One-Pot Reactions of *N*-(Mesyloxy)phthalimides with Secondary Amines to 2-Ureidobenzamides, 2-Ureidobenzoic Acids, Ethyl 2-Ureidobenzoates, or Isatoic Anhydrides

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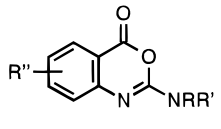
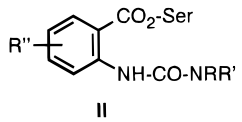
The reaction of *N*-(mesyloxy)phthalimides with secondary amines was examined. Transformations are accomplished by one-pot reactions to optionally afford corresponding 2-ureidobenzamides, 2-ureidobenzoic acids, ethyl 2-ureidobenzoates, or isatoic anhydrides, respectively. The mechanism of the acid-catalyzed hydrolysis (or alcoholysis) of intermediate 2-ureidobenzamides to 2-ureidobenzoic acids (or esters) is discussed. A proton transfer mechanism involving the ureido moiety as an internal acid catalyst is proposed. Intermediate 2-ureidobenzoic acids undergo a further transformation to isatoic anhydrides. The utilization of the obtained 2-ureidobenzamides, 2-ureidobenzoic acids, and ethyl 2-ureidobenzoates to prepare 3,1-benzoxazin-4-ones is demonstrated.

Introduction

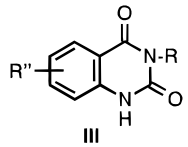
4*H*-3,1-Benzoxazin-4-ones have attracted considerable attention as inhibitors of serine proteases. The interaction of 3,1-benzoxazin-4-ones with serine proteases involves enzyme acylation due to the nucleophilic attack of the active site serine on the lactone carbon, ring cleavage, and the subsequent deacylation of the acyl-enzyme formed. For such acyl-enzyme inhibitors (alternate substrate inhibitors), strong inhibition can be achieved by increasing the rate of acylation as well as decreasing the rate of deacylation. Efforts have focused on improving both the kinetic parameters of enzyme inhibition and intrinsic stability (in aqueous hydrolysis). Introduction of 2-amino substituents has been used as a successful strategy to improve the chemical stability of benzoxazin-4-ones[1] and isosteric thieno[2,3-*d*][1,3]oxazin-4-ones.[2] The inhibition of amino-substituted benzoxazinones **I** toward human leukocyte elastase,[1,3,4] human cathepsin G,[5] chymotrypsin,[5−7] C1r serine protease of the complement system,[8] thrombin,[9] and human cytomegalovirus protease[10] has been reported. The deacylation of acyl-enzymes **II** (Ser-OH = active site serine) formed in the reaction of amino-substituted benzoxazinones **I** with serine proteases can favorably be decelerated by preventing an intramolecular quinazoline cyclization to **III**. This can be achieved either by introduction of branched substituents R (R′ = H) or with 2-*sec*-amino substituted benzoxazinones **I** (R, R′ ≠ H).[1−6] Therefore, 2-*sec*-aminobenzoxazinone represents an attractive structure for the ongoing efforts in the design of serine protease inhibitors.



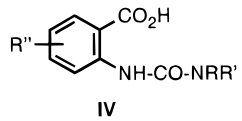
I



II



III



IV

Compounds **I** (R, R′ ≠ H) were usually obtained by cyclocondensation of ureidobenzoic acids **IV** on treatment with concd H_2SO_4 or carbodiimides.[1,7,8,11] The precursors **IV** (R, R′ ≠ H) can be prepared either by the reaction of isatoic anhydrides with secondary amines[12] or by alkaline hydrolysis of the corresponding alkyl 2-ureidoben-

(1) Krantz, A.; Spencer, R. W.; Tam, T. F.; Liak, T. J.; Copp, L. J.; Thomas, E. M.; Rafferty, S. P. *J. Med. Chem.* **1990**, *33*, 464.
(2) Gütschow, M.; Neumann, U. *J. Med. Chem.* **1998**, *41*, 1729.
(3) Krantz, A.; Spencer, R. W.; Tam, T. F.; Thomas, E.; Copp, L. J. *J. Med. Chem.* **1987**, *30*, 589.
(4) (a) Uejima, Y.; Kokubo, M.; Oshida, J.; Kawabata, H.; Kato, Y.; Fujii, K. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 516. (b) Uejima, Y.; Oshida, J.; Kawabata, H.; Kokubo, M.; Kato, Y.; Fujii, K. *Biochem. Pharmacol.* **1994**, *48*, 426.
(5) Gütschow, M.; Neumann, U. *Bioorg. Med. Chem.* **1997**, *5*, 1935.
(6) Neumann, U.; Gütschow, M. *Bioorg. Chem.* **1995**, *23*, 72.
(7) Hedstrom, L.; Moorman, A. R.; Dobbs, J.; Abeles, R. H. *Biochemistry* **1984**, *23*, 1753.
(8) Hays, S. J.; Caprathe, B. W.; Gilmore, J. L.; Amin, N.; Emmerling, M. R.; Michael, W.; Nadimpalli, R.; Nath, R.; Raser, K. J.; Stafford, D.; Watson, D.; Wang, K.; Jaen, J. C. *J. Med. Chem.* **1998**, *41*, 1060.
(9) Brown, A. D.; Powers, J. C. *Bioorg. Med. Chem.* **1995**, *3*, 1091.
(10) Abood, N. A.; Schretzman, L. A.; Flynn, D. L.; Houseman, K. A.; Wittwer, A. J.; Dilworth, V. M.; Hippenmeyer, P. J.; Holwerda, B. C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2105.

(11) Other synthetic routes to **I** (R, R′ ≠ H): (a) From anthranilic acid via 2-benzotriazolyl-4*H*-3,1- benzoxazin-4-one: Butula, I.; Vela, V.; Zorc, B. *Croat. Chem. Acta* **1981**, *54*, 105. (b) From isatoic anhydride via 2-isothiocyanatobenzoyl chloride: Ulrich, H.; Tucker, B.; Sayigh, A. A. R. *J. Org. Chem.* **1967**, *32*, 4052. (c) From methyl 2-aminobenzoate via 2-methoxycarbonylphenylcarbamoyl chloride: ref 1. (d) From methyl 2-aminobenzoate and phosgene−iminium salts: Bitter, I.; Szöcs. L.; Töke, L. *Acta Chim. Acad. Hung.* **1981**, *107*, 57.
(12) The reaction of isatoic anhydrides with amines (or alcohols) produce two different types of products, 2-aminobenzamides (or alkyl esters) and 2-ureidobenzoic acids (or 2-alkoxycarbonylaminobenzoic acids) depending on the nucleophile and the reaction conditions. For examples see: (a) Staiger, R. P.; Wagner, E. C. *J. Org. Chem.* **1953**, *18*, 1427. (b) Bunnett, J. F.; Naff, M. B. *J. Am. Chem. Soc.* **1966**, *88*, 4001. (c) Hegarty, A. F.; Ahern, E. P.; Frost, L. N.; Hegarthy, C. N. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1935. (d) Coppola, G. M. *Synthesis* **1980**, 505. (e) Kappe, T.; Stadlbauer, W. *Adv. Heterocycl. Chem.* **1981**, *28*, 127. (f) Heyman, D. *J. Heterocycl. Chem.* **1978**, *15*, 1131. (g) Hinman, C.; Vaughan, K. *Synthesis* **1980**, 719.

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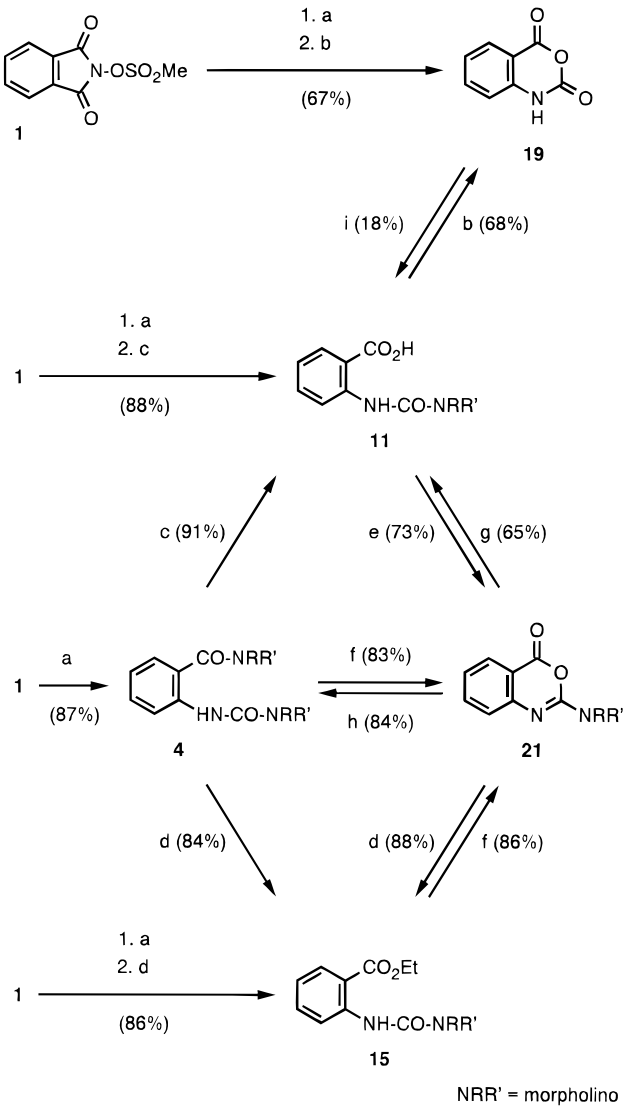
Scheme 1[a]



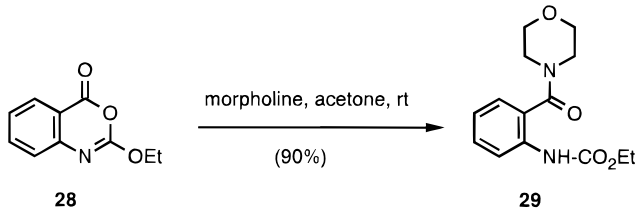
[a] Reagents and conditions: (a) morpholine, acetone, reflux, 25 min; (b) 0.25 M HCl, reflux, 2 min; then 5 °C; (c) 0.25 M HCl, 5 °C, 14 d; (d) 0.25 M ethanolic HCl, reflux, 2 min; then −15 °C; (e) acetic anhydride reflux, 15 min; (f) concd H_2SO_4, rt; (g) Na_2CO_3, H_2O, acetone, rt, 16 h; (h) morpholine, acetone, rt, 24 h; (i) morpholine, H_2O, rt, 15 min.

zoates.[1,8] To extend these synthetic methods to precursors of 2-*sec*-aminobenzoxazinones the reaction of *N*-(mesyloxy)phthalimides with secondary amines was investigated and is described in this report. The reaction of *N*-(mesyloxy)phthalimide with morpholine was chosen as a model reaction. The mechanisms of the observed transformations are discussed and some applications with substituted *N*-(mesyloxy)phthalimides and other secondary amines are described. The utilization of the precursors to synthesize 2-*sec*-aminobenzoxazinones is also reported herein.

Results and Discussion

Scheme 1 summarizes the transformations which occur as a result of the reaction of *N*-(mesyloxy)phthalimide **1** with morpholine under different conditions. A mixture of **1**, morpholine, and acetone was refluxed, the solvent was evaporated, and the residue was boiled in 0.25 M HCl for a short time. The precipitate formed was shown to be pure isatoic anhydride **19**. Clearly, the unexpected formation of **19** is a result of a consecutive transformation, and the intermediates were elucidated as follows. First, the reaction was carried out under similar conditions, and the residue was treated with 0.25 M HCl, but cooled for several days instead of being heated to produce the pure ureidobenzoic acid **11**. Compound **11** was found to be converted in boiling HCl to isatoic anhydride **19**, indicating **11** as an intermediate of the transformation of **1** to **19**. When **1** was reacted with morpholine and the mixture was not treated with HCl, the ureidobenzamide **4** was formed. Addition of HCl to **4** led to the formation of the ureidobenzoic acid **11** when the cooled mixture was stored for several days. Thus, **4** is the first intermediate of the transformation of **1** to **19**.

Scheme 2



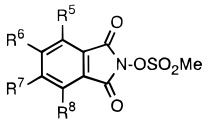
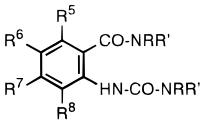
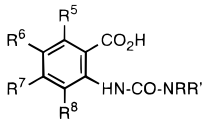
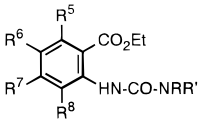
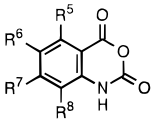
The reaction of **1** with morpholine followed by treatment with ethanolic HCl yielded the ethyl 2-ureidobenzoate **15** in high purity. Again, the transformation occurs via the ureidobenzamide **4**, which was found to be converted to **15** upon treatment with ethanolic HCl. To elucidate structure **15** unambiguously, the isomeric carbamate **29** was prepared from **28** (Scheme 2) and proved to be distinct from **15**.

The three urea derivatives obtained could easily be converted to 2-morpholino-3,1-benzoxazin-4-one **21**: For that, compound **11** was treated with acetic anhydride, and compound **4** and **15**, respectively, with concd H_2SO_4 (Scheme 1). In each case, the final benzoxazinone **21** was obtained in high purity. Under both basic or acidic conditions, **21** underwent a ring cleavage as a result of the attack of the corresponding nucleophile at the lactone structure. Thus, alkaline hydrolysis of **21** furnished **11**, reaction with morpholine gave **4**, and treatment with ethanolic HCl yielded **15**.

On the basis of the results shown in Scheme 1, one-pot reactions were applied to prepare isatoic anhydride **19** also from pyrrolidine, diethylamine, respectively, and *N*-(mesyloxy)phthalimide **1** (Table 1). Accordingly, the dimethyl-substituted isatoic anhydride **20** was obtained from **2** and morpholine. The 2-ureidobenzamides **5**−**9**, 2-ureidobenzoic acids **12**−**14**, and ethyl 2-ureidobenzoates **16**−**18** could be prepared conveniently by one-pot reactions from *N*-(mesyloxy)phthalimides **1**−**3** and appropriate secondary amines (Table 1). The resulting urea derivatives were used as substrates to synthesize 2-*sec*-amino-4*H*-3,1-benzoxazin-4-ones. These results are summarized in Table 2. The conditions for the cyclization of the corresponding morpholino derivatives **4**, **11**, and **15** to prepare morpholinobenzoxazinon **21** (Scheme 1) were applied to the synthesis of benzoxazinones **22**−**27** from various precursors.

The reaction of *N*-(mesyloxy)phthalimide **1** with morpholine (Scheme 1) to isatoic anhydride **19** via **4** and **11** was unexpected in the light of the mild conditions used.

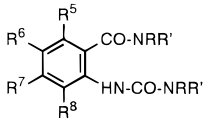
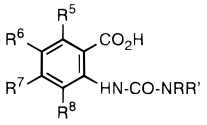
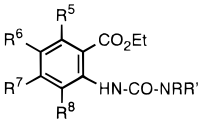
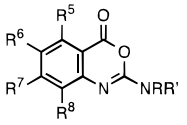
Table 1. Transformations of *N*-(Mesyloxy)phthalimides 1−3 to 2-Ureidobenzamides 4−9, 2-Ureidobenzoic Acids 11−14, Ethyl 2-Ureidobenzoates 15−18, and Isatoic Anhydrides 19 and 20

	substrate					product (% yield)			
									
	R^5	R^6	R^7	R^8	NRR'				
1	H	H	H	H	4-morpholinyl	**4** (87)[a]	**11** (88)[b]	**15** (86)[b]	**19** (67)[b]
2	H	Me	Me	H	4-morpholinyl	**5** (72)[a]	**12** (82)[a]	**16** (91)[b]	**20** (75)[b]
3	Me	H	H	Me	4-morpholinyl	**6** (64)[a]			
1	H	H	H	H	1-pyrrolidinyl	**7** (70)[a]	**13** (66)[a]		**19** (54)[b]
1	H	H	H	H	$N(Et)_2$	**8** (88)[b]	**14** (70)[b]		**19** (46)[b]
1	H	H	H	H	N(Me)cyclohexyl	**9** (90)[a]		**17** (77)[b]	
2	H	Me	Me	H	N(Me)cyclohexyl			**18** (66)[a]	

[a] Yields refer to products recrystallized or purified as indicated (Experimental Section).

[b] Yields refer to pure crude products.

Table 2. Cyclizations to 4*H*-3,1-Benzoxazin-4-ones 21−27

					substrate (% yield of product)			product
								
R^5	R^6	R^7	R^8	NRR'				
H	H	H	H	4-morpholinyl	**4** (83)[a]	**11** (73)[a]	**15** (86)[a]	**21**
H	Me	Me	H	4-morpholinyl	**5** (47)[b]	**12** (93)[a]	**16** (85)[a]	**22**
Me	H	H	Me	4-morpholinyl	**6** (51)[a]			**23**
H	H	H	H	1-pyrrolidinyl	**7** (58)[b]	**13** (71)[a]		**24**
H	H	H	H	$N(Et)_2$	**8** (71)[a]	**14** (76)[a]		**25**
H	H	H	H	N(Me)cyclohexyl	**9**[c]		**17** (98)[a]	**26**
H	Me	Me	H	N(Me)cyclohexyl			**18** (97)[a]	**27**

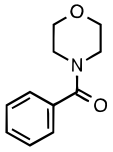
[a] Yields refer to pure crude products.

[b] Yields refer to products recrystallized as indicated (Experimental Section).

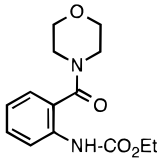
[c] No succesful cyclization upon treatment with concd H_2SO_4 under different temperatures.

However, *the first step*, formation of the ureidobenzamide **4**,[13] can easily be explained as a result of nucleophilic attack of morpholine at the lactam carbon of **1**, followed by ring cleavage, elimination of methanesulfonic acid, Lossen rearrangement to 4-(2-isocyanatobenzoyl)morpholine, and subsequent addition of morpholine.[15]

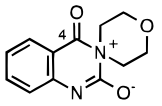
The second step, transformation of the ureidobenzamide **4** to the ureidobenzoic acid **11** (Scheme 1), is formally an acid-catalyzed amide hydrolysis. However, neither benzoylmorpholine **30** nor the carbamate **29** were found to react on treatment with HCl under conditions used for the transformation of **4** to **11**.



30



29



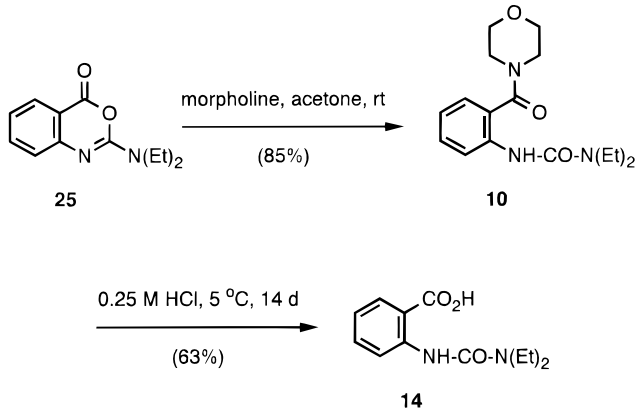
31

An elimination−addition mechanism[17] was taken into consideration to explain the ready hydrolysis (or alcoholysis) of **4**: Elimination of morpholine from the ureido residue, followed by intramolecular addition to the intermediate, masked isocyanate **31**,[18] which could be attacked by water (or ethanol) at C-4 might produce **11** (or **15**). Consequently, an acyl transfer would occur and the morpholine portion of the amide residue in **4** would

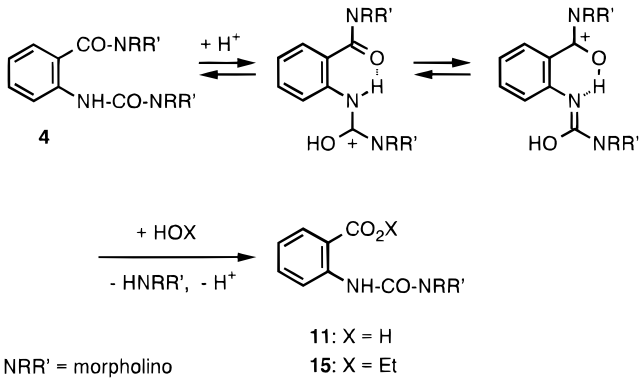
(13) *N*-(Mesyloxy)phthalimide was reported to react with piperidine to the analogue 2-ureidobenzamide derivative; see ref 14.

(14) Kühle, E.; Wegler, R. *Liebigs Ann. Chem.* **1958**, *616*, 183.

Scheme 3

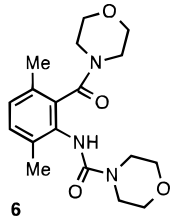


Scheme 4

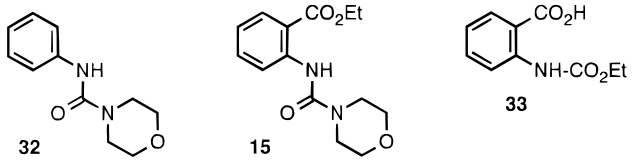


become part of the urea residue in **11** (or **15**). To check this hypothesis, compound **10** was prepared from benzoxazinone **25** and morpholine and then treated with HCl (Scheme 3). The diethylurea derivative **14** was obtained exclusively, clearly indicating that the acyl transfer did not occur.

Therefore, the mechanism outlined in Scheme 4 was proposed for the acid-catalyzed hydrolysis (or alcoholysis) of **4**. Protonation of the urea residue,[19] followed by proton transfer to the amide oxygen provides enhanced susceptibility of the amide group to nucleophilic attack. Likely, the intramolecular acid catalysis of the appropriately placed, protonated urea group is assisted by internal hydrogen bonding.[20] An intramolecular hydrogen bond in the 2-ureidobenzamides **4**−**10** as it was concluded from ^{1}H NMR data in $CDCl_3$ (see below) and NOE experiments[21] might also be operative in aqueous or ethanolic solution.[20b] Furthermore, if the formation of an intramolecular hydrogen bonding in 2-ureidobenzamides is prevented by steric hindrance, the ready conversion did not occur. Thus, when compound **6** was treated with 0.25 M ethanolic HCl under conditions used for the conversion of **4** to **15**, unchanged starting material was isolated quantitatively.



The third step in the conversion of *N*-(mesyloxy)-phthalimide **1** to isatoic anhydride **19** (Scheme 1), the transformation of the 2-ureidobenzoic acid **11** to **19**, is proposed to occur by direct nucleophilc attack of the carboxyl oxygen at the protonated urea structure rather then by an elimination−addition mechanism. This is supported by the following experiments. The urea derivatives **32** and **15**, respectively, failed to react when treated with 0.25 M HCl under conditions used for the preparation of isatoic anhydride **19** from **11** (Scheme 1). Thus, the neighboring carboxyl group is prerequisite to the transformation of the ureido residue. Furthermore, the urea moiety in **11** was replaced by the urethane moiety in **33**. No reaction occurred when compound **33** was treated similarly with 0.25 M HCl, indicating the ureido residue to be prerequisite to isatoic anhydride formation under the acidic conditions used.[22]



The ^{1}H NMR spectra ($CDCl_3$) of the 2-ureidobenzamides **4**−**10**, 2-ureidobenzoic acids **11**−**14**, and ethyl 2-ureidobenzoates **15**−**18** show significant downfield shifts of the H-3 protons.[23] This is interpreted as a result of the anisotropic deshielding effect of the urea carbonyl on the H-3 proton, indicating that the urea C═O bond is

(15) The reaction of *N*-(sulfonyloxy)phthalimides with primary amines as well as O-, S-, and C-nucleophiles has widely been utilized in organic syntheses. For examples, see: (a) Bauer, L.; Exner, O. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 376. (b) Fahmy, A., F. M.; Aly, N. F.; Nada, A.; Aly, N. Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2678. (c) Fahmy, A. F. M.; Aly, N. F.; Orabi, M. O. *Bull. Chem. Soc. Jpn.* **1978**, 1*50*, 2148. (d) Gütschow, M.; Tonew, E.; Leistner, S. *Pharmazie* **1995**, *50*, 672. (e) Chapman, T. M.; Freedman, E. A. *J. Org. Chem.* **1973**, *38*, 3908. (f) Sheradsky, T.; Itzhak, N. *J. Chem. Soc., Perkin Trans. 1* **1986**, 13. See also ref 14. For an application of the Lossen rearrangement of *N*-(sulfonyloxy)phthalimides in the design of mechanism-based inhibitors of serine proteases, see ref 16.

(16) Neumann, U.; Gütschow, M. *J. Biol. Chem.* **1994**, *269*, 21561.

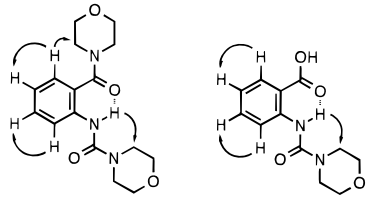
(17) For a review on E1cB processes in acyl transfer reactions, see: Williams, A.; Douglas, K. T. *Chem. Rev.* **1975**, *75*, 627. See also: Gütschow, M.; Hecker, T.; Eger, K. *Synthesis* **1999**, 410.

(18) For the formation of mesoionic quinazolines from 2-isocyanatobenzamides, see ref 14.

(19) For comparison, pK_a values of $PhNHCONH_2$ (−0.3) and $PhCONH_2$ (≈−2): Collumeau, A. *Bull. Soc. Chim. Fr.* **1968**, 5087.

(20) For the interdependence of intramolecular hydrogen bonding and intramolecular general catalysis, see: (a) Benkovic, S. J., Dunikoski, L. K., Jr. *Biochemistry* **1970**, *9*, 1390. For intramolecular acid catalysis of the hydrolysis of 3,1-benzoxazin-4-ones by a neighboring carboxyl group, see: (b) Hegarty, A. F.; Pratt, R. F.; Giudici, T.; Bruice, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 1428. (c) Cremin, D. J.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 2* **1978**, 208.

(21) Relevant NOE enhancements in **4** and **11**:



(22) Isatoic anhydride was obtained from benzoic acids with an adjacent carbamate residue under basic conditions or on thermal treatment: (a) Frost, L. N.; Hegarty, A. F. *J. Chem. Soc., Chem. Commun.* **1973**, 82. (b) Hegarty, A. F.; Frost, L. N.; Cremin, D. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1249. See also ref 12f.

situated in the plane of the phenyl ring. A internal hydrogen bond between the urea hydrogen and the carbonyl oxygen of the adjacent carboxamide, carboxyl, or ester group, respectively, would cause an orientation of the urea carbonyl into the plane of the phenyl ring. The hydrogen bonding is further indicated by the chemical shifts of the urea NH protons in 2-ureidobenzamides **4**−**10** (8.35−9.14 ppm, except **6**), 2-ureidobenzoic acids **11**−**14** (10.42−10.63 ppm), and ethyl 2-ureidobenzoates **15**−**18** (10.52−10.81 ppm). For a comparison, in 4-(phenylcarbamoyl)morpholine **32** bearing no adjacent hydrogen bond acceptor, the NH signal appeared at 6.63 ppm. In the case of the dimethyl-substituted 2-ureidobenzamide **6** (see above), a planar orientation of the substituents and therefore the formation of an internal hydrogen bond is sterically hindered. The NH signal of **6** appeared at 6.63 ppm. The prevented rotation about the C1−CO single bond leads to atropisomerism. The molecule is chiral, and the eight methylene hydrogen atoms of the amide structure are diasterotopic and gave eight distinct signals in the ^{1}H NMR spectrum of **6**. As it has been mentioned, compound **6** failed to react in the acid-catalyzed alcoholysis. These results provide supporting evidence for the postulated proton-transfer mechanism of the hydrolysis (or alcoholysis) of 2-ureidobenzamides assisted by internal hydrogen bonding (Scheme 4).

In summary, an efficient synthetic entry to 2-*sec*-amino-3,1-benzoxazin-4-ones based on the reaction of *N*-(mesyloxy)phthalimides **1**−**3** with secondary amines has been found. This approach is particularly attractive to utilize symmetrically disubstituted phthalimide derivatives. Thus, dimethyl-substituted benzoxazinones (e.g., **22**, **23**, **27**) can be obtained in two-step routes. The enzymatic assays of the new benzoxazinones as inhibitors of serine proteases will be presented in due course.

The transformation of *N*-(mesyloxy)phthalimides involves the formation of 2-ureidobenzamides which undergo a ready hydrolysis, or alcoholysis, to corresponding 2-ureidobenzoic acids, or ethyl esters, respectively. The synthesis of these compounds can be achieved by convenient one-pot procedures using *N*-(mesyloxy)phthalimides as substrates. The reactivity of the intermediate 2-ureidobenzamides is proposed to arise from intramolecular acid catalysis. Minor changes in the acidic reaction conditions lead to a further transformation of intermediate 2-ureidobenzoic acids and allow for the controlled preparation of isatoic anhydrides. For example, a one-pot procedure was accomplished to prepare 4,5-dimethylisatoic anhydride **20** from **2**. This route to isatoic anhydrides involves the stepwise elimination of both secondary amine portions. A ring-opening attack of the released amine at the final isatoic anhydride is prevented due to the acidic conditions used.

Experimental Section

Melting points are not corrected. ^{13}C NMR spectra (75 MHz) and ^{1}H NMR spectra (300 MHz) were recorded in $CDCl_3$, unless otherwise stated. NOE difference spectra were obtained for the following compounds: **4**, **11**, **20**, **23**. Mass spectra were performed using electron impact ionization (EI, 70 eV). Thin-layer chromatography was performed on Merck aluminum sheets, silica gel 60 F_{254}.

2-[(Morpholinocarbonyl)amino]benzoic acid (**11**) was prepared from 2-morpholino-4*H*-3,1-benzoxazin-4-one (**21**) or isatoic anhydride (**19**), respectively, as previously reported.[6,12a]

4-Benzoylmorpholine (**30**)[24] and 2-(ethoxycarbonyl)aminobenzoic acid (**33**)[7] were synthesized as reported.

4,5-Dimethylphthalic anhydride[25] and 3,6-dimethylphthalic anhydride[26] were reacted with hydroxylamine hydrochloride to afford the corresponding *N*-hydroxyphthalimide derivatives.

N-(Mesyloxy)phthalimides (**1**−**3**) were obtained from *N*-hydroxyphthalimides and methanesulfonyl chloride using a standard procedure.[16]

N-(Mesyloxy)-4,5-dimethylphthalimide (**2**): mp 179−180 °C (EtOH); ^{1}H NMR δ 2.44 (s, 6H), 3.45 (s, 3H), 7.67 (s, 2H). Anal. Calcd for $C_{11}H_{11}NO_5S$: C, 49.07; H, 4.12; N, 5.20, S, 11.91. Found: C, 49.03; H, 4.17; N, 5.43; S, 12.29.

N-(Mesyloxy)-3,6-dimethylphthalimide (**3**): mp 113−114 °C (acetone/petroleum ether); ^{1}H NMR δ 2.67 (s, 6H), 3.46 (s, 3H), 7.44 (s, 2H). Anal. Calcd for $C_{11}H_{11}NO_5S$: C, 49.07; H, 4.12; N, 5.20, S, 11.91. Found: C, 49.22; H, 4.05; N, 5.37; S, 11.80.

General Procedure for the Preparation of 2-Ureidobenzamides 4, 5, 6, 9 from *N*-(Mesyloxy)phthalimides. A solution of **1**, **2**, or **3** (7.5 mmol) in anhydrous acetone (25 mL) was stirred under argon and heated. As soon as the solution started refluxing, a solution of morpholine (1.96 g, 22.5 mmol) or *N*-methylcyclohexylamine (2.55 g, 22.5 mmol) in anhydrous acetone (7 mL) was added dropwise over 10 min. The mixture was refluxed for additional 15 min, and the precipitate was separated by filtration. The filtrate was evaporated to dryness to obtain the product. See Table 1 for yields.

4-[2-[(Morpholinocarbonyl)amino]benzoyl]morpholine (**4**):[5] mp 78−80 °C (MeOH); IR (KBr) 1650, 1605 cm^{-1}; ^{1}H NMR δ 3.47−3.51 (m, 4H) 3.65−3.77 (m, 12H), 6.98−7.04 (m, 1H), 7.19 (dd, 1H, J = 7.7, 1.3 Hz), 7.37−7.44 (m, 1H), 8.17 (dd, 1H, J = 8.5, 1.1 Hz), 8.83 (s, 1H); EIMS (*m*/*z*, %)[27] 319 (M$^+$, 80), 233 (24), 146 (100).

4-[4,5-Dimethyl-2-[(morpholinocarbonyl)amino]benzoyl]-morpholine (**5**): mp 158−159 °C (MeOH/H_2O); IR (KBr) 1654, 1606; ^{1}H NMR δ 2.20 (s, 3H), 2.26 (s, 3H), 3.42−3.50 (m, 4H), 3.62−3.78 (m, 12H), 6.92 (s, 1H), 7.92 (s, 1H), 8.71 (s, 1H); EIMS (*m*/*z*, %)[27] 347 (M$^+$, 36), 261 (92), 174 (100). Anal. Calcd for $C_{18}H_{25}N_3O_4$: C, 62.23; H, 7.25; N, 12.10. Found: C, 61.61; H, 7.09; N, 11.85.

4-[3,6-Dimethyl-2-[(morpholinocarbonyl)amino]benzoyl]-morpholine (**6**). The mixture was refluxed and then cooled at 5 °C for 2 d. The precipitate was collected by filtration, suspended in ice−water (200 mL), and filtered: mp 247−250 °C (MeOH); IR (KBr) 1654, 1610 cm^{-1}; ^{1}H NMR δ 2.20 (s, 3H), 2.21 (s, 3H), 3.12−3.31 (m, 2H), 3.41−3.62 (m, 8H), 3.68−3.72 (m, 4H), 3.81−3.88 (m, 1H), 4.04−4.12 (m, 1H), 6.63 (s, 1H, NH), 6.99 (d, 1H, J = 7.9 Hz), 7.12 (d, 1H, J = 7.9 Hz); EIMS (*m*/*z*, %)[27] 347 (M$^+$, 24), 261 (87), 174 (100). Anal. Calcd for $C_{18}H_{25}N_3O_4$: C, 62.23; H, 7.25; N, 12.10. Found: C, 62.31; H, 7.47; N, 11.70.

2-(3-Cyclohexyl-3-methylureido)-*N*-cyclohexyl-*N*-methylbenzamide (**9**): mp 112.5−113.5 °C (MeOH/H_2O); IR (KBr) 1662, 1618 cm^{-1}; ^{1}H NMR δ 1.00−1.83 (m, 20H), 2.84 (s, 3H), 2.90 (br s, 3H), 3.97−4.52 (m, 2H), 6.94−7.00 (m, 1H), 7.16 (dd, 1H, J = 7.6, 1.5 Hz), 7.32−7.38 (m, 1H), 8.21 (d, 1H, J = 8.3 Hz), 8.52 (br s, 1H); EIMS (*m*/*z*, %)[28] 371 (M$^+$, 3), 258 (13), 146 (100). Anal. Calcd for $C_{22}H_{33}N_3O_2$: C, 71.12; H, 8.95; N, 11.31. Found: C, 71.44; H, 8.63; N, 11.06.

General Procedure for the Preparation of 2-Ureidobenzamides 7, 8 from *N*-(Mesyloxy)phthalimide. A mixture of **1** (2.41 g, 10 mmol) and anhydrous toluene (20 mL)

(23) Values were calculated based on the ^{1}H NMR data of the urea derivative **32** (δ_{H-2} = 7.3 ppm) and substituent parameters for CO_2H, CO_2Et, CONRR′, and Me, respectively, and compared to the observed values. The shift differences were 0.77−0.85 ppm for 2-ureidobenzamides (**4**, **5**, **7**−**10**), 1.09−1.19 ppm for 2-ureidobenzoic acids (**11**−**14**), and 1.16−1.32 ppm for ethyl 2-ureidobenzoates (**15**−**18**).

(24) Iwata, C.; Watanabe, M.; Okamoto, S.; Fujimoto, M.; Sakae, M.; Katsurada, M., Imanishi, T. *Heterocycles* **1988**, *27*, 323.

(25) Hennige, H.; Kreher, R. P.; Konrad, M.; Jelitto, F. *Chem. Ber.* **1988**, *121*, 243.

(26) Newman, M. S.; Lord, B. T. *J. Am. Chem. Soc.* **1944**, *66*, 733.

(27) First mass spectral fragment: (M$^+$ − NRR′); second fragment: (M$^+$ − NRR′ − HNRR′).

(28) First mass spectral fragment: (M$^+$ − HNRR′); second fragment: (M$^+$ − HNRR′ − NRR′).

was stirred at 0 °C. Pyrrolidine (2.4 g, 34 mmol) or diethylamine (2.5 g, 34 mmol) was added slowly. The mixture was stirred at room temperature for 7 h, diluted with brine (100 mL), and extracted with ethyl acetate. The combined organic layers were washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo. See Table 1 for yields.

1-[2-[(Pyrrolidinocarbonyl)amino]benzoyl]pyrrolidine (**7**): mp 132−133 °C (MeOH/H_2O); IR (KBr) 1670, 1620 cm^{-1}; ^1H NMR δ 1.82−2.00 (m, 8H), 3.42−3.68 (m, 8H), 6.91−6.98 (m, 1H), 7.30−7.39 (m, 2H), 8.25 (d, 1H, J = 8.3 Hz), 9.14 (s, 1H); EIMS (*m*/*z*, %)[27] 287 (M^+, 5), 217 (72), 146 (52), 55 (100). Anal. Calcd for $C_{16}H_{21}N_3O_2 \cdot 0.5H_2O$: C, 64.84; H, 7.48; N, 14.19. Found: C, 64.85; H, 7.22; N, 13.99.

2-(3,3-Diethylureido)-*N*,*N*-diethylbenzamide (**8**): colorless oil; IR (KBr) 1670, 1622 cm^{-1}; ^1H NMR δ 1.18−1.26 (m, 12H), 3.35 (q, 4H, J = 7.1 Hz), 3.30−3.50 (m, 4H), 6.93−7.00 (m, 1H), 7.18 (dd, 1H, J = 7.7, 1.6 Hz), 7.30−7.38 (m, 1H), 8.19 (d, 1H, J = 8.5 Hz), 8.35 (s, 1H); EIMS (*m*/*z*, %)[27] 291 (M^+, 5), 219 (63), 146 (100).

Preparation of 4-[2-[(Morpholinocarbonyl)amino]benzoyl]morpholine (4) from 2-Morpholino-4*H*-3,1-benzoxazin-4-one (21). A mixture of **21** (929 mg, 4 mmol), morpholine (1.4 g, 16 mmol), and anhydrous acetone (12 mL) was stirred at room temperature for 24 h and concentrated in vacuo. The residue was recrystallized from MeOH to yield **4** (1.13 g, 84%).

4-[2-(3,3-Diethylureido)benzoyl]morpholine (10). A mixture of **25** (873 mg, 4 mmol), morpholine (1.4 g, 16 mmol), and anhydrous acetone (12 mL) was stirred at room temperature for 3 d and concentrated in vacuo. The residue was dissolved in ethyl acetate. Silica gel was added, and the mixture was stirred for 2 min and filtered. The filtrate was evaporated in vacuo to yield **10** (1.04 g, 85%) as a colorless oil; IR (KBr) 1654, 1625 cm^{-1}; ^1H NMR δ 1.22 (t, 6H, J = 7.1 Hz), 3.37 (q, 4H, J = 7.1 Hz), 3.60−3.78 (m, 8H), 6.94−7.01 (m, 1H), 7.16 (dd, 1H, J = 7.7, 1.6 Hz), 7.34−7.41 (m, 1H), 8.20 (d, 1H, J = 8.3 Hz,), 8.55 (s, 1H); EIMS (*m*/*z*, %) 305 (M^+, 45), 219 (44), 146 (100).

General Procedure for the Preparation of 2-Ureidobenzoic Acids 11−14 from *N*-(Mesyloxy)phthalimides. A solution of **1** or **2** (7.5 mmol) in anhydrous acetone (25 mL) was stirred under argon and heated to reflux. A solution of the appropriate secondary amine (22.5 mmol) in anhydrous acetone (7 mL) was added dropwise over 10 min. The mixture was refluxed for additional 15 min and evaporated to dryness. The residue was stirred with 0.25 M HCl (100 mL) to obtain a solution which was kept at 5 °C for 14 d. The precipitate was collected by filtration. See Table 1 for yields.

2-[(Morpholinocarbonyl)amino]benzoic acid (**11**): mp 156−160 °C, lit.[12a] mp 164 °C; IR (KBr) 1690, 1630 cm^{-1}; ^1H NMR δ 3.56−3.62 (m, 4H), 3.75−3.81 (m, 4H), 7.00−7.06 (m, 1H), 7.54−7.60 (m, 1H), 8.07 (dd, 1H, J = 8.0, 1.4 Hz), 8.57 (d, 1H, J = 8.5 Hz), 10.63 (s, 1H).

4,5-Dimethyl-2-[(morpholinocarbonyl)amino]benzoic acid (**12**). The crude product was partionated between ethyl acetate and $NaHCO_3$ solution. The aqueous layer was acidified, and the precipitate was collected by filtration: mp 159−161 °C; IR (KBr) 1674 (br), 1640 (br) cm^{-1}; ^1H NMR δ 2.23 (s, 3H), 2.31 (s, 3H), 3.55−3.61 (m, 4H), 3.75−3.81 (m, 4H), 7.81 (s, 1H), 8.35 (s, 1H), 10.50 (s, 1H). Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.13; H, 6.85; N, 9.95.

2-[(Pyrrolidinocarbonyl)amino]benzoic acid (**13**). The crude product was purified as described above: mp 169−170 °C; IR (KBr) 1690, 1652 cm^{-1}; ^1H NMR δ 1.96−2.04 (m, 4H), 3.51−3.59 (m, 4H), 6.96−7.03 (m, 1H), 7.52−7.58 (m, 1H), 8.08 (dd, 1H, J = 8.0, 1.6 Hz), 8.67 (d, 1H, J = 8.6 Hz), 10.42 (s, 1H). Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.63; H, 6.11; N, 11.56.

2-(3,3-Diethylureido)benzoic acid (**14**): mp 133−139 °C, lit.[12a] mp 151 °C; IR (KBr) 1690, 1644 cm^{-1}; ^1H NMR δ 1.27 (t, 6H, J = 7.1 Hz), 3.46 (q, 4H, J = 7.1 Hz), 6.95−7.01 (m, 1H), 7.51−7.57 (m, 1H), 8.08 (dd, 1H, J = 8.0, 1.6 Hz), 8.64 (d, 1H, J = 8.6 Hz), 10.59 (s, 1H).

Preparation of 2-[(Morpholinocarbonyl)amino]benzoic Acid (11) from 4-[2-[(Morpholinocarbonyl)amino]-benzoyl]morpholine (4). Compound **4** (2.53 g, 7.5 mmol) was stirred with 0.25 M HCl (100 mL) to obtain a solution which was kept at 5 °C for 14 d. The precipitate was collected by filtration to obtain **11** (1.7 g, 91%).

Preparation of 2-(3,3-Diethylureido)benzoic Acid (14) from 4-[2-(3,3-Diethylureido)benzoyl]morpholine (10). Compound **10** (1.15, 3.75 mmol) was treated with 0.25 M HCl (50 mL) as described above to obtain **14** (560 mg, 63%).

General Procedure for the Preparation of Ethyl 2-Ureidobenzoates 15−18 from *N*-(Mesyloxy)phthalimides. A solution of **1** or **2** (7.5 mmol) in anhydrous acetone (25 mL) was stirred under argon and heated to reflux. A solution of the appropriate secondary amine (22.5 mmol) in anhydrous acetone (7 mL) was added dropwise over 10 min. The mixture was refluxed for additional 15 min and evaporated to dryness. The residue was dissolved in 0.25 M anhydrous ethanolic HCl (48 mL), refluxed for 2 min, and kept at −15 °C overnight. The precipitate was collected by filtration, washed with H_2O, and dried. See Table 1 for yields.

Ethyl 2-[(morpholinocarbonyl)amino]benzoate (**15**): mp 117−118 °C (EtOH), IR (KBr) 1676 (br) cm^{-1}; ^1H NMR δ 1.42 (t, 3H, J = 7.1 Hz), 3.55−3.62 (m, 4H), 3.74−3.80 (m, 4H), 4.37 (q, 2H, J = 7.1 Hz), 6.95−7.02 (m, 1H), 7.48−7.55 (m, 1H), 8.03 (dd, 1H, J = 8.0, 1.6 Hz), 8.56 (d, 1H, J = 8.6 Hz), 10.81 (s, 1H). Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.58; H, 6.52; N, 10.07. Found: C, 60.21; H, 6.90; N, 9.83.

Ethyl 4,5-dimethyl-2-[(morpholinocarbonyl)amino]benzoate (**16**): mp 128−130 °C; IR (KBr) 1670 (br) cm^{-1}; ^1H NMR δ 1.40 (t, 3H, J = 7.1 Hz), 2.21 (s, 3H), 2.29 (s, 3H), 3.53−3.59 (m, 4H), 3.72−3.78 (m, 4H), 4.33 (q, 2H, J = 7.1 Hz), 7.74 (s, 1H), 8.35 (s, 1H), 10.67 (s, 1H). Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.39; H, 7.18; N, 9.12.

Ethyl 2-(3-cyclohexyl-3-methylureido)benzoate (**17**). The residue was dissolved in ethanolic HCl and refluxed. The solution was concentrated in vacuo to obtain 30 mL and then cooled: mp 80−81 °C; IR (KBr) 1688, 1664 cm^{-1}; ^1H NMR δ 1.03−1.88 (m, 10H), 1.40 (t, 3H, J = 7.1 Hz), 2.94 (s, 3H), 4.10−4.21 (m, 1H), 4.36 (q, 2H, J = 7.1 Hz), 6.91−7.00 (m, 1H), 7.45−7.52 (m, 1H), 8.01 (dd, 1H, J = 8.0, 1.7 Hz), 8.61 (d, 1H, J = 8.6 Hz) 10.65 (s, 1H). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found C, 66.97; H, 7.62; N, 9.02.

Ethyl 2-(3-cyclohexyl-3-methylureido)-4,5-dimethylbenzoate (**18**). The crude product was obtained as described above and recrystallized from EtOH/H_2O: mp 89−90 °C; IR (KBr) 1682, 1664 cm^{-1}; ^1H NMR δ 1.04−1.87 (m, 10H), 1.41 (t, 3H, J = 7.1 Hz), 2.22 (s, 3H), 2.29 (s, 3H), 2.94 (s, 3H), 4.12−4.23 (m, 1H), 4.35 (q, 2H, J = 7.1 Hz), 7.74 (s, 1H), 8.44 (s, 1H), 10.52 (s, 1H). Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.35; H, 8.57; N, 8.37.

Preparation of Ethyl 2-[(Morpholinocarbonyl)amino]-benzoate (15) from 4-[2-[(Morpholinocarbonyl)amino]-benzoyl]morpholine (4). Compound **4** (1.27 g, 3.75 mmol) was refluxed with 0.25 M anhydrous ethanolic HCl (24 mL) for 2 min and kept at −15 °C overnight. The precipitate was collected by filtration, washed with H_2O, and dried to obtain **15** (880 mg, 84%).

Preparation of Ethyl 2-[(Morpholinocarbonyl)amino]-benzoate (15) from 2-Morpholino-4*H*-3,1-benzoxazin-4-one (21). Compound **21** (871 mg, 3.75 mmol) was treated with ethanolic HCl using the procedure given above to obtain **15** (920 mg, 88%).

General Procedure for the Preparation of Isatoic Anhydrides 19−20 from *N*-(Mesyloxy)phthalimides. A solution of **1** or **2** (7.5 mmol) in anhydrous acetone (25 mL) was stirred under argon and heated to reflux. A solution of the appropriate secondary amine (22.5 mmol) in anhydrous acetone (7 mL) was added dropwise over 10 min. The mixture was refluxed for additional 15 min and evaporated to dryness. After addition of 0.25 M HCl (100 mL), the mixture was vigorously stirred and refluxed for 2 min (10 min in the case of the reaction with diethylamine). The mixture was kept at 5 °C for 24 h. The precipitate was collected by filtration. For yields and secondary amines used, see Table 1.

Isatoic anhydride (**19**): mp >230 °C, dec (ethyl acetate), lit.[29] mp 243−247 °C; IR (KBr) 1766, 1728, 1618 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.15 (d, 1H, J = 8.0 Hz), 7.22−7.28 (m, 1H), 7.71−7.77 (m, 1H), 7.91 (dd, 1H, J = 7.9, 1.3 Hz), 11.71 (s, 1H); EIMS (*m*/*z*, %) 163 (M^+, 18), 119 ($M^+ - CO_2$, 94), 92 (100).

4,5-Dimethylisatoic anhydride (**20**). After evaporation, the residue was refluxed with 0.25 M HCl (450 mL): mp 251−254 °C; IR (KBr) 1778, 1732, 1632 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.24 (s, 3H), 2.30 (s, 3H), 6.92 (s, 1H), 7.67 (s, 1H), 11.57 (s, 1H); EIMS (*m*/*z*, %) 191 (M^+, 46), 147 ($M^+ - CO_2$, 100). Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.90; H, 4.93; N, 7.66.

Preparation of Isatoic Anhydride (19) from 2-[(Morpholinocarbonyl)amino]benzoic Acid (11). A mixture of **11** (1.88 g, 7.5 mmol) and 0.25 M HCl (100 mL) was vigorously stirred and refluxed for 2 min. After being kept at 5 °C for 24 h, the preciptate was filtered to obtain **19** (830 mg, 68%).

General Procedure for the Preparation of 4*H*-3,1-Benzoxazin-4-ones from 2-Ureidobenzamides 4−8. A mixture of the appropiate 2-ureidobenzamide (3 mmol) and concd H_2SO_4 (12 mL) was kept at room temperature for overnight. It was poured onto a stirred mixture of ice−water, $NaHCO_3$, and ethyl acetate. After neutralization, the aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. See Table 2 for yields.

2-Morpholino-4*H*-3,1-benzoxazin-4-one (**21**):[5] mp 150.5−151.5 °C (diethyl ether/petroleum ether), lit.[1] mp 150−151 °C; IR (KBr) 1760 (br) cm^{-1}; ^1H NMR δ 3.70−3.83 (m, 8H), 7.12−7.27 (m, 2H), 7.59−7.66 (m, 1H), 8.02 (dd, 1H, J = 7.9, 1.3 Hz).

6,7-Dimethyl-2-morpholino-4*H*-3,1-benzoxazin-4-one (**22**): mp 161−162 °C (ethyl acetate/petroleum ether); IR (KBr) 1768 cm^{-1}; ^1H NMR δ 2.29 (s, 3H), 2.33 (s, 3H), 3.70−3.79 (m, 8H), 7.06 (s, 1H), 7.27 (s, 1H); EIMS (*m*/*z*, %) 260 (M^+, 82), 174 (100). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.72; H, 6.21; N, 10.84.

5,8-Dimethyl-2-morpholino-4*H*-3,1-benzoxazin-4-one (**23**). The mixture of **6** and concd H_2SO_4 was kept at room temperature for 3 d and poured onto ice−water (150 mL). The precipitate was collected by filtration, washed with $NaHCO_3$ solution and H_2O, and dried: mp: 180−183 °C (ethyl acetate); IR (KBr) 1738 cm^{-1}; ^1H NMR δ 2.35 (s, 3H), 2.67 (s, 3H), 3.71−3.82 (m, 8H), 6.86 (d, 1H, J = 7.7 Hz), 7.35 (d, 1H, J = 7.7 Hz); ^{13}C NMR δ 17.3, 22.5, 44.4, 66.4, 111.0, 125.5, 130.3, 136.3, 140.0, 150.0, 152.5, 159.4; EIMS (*m*/*z*, %) 260 (M^+, 61), 174 (100). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.36; H, 5.84; N, 10.44.

2-Pyrrolidino-4*H*-3,1-benzoxazin-4-one (**24**). The mixture of **7** and concd H_2SO_4 was heated at 80 °C for 8 h: mp 108−109 °C (diethyl ether/petroleum ether), lit.[1] mp 116−118 °C; IR (KBr) 1760 cm^{-1}; ^1H NMR δ 1.93−2.01 (m, 4H), 3.55−3.62 (m, 4H), 7.03−7.11 (m, 1H), 7.21 (d, 1H, J = 8.3 Hz), 7.52−7.60 (m, 1H), 7.97 (d, 1H, J = 7.7 Hz).

2-(Diethylamino)-4*H*-3,1-benzoxazin-4-one (**25**). The mixture of **8** and concd H_2SO_4 was heated at 80 °C for 3 h: mp 34−35 °C (diethyl ether/petroleum ether), lit.[1] mp 46−47 °C; IR (KBr) 1760 cm^{-1}; ^1H NMR δ 1.26 (t, 6H, J = 7.1 Hz, 3.57 (q, 4H, J = 7.1 Hz), 7.07−7.13 (m, 1H), 7.22 (d, 1H, J = 7.2 Hz), 7.55−7.62 (m, 1H), 8.00 (dd, 1H, J = 7.9, 1.2 Hz).

General Procedure for the Preparation of 4*H*-3,1-Benzoxazin-4-ones from 2-Ureidobenzoic Acids 11−14. A mixture of the appropiate 2-ureidobenzoic acid (2 mmol) and acetic anhydride (7 mL) was refluxed for 15 min. After cooling, it was poured onto ice−water (100 mL). The precipitate was filtered, washed with H_2O, and dried. See Table 2 for yields.

General Procedure for the Preparation of 4*H*-3,1-Benzoxazin-4-ones from Ethyl 2-Ureidobenzoates 15−18. A mixture of the appropriate ethyl 2-ureidobenzoate (5 mmol) and concd H_2SO_4 (5 mL) was kept at room temperature for 3 h. It was poured onto a mixture of ice−water and $NaHCO_3$. After neutralization, the precipitate was collected by fitration, washed with H_2O, and dried. See Table 2 for yields.

2-(*N*-Methylcyclohexylamino)-4*H*-3,1-benzoxazin-4-one (**26**): mp 127.5−128 °C; IR (KBr) 1766 cm^{-1}; ^1H NMR δ 1.04−1.90 (m, 10H), 3.03 (s, 3H), 4.25−4.40 (m, 1H), 7.06−7.13 (m, 1H), 7.24 (d, 1H, J = 8.2 Hz), 7.55−7.62 (m, 1H), 7.99 (d, 1H, J = 7.9 Hz); EIMS (*m*/*z*, %) 258 (M^+, 39), 176 (88), 146 (100). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.98; H, 6.78; N, 11.15.

6,7-Dimethyl-2-(*N*-methylcyclohexylamino)-4*H*-3,1-benzoxazin-4-one (**27**): mp 149−150 °C (diethyl ether/petroleum ether); IR (KBr) 1762 cm^{-1}; ^1H NMR δ 1.03−1.90 (m, 10H), 2.27 (s, 3H), 2.31 (s, 3H), 3.00 (s, 3H), 4.24−4.39 (m, 1H), 7.05 (s, 1H), 7.74 (s, 1H); EIMS (*m*/*z*, %) 286 (M^+, 50), 204 (100), 174 (78). Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 70.90; H, 7.55; N, 9.72.

4-[2-[(Ethoxycarbonyl)amino]benzoyl]morpholine (29). A mixture of **28**[5] (1.15 g, 6 mmol), morpholine (2.1 g, 24 mmol), and anhydrous acetone (18 mL) was stirred at room temperature for 15 min. After being concentrated to dryness, the residue was cooled and suspended in *n*-hexane. The precipitate was collected by filtration to obtain **29** (1.5 g, 90%): mp 96−97 °C (ethyl acetate/petroleum ether); IR (KBr) 1726, 1718 cm^{-1}; ^1H NMR δ 1.31 (t, 3H, J = 7.1 Hz), 3.45−3.80 (m, 8H), 4.21 (q, 2H, J = 7.1 Hz), 7.02−7.08 (m, 1H), 7.16 (dd, 1H, J = 7.7, 1.6 Hz), 7.37−7.43 (m, 1H), 8.12 (d, 1H, J = 8.0 Hz), 8.12 (s, 1H). Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.12; H, 6.23; N, 9.91.

4-(Phenylcarbamoyl)morpholine (32). A solution of phenyl isocyanate (3 g, 25 mmol) in diethyl ether (22 mL) was added dropwise to a stirred solution of morpholine (2.18 g, 25 mmol) in diethyl ether (22 mL). The mixture was stirred at room temperature for 45 min. The precipitate was collected by filtration and washed with diethyl ether to obtain **32** (5 g, 97%): mp 161−162 °C (EtOH), lit.[30] mp 161.5−162 °C; IR (KBr) 1635 (br) cm^{-1}; ^1H NMR δ 3.41−3.46 (m, 4H), 3.66−3.70 (m, 4H), 6.63 (s, 1H), 7.00−7.08 (m, 1H), 7.24−7.37 (m, 4H).

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