirred at 110 °C under an atmosphere of nitrogen. After 30 min, the mixture was cooled and diluted with water and a white solid filtered off. Recrystallization from a mixture of *i*-PrOH and CH_2Cl_2 gave **21a** (0.56 g, 45%), mp 223–226 °C. IR (KBr) 1800, 1780, 1740, cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.38 (3H, t, J = 7 Hz), 2.02 (2H, quintet, J = 7 Hz), 2.50 (2H, t, J = 7 Hz), 3.60 (3H, s), 4.07 (2H, t, J = 7 Hz), 4.42 (2H, q, 7 Hz), 7.22 (1 H, dd, J = 9 Hz, J' = 2.3 Hz), 7.44 (1H, d, J = 2.3 Hz), 7.69 (1H, d, J = 9 Hz), 8.24 (1H, s), 12.01 (1H, bs, NH); MS *m/z* 374 (MH^+). Anal. Calcd for $C_{18}H_{19}N_3O_6$: C, 57.91; H, 5.13; N, 11.25. Found: C, 57.81; H, 5.28; N, 11.44.

Ethyl 2,3-Dihydro-2-oxo-7-[[4-(phenylsulfonyl)butyl]-oxy]-1*H*-imidazo[4,5-*b*]quinoline-1-carboxylate (21b). NaH (0.53 g of a 50% dispersion in mineral oil, 11 mmol) was washed twice with hexanes and covered with dry THF (50 mL), and **20b** (2.00 g, 5 mmol) was added. The mixture was stirred for 15 min before adding ethyl 4-nitrophenyl carbonate (1.27 g, 6 mmol) and then stirred overnight at room temperature. After diluting with 1 N HCl solution, the mixture was extracted with CH_2Cl_2 to give a solid which was dissolved in hot $CHCl_3$ containing a small amount of MeOH and diluted with Et_2O to provide **21b** (1.45 g, 82%), mp 229–231 °C. IR (KBr) 1790, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.41 (3H, t, J = 7 Hz), 1.60 to 2.00 (4H, m), 3.43 (2H, t, J = 8 Hz), 4.07 (2H, t, J = 6 Hz), 4.46 (2H, q, J = 7 Hz), 7.21 (1H, dd, J = 9 Hz, J' = 2.5 Hz), 7.43 (1H, d, J = 2.5 Hz), 7.55 to 8.00 (6H, m), 8.24 (1H, s); MS *m/z* 470 (MH^+). Anal. Calcd for $C_{23}H_{23}N_3O_6$: C, 58.84; H, 4.94; N, 8.95. Found: C, 58.37; H, 4.97; N, 8.71.

1,2-Dihydro-2-oxo-3*H*-imidazo[4,5-*c*]pyridine-3-carboxylic acid, 1,1-Dimethylethyl Ester (23). NaH (3.52 g of a 60% dispersion in oil, 88 mmol) was added portionwise to a stirred suspension of **22** (11.3 g, 84 mmol) in dry DMF (80 mL). After 10 min, the mixture was cooled in an ice bath and a solution of di-*tert*-butyl dicarbonate (20.10 g, 92 mmol) in dry DMF (20 mL) added dropwise. The mixture was stirred at room temperature for 2 h, concentrated to about one-third of the original volume, and diluted with 5% $NaHCO_3$ solution (150 mL). The mixture was extracted with EtOAc and concentrated to approximately 100 mL. Filtration afforded **23** (9.78 g, 50%), mp 158–160 °C. IR (KBr) 1800, 1610, 1595, 1484, 1340, 1140 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.57 (9H, s), 7.01 (1H, d, J = 5 Hz), 8.23 (1H, d, J = 5 Hz), 8.66 (1H, s); MS *m/z* 236 (MH^+), 136 (MH^+ – Boc, base peak). Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 55.99; H, 5.55; N, 17.70.

3-(Phenylmethyl)-2,3-dihydro-2-oxo-1*H*-imidazo[4,5-*c*]pyridine-1-carboxylic Acid, 1,1-Dimethylethyl Ester (25a). A sample of **23** (705 mg, 3 mmol) was reacted with benzyl alcohol in dry THF (25 mL) for 1 h under Mitsunobu conditions to afford **25a** (689 mg, 70%), mp 123–125 °C, after chromatography on a column of silica gel using a mixture of hexane and EtOAc (3:1) as eluant. IR (KBr) 1750, 1610, 1595, 1490, 1360, 1140 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.60 (9H, s), 5.04 (2H, s); 7.20–7.40 (6H, m), 8.30 (1H, d, J = 5 Hz), 8.77 (1H, s); MS *m/z* 326 (MH^+), 270 ($MH^+ - (CH_3)_2C{=}CH_2$), 226 (MH^+ – Boc). Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.46; H, 6.02; N, 12.85.

1,3-Dihydro-1-(phenylmethyl)-2*H*-imidazo[4,5-*c*]pyridin-2-one Hydrochloride (26a). A sample of **25a** (509 mg, 1.6 mmol) was deprotected in 1 N HCl in MeOH solution (10 mL) at reflux for 2 h to afford **26a** (343 mg, 87%), mp 267–269 °C. IR (KBr) 3080, 2700, 1750, 1630, 1520, 830 cm^{-1}; ^1H NMR (D_2O) δ 5.06 (2H, s), 7.10–7.25 (5H, m), 7.45 (1H, d, J = 5 Hz), 8.24 (1H, d, J = 5 Hz), 8.40 (1H, s); MS *m/z* 226 (MH^+). Anal. Calcd for $C_{13}H_{11}N_3O$. $HCl{\cdot}0.1H_2O$: C, 59.48; H, 4.30; N, 16.00. Found: C, 59.28; H, 4.29; N, 15.98.

1-(Cyclohexylmethyl)-1,2-dihydro-2-oxo-3*H*-imidazo-[4,5-*c*]pyridine-3-carboxylic Acid, 1,1-Dimethylethyl Ester (25b). A sample of **23** (940 mg, 4 mmol) was reacted with cyclohexylmethyl alcohol in dry THF (25 mL) under Mitsunobu conditions for 1 h and the crude material chromatographed on a column of silica gel. Elution with a mixture of hexane and EtOAc (4:1) afforded **25b** (1.04 g, 79%), mp 142–143 °C.

IR (KBr) 3040, 1760, 1730, 1610, 1595, 1495, 1160, 1120 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.90–1.20 (5H, m), 1.59 (9H, s), 1.50–1.80 (6H, m), 3.62 (2H, d, J = 7.2 Hz), 7.33 (1H, d, J = 5 Hz), 8.32 (1H, J = 5 Hz), 8.74 (1H, s); MS m/z 332 (MH^+), 276 ($MH^+ - (CH_3)_2C{=}CH_2$), 232 (MH^+ – Boc). Anal. Calcd for $C_{18}H_{25}N_3O_3$: C, 65.24; H, 7.60; N, 12.68. Found: C, 65.15; H, 7.54; N, 12.66.

1-(Cyclohexylmethyl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]pyridin-2-one Hydrochloride (26b). A sample of **25b** (296 mg, 0.9 mmol) was deprotected by stirring at room temperature in 3 N HCl in MeOH solution (5 mL) to afford **26b** (242 mg, 100%), mp 265–267 °C. IR (KBr) 2930, 1740, 1610, 1510 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.90–1.20 (5H, m), 1.50–1.90 (6H, m), 3.77 (2H, d, J = 7.2 Hz), 7.82 (1H, d, J = 5 Hz), 8.49 (2H, m), 12.44 (1H, bs, N*H*); MS m/z 232 (MH^+). Anal. Calcd for $C_{13}H_{17}N_3O$. HCl: C, 58.32; H, 6.78; N, 15.69. Found: C, 58.27; H, 6.43; N, 15.62.

1-(2-Methoxyethyl)-1,3-dihydro-2*H*-imidazo[4,5-*c*]pyridin-2-one Hydrochloride (26c). A sample of **23** (705 mg, 3 mmol) was reacted with 2-methoxyethanol under Mitsunobu conditions in dry THF (10 mL) for 1 h. The crude product was chromatographed on a column of silica gel, eluting with a mixture of hexane and EtOAc (3:1), to afford the alkylated product (770 mg) which was contaminated with $Ph_3P{=}O$ (approximately 14% by ^1H NMR). ^1H NMR (DMSO-d_6) δ 1.58 (9H, s), 3.31 (3H, s), 3.57 (2H, t, J = 5 Hz), 3.97 (2H, t, J = 5 Hz), 7.32 (1H, d, J = 5 Hz), 8.32 (1H, d, J = 5 Hz), 8.74 (1H, s); MS m/z 294 (MH^+). A sample of this material (579 mg) was deprotected without further purification by dissolution in 3 N HCl in MeOH (10 mL) for 72 h to give **26c** (359 mg, 94%), mp 201–203 °C. IR (KBr) 1730 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.20 (3H, s), 3.60 (2H, t, J = 5 Hz), 4.12 (2H, t, J = 5 Hz), 7.74 (1H, d, J = 5 Hz), 8.50 (2H, m), 12.48 (1H, bs, N*H*); MS m/z 194 (MH^+). Anal. Calcd for $C_9H_{11}N_3O_2{\cdot}HCl{\cdot}0.1H_2O$: C, 46.70; H, 5.31; N, 18.15. Found: C, 46.57; H, 5.25; N, 18.10.

Ethyl 2,3-Dihydro-2-oxo-4-phenyl-1*H*-imidazole-1-carboxylate (28). A mixture of **27** (10.00 g, 60 mmol), ethyl 2-pyridyl carbonate[36] (12.50 g, 70 mmol), K_2CO_3 (10.34 g, 70 mmol), and DMF (250 mL) was stirred at 75 °C for 25 min. The mixture was poured onto 1 N HCl solution (1000 mL) and filtered to afford **28** (13.80 g, 95%). An analytical sample recrystallized from CH_3CN had mp 211–214 °C. IR (KBr) 1740, 1720, 1375, 1295, 1220 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.30 (3H, t, J = 7 Hz), 4.30 (2H, q, J = 7 Hz), 7.20–7.30 (2H, m), 7.38 (2H, t, J = 7.2 Hz), 7.63 (2H, dd, J = 7.2 Hz, J' = 1.25 Hz), 11.13 (1H, s, N*H*); MS m/z 233 (MH^+). Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.81; H, 5.18; N, 12.00.

2-Oxo-4-phenyl-1*H*-imidazole-1,3(2*H*)-dicarboxylic Acid, 1-Ethyl-3-(1,1-dimethylethyl) Ester (30). Di-*tert*-butyl dicarbonate (2.25 g, 10 mmol) was added to a stirred solution of **28** (2.00 g, 10 mmol) and DMAP (catalytic quantity) in dry THF (40 mL). After 18 h, the mixture was heated to reflux for 1 h, additional di-*tert*-butyl dicarbonate (0.30 g, 1.3 mmol) added, and the mixture heated at reflux for 1 h. After cooling, unreacted imidazolone starting material (0.50 g) was filtered off and the filtrate concentrated and chromatographed on a column of silica gel. Elution with a mixture of Et_2O and hexane (2:1) afforded **30** (1.71 g, 80% based on recovered starting material), mp 95–97 °C. IR (KBr) 1820, 1760, 1370, 1360, 1250, 1230 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.21 (9H, s), 1.27 (3H, t, J = 7 Hz), 4.31 (2H, q, J = 7 Hz), 6.99 (1H, s), 7.30–7.45 (5H, m); MS m/z 333 (MH^+), 277 ($MH^+ - CH_2{=}(CH_3)_2$), 233 ($MH^+ - CO_2{}^t$Bu). Anal. Calcd for $C_{17}H_{20}N_2O_5{\cdot}0.1H_2O$: C, 61.11; H, 6.09; N, 8.38. Found: C, 60.80; H, 5.95; N, 8.10.

2,3-Dihydro-2-oxo-5-phenyl-1*H*-imidazole-1-carboxylic Acid, 1,1-Dimethylethyl Ester (31). Di-*tert*-butyl dicarbonate (7.05 g, 32 mmol) was added to a stirred solution of **28** (5.00 g, 21 mmol) and DMAP (catalytic quantity) in dry THF (80 mL), and the mixture was stirred at room temperature for 15 min and then heated to reflux. After 1.5 h, the mixture was cooled, i-$PrNH_2$ (8 mL) added and the mixture stirred at room temperature for 15 min. The solvent was evaporated and the residue was triturated with hexane to afford **31** (4.00 g, 71%). An analytical sample recrystallized from CH_2Cl_2 and hexane had mp 153–155 °C dec. IR (KBr) 3320, 1780, 1755, 1310, 1145, 1070 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.21 (9H, s), 6.61 (1H, d, J = 2.5 Hz), 7.20–7.40 (5H, m), 10.54 (1H, bs, N*H*); MS m/z 261 (MH^+), 205 ($MH^+ - (CH_3)_2C{=}CH_2$), base peak), 161 ($MH^+ - CO_2{}^t$Bu). Anal. Calcd for $C_{14}H_{16}N_2O_3{\cdot}0.1H_2O$: C, 64.16; H, 6.23; N, 10.69. Found: C, 64.03; H, 6.08; N, 10.56.

1,3-Dihydro-4-phenyl-1-(phenylmethyl)-2*H*-imidazol-2-one (32a). A sample of **31** (1.00 g, 3.8 mmol) was alkylated with benzyl bromide in CH_3CN (15 mL) at reflux for 30 min and the crude product deprotected by dissolving in CF_3CO_2H (10 mL). Recrystallization from CH_2Cl_2 and hexane afforded **32a** (0.55 g, 57%), mp 253–255 °C. IR (KBr) 1675, 1455, 720, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.73 (2H, s), 7.05 (1H, d, J = 1.6 Hz), 7.16 (1H, dt, J = 8 Hz, J' = 1.5 Hz), 7.20–7.40 (7H, m), 7.47 (2H, dd, J = 7 Hz, J' = 1.5 Hz), 10.79 (1H, bs, N*H*); MS m/z 251 (MH^+). Anal. Calcd for $C_{16}H_{14}N_2O{\cdot}0.2H_2O$: C, 75.69; H, 5.72; N, 11.03. Found: C, 75.63; H, 5.64; N, 11.20.

X-ray Structural Determinations. X-ray diffraction experiments were performed at room temperature on a Enraf-Nonius CAD4 diffractometer using graphite-monochromated Cu Kα radiation (λ = 1.5418 Å). Unit cell constants were obtained from a least-squares fit to data for 25 well-centered reflections. The intensity data were measured using $\omega/2\theta$ scan modes. Lorentz and polarization effects were corrected and empirical absorption corrections were applied based on φ-scans of selected reflections. The structures were solved by direct methods and were refined by full-matrix least-squares techniques using computer software MolEN.[81] Although all hydrogen atoms were observed in difference electron density maps, only hydroxyl hydrogens were located from the maps and positions of the other hydrogen atoms were calculated from an idealized geometry with standard bond lengths and angles. They were given isotropic temperature factors and were included in structure factor calculations with fixed parameters. Final refinements included the following variables: a scale factor, an extinction coefficient, atomic coordinates, and anisotropic temperature factors for non-hydrogen atoms. The final difference electron density map showed no recognizable residual features.[82]

Acknowledgment. We extend our gratitude to C. M. Combs, S. Huang, and M. D'Andrea for performing and interpreting NMR experiments and for helpful discussions. M. Cadiz is thanked for providing mass spectral data, and Dr. Yi Li is acknowledged for stimulating discussions. We thank S. Drechsler for help in preparing the manuscript.

Supplementary Material Available: Preparative procedures and spectroscopic and analytical data for compounds listed in Tables 1–3 (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; ordering information is given on any current masthead page.

JO941767A

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(82) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.