Organic Process Research & Development **2006**, *10,* 1184–1191

Beating the Hydrogen Bond: First Selective and High-Yielding *N*-Acylation Process for an α,*β*-Diaminoalcohol

Thomas Storz,* Peter Dittmar, Dominique Grimler, and Maria Testa

Process R&D, Chemical & Analytical Development, Novartis Pharma AG, CH-4002 Basel, Switzerland

Heiko Potgeter and Didier Chappel

Analytical R&D, Chemical & Analytical Development, Novartis Pharma AG, CH-4002 Basel, Switzerland

Otto Hartmann, Daniel Niederer, and Martin Trüby

Pilot Plant Operations, Chemical & Analytical Development, Novartis Pharma AG, CH-4002 Basel, Switzerland

Abstract:

The first selective and high-yielding *N*-acylation of an α,*β*-diaminoalcohol is reported, as well as the first use as *N*-acylation agent of a *S*-mercaptobenzothiazolyl thioester of an α,*β*-unsaturated carboxylic acid. Other conventional coupling methods (acid chloride, uronium salt, carbonyl diimidazole, phosphonium salt) gave low yields respectively difficult to purify mixtures of *N*- and *O*,*N*-diacylated product (4b), due to the unusually high reactivity of the primary hydroxyl group caused by an intramolecular hydrogen bond to the dialkylamino moiety in the *β*-position. Both the cinnamic thioester preparation and the coupling step were safely and reproducibly scaled up to a chromatography-free process in the pilot plant.

Introduction

Vicinal diaminoalcohols as well as 1,2- and 1,3-aminoalcohols and their derivatives are among the most widely used structural motives in active pharmaceuticals ingredients, agrochemicals, and chiral auxiliaries alike.[1−8] For one of our development projects,[9] we were faced with the seemingly simple challenge of attaching a substituted cinnamic acid side chain[9] to the primary amino group of the α,*β*-diamino alcohol **1**[10] (Figure 1).

While there is certainly ample precedence for selective *N*-acylations of simple α- and *β*-aminoalcohols,[11] to our astonishment, we found very little published material on the *N*-acylation of α,*β*-diaminoalcohols: Charlton et al.[12] had reported the *N*-acylation of diaminoalcohols **A** and **B** by a benzoic acid carbonyl imidazolide in the presence of triethylamine; Naylor et al.[13] synthesized the amide **D** from the cyclic diaminoalcohol **C**; and Chandrakumar et al.[14] obtained the amino acid amide **F** from the diaminoalcohol **E** (Scheme 1). To the best of our knowledge, these are the only reported examples of this reaction type to date.[15] They all appear to proceed in mediocre to poor yield (18−42%, Scheme 1).

Our goal was to find a reproducible, high-yielding, and selective method for the *N*-acylation of this type of diaminoalcohol.

Results and Discussion

Our starting material, the chiral diaminoalcohol dihydrochloride **1**, was conveniently obtained from the *N*,*O*-isopropylidene-, *N*-BOC-protected aminoalcohol precursor **2**[16] by simultaneous *N*,*O*-deprotection with a small excess of concentrated, aqueous hydrochloric acid in *n*-butyl acetate.

* To whom correspondence should be addressed. Amgen Inc., One Amgen Center Drive, P.O. Box, Thousand Oaks, CA 91320-1799, U.S.A. E-mail: tstorz@amgen.com.

(1) Katz, S. J.; Bergmeier, S. C. *Tetrahedron Lett.* **2002**, *43*, 557.
(2) Rozzell, J. D. *Applied Biocatalysis in Specialty Chemicals and Pharmaceuticals*; ACS Symposium Series No. 776; American Chemical Society: Washington, DC, 2001; pp 191−199.
(3) Mulzer, J. In *Stereoselective Synthesis*; Ottow, E., Schoellkopf, K., Schulz, B.-G., Eds.; Springer-Verlag: Germany, 1993; pp 37−61.
(4) Bartoli, G.; Cupone, G.; Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Tagarelli, A. *Tetrahedron Lett.* **2002**, *43*, 7441.
(5) Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E.; Etxebarria, J. *Curr. Org. Chem.* **2005**, *9*, 219.
(6) Ishizuka, T. *Yakugaku Zasshi* **1997**, *117*, 339.
(7) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Stuermer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788.
(8) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561.
(9) *Expert Opin. Ther. Pat.* **2002**, *12*, 1741.
(10) Howe, T.; Bhalay, G.; Le Grand, M.; Storz, T. *PCT Int. Appl.* **2002**, WO 0204420; U.S. Patent 6,670,379, 2003.
(11) For instance, see: (a) Smeets, J. W. H.; Weber, P. G. *PCT Int. Appl.* **1993** WO 9320038. (b) Eckstein, M.; Cegla, M.; Gajewczyk, L. *Pol. J. Chem.* **1984**, *58*, 607. (c) Sakurai, K.; Ishida, K.; Ogura, M. *Eur. Pat. Appl.* EP 835864 **1998**0415. (d) Bouzoubaa, M.; Leclerc, G.; Ehrhardt, J. D.; Andermann, G. *Bull. Soc. Chim. Fr.* **1985**, 1230. (e) Gotor, V. *Org. Process Res. Dev.* **2002**, *6*, 420. (f) Ranu, B. C.; Dutta, P.; Sarkar, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2223. (g) Morcuende, A.; Ors, M.; Valverde, S.; Herradon, B. *J. Org. Chem.* **1996**, *61*, 5264. (h) Kunieda, T.; Higuchi, T.; Abe, Y.; Hirobe, M. *Tetrahedron Lett.* **1980**, *21*, 3065. (i) Hanessian, S.; Patil, G. *Tetrahedron Lett.* **1978**, *19*, 1035.
(12) Vicker, N.; Burgess, L.; Chuckowree, I. S.; Dodd, R.; Folkes, A. J.; Hardick, D. J.; Hancox, T. C.; Miller, W.; Milton, J.; Sohal, S.; Wang, S.; Wren, S. P.; Charlton, P. A.; Dangerfield, W.; Liddle, C.; Mistry, P.; Stewart, A. J.; Denny, W. A. *J. Med. Chem.* **2002**, *45*, 721.
(13) Naylor, A.; Judd, D. B.; Lloyd, J. E.; Scopes, D. I. C.; Hayes, A. G.; Birch, P. J. *J. Med. Chem.* **1993**, *36*, 2075.
(14) Chandrakumar, N. S.; Yonan, P. K.; Stapelfeld, A.; Savage, M.; Rorbacher, E.; Contreras, P. C.; Hammond, D. *J. Med. Chem.* **1992**, *35*, 223.
(15) SciFinder, Beilstein and various reaction database (RXLBRO, MDL) searches, August 2006.
(16) Obtained via reductive amination of (*R*)-*Garner's aldehyde*[17] with 4-(4-chlorobenzoyl)-piperidine,[18] isolated as dibenzoyl(hemi)-L-tartaric acid salt.[10]

Published on Web 10/27/2006
10.1021/op0601464 CCC: $33.50

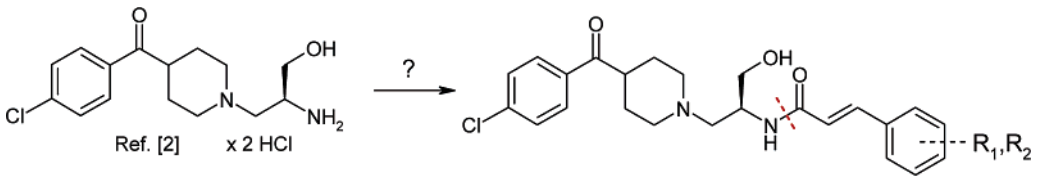
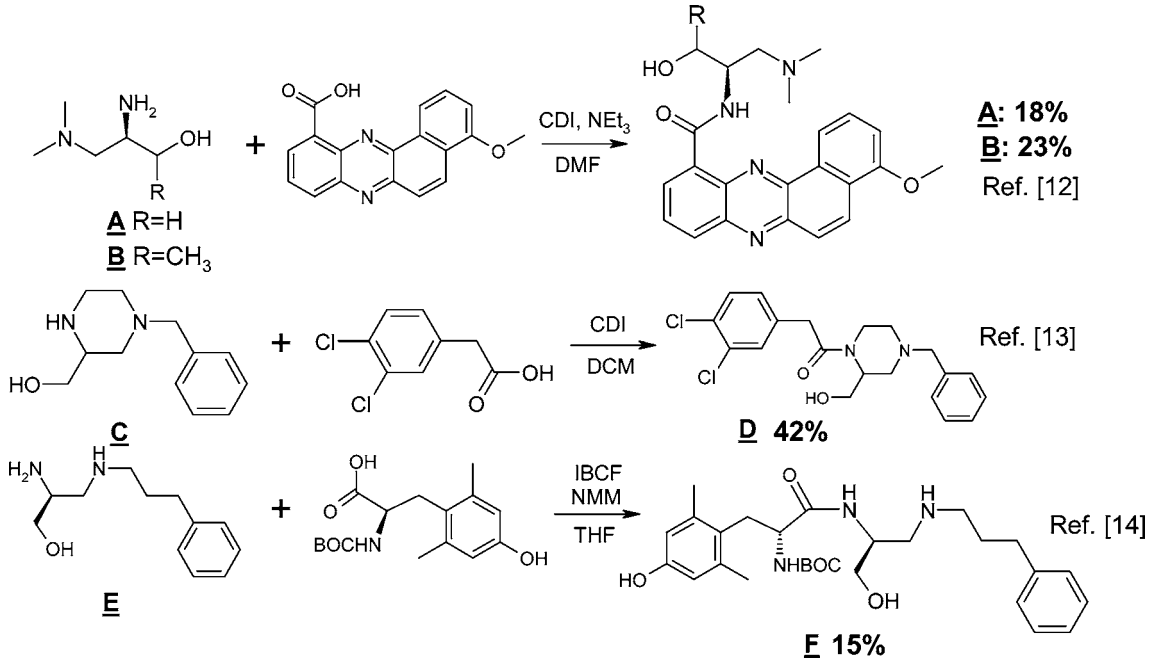
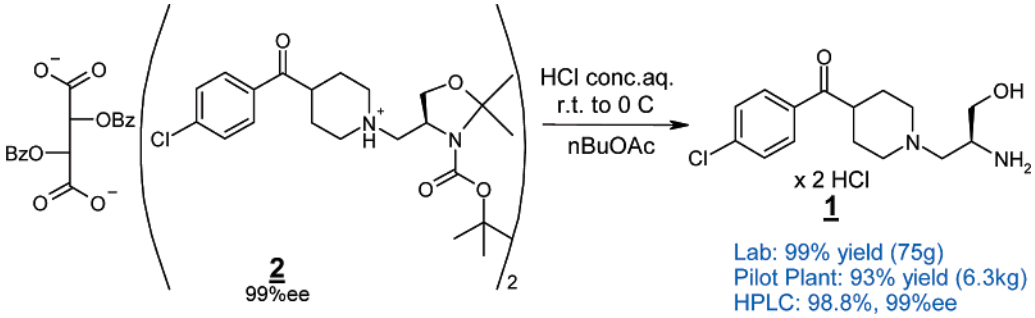


Figure 1. **Diaminoalcohol 1.**

Scheme 1. **Reported diaminoalcohol *N*-acylations to date**



Scheme 2. **Synthesis of diaminoalcohol 1**



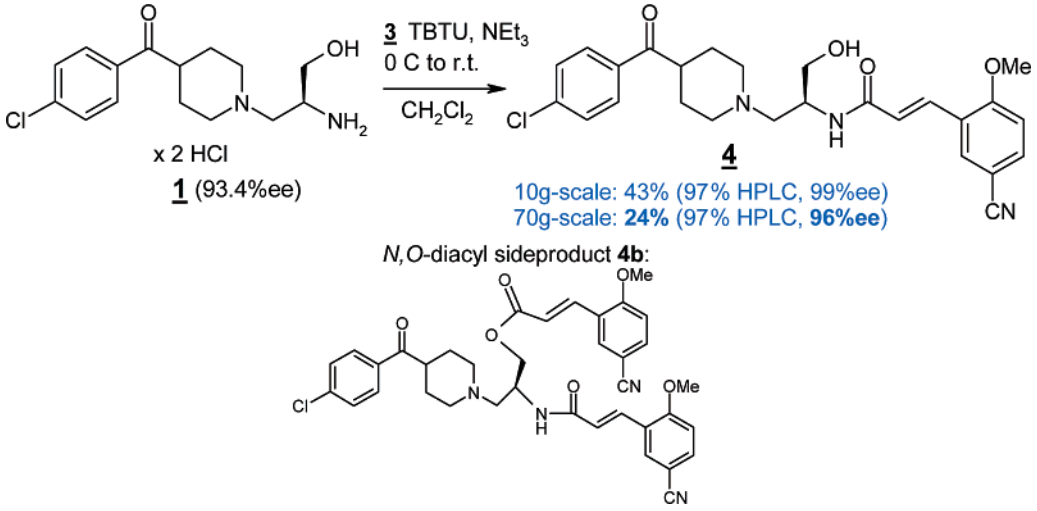
Under these conditions, the dihydrochloride of **1** precipitates in near quantitative yield and excellent purity, whereas the dibenzoyl tartaric acid remains behind exclusively in the butyl acetate mother liquor, obviating the need for additional purification of **1**. This deprotection scaled up very well in the pilot plant (Scheme 2).[19]

Early discovery stage coupling studies of the diaminoalcohol **1** with 3′-cyano-6′-methoxy-cinnamic acid **3**[10] employing different activating agents (via acid chloride, carbodiimides, CDI, various uronium, and phosphonium reagents) had shown unsatisfactory yields and selectivities (data not shown). For a quick initial multigram scale-up, a uronium salt coupling procedure was used (Scheme 3).[24]

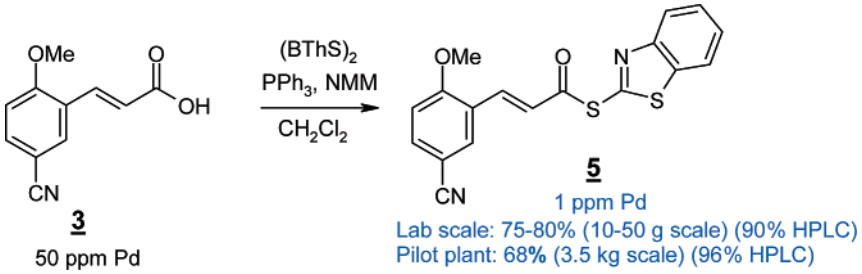
The unsatisfactory throughput on a 10-g scale (43%) was well in line with the poor yields seen in the few known examples (vide supra, Scheme 1). However, upon scaling up from 10 g to 70 g, the yield dropped even further, as extensive chromatographic purification was needed to remove unwanted *N*,*O*-diacyl side product[25] **4b** and upgrade

(17) Garner, P.; Park, J. M. *Org. Synth.* **1992**, *70*, 18.
(18) Helsley, G. C.; Gardner, B. A.; Strupczewski, J. T. *Ger. Offen.* **1977**, DE 2708913.
(19) This constitutes a less hazardous, more practical, and cheaper (*n*-butylacetate vs dioxane, aq HCl vs HCl-gas and TFA) deprotection protocol than the HCl(gas)/dioxane or TFA/CH_2Cl_2 conditions often used (see refs 20−23) and might be of general usefulness for the deprotection of *N*-BOC-, *N*-isopropylidene-protected water soluble amines. It also enabled potential recycling of the chiral auxiliary acid (not investigated further at this stage).
(20) Dondoni, A.; Perrone, D. *Tetrahedron Lett.* **1997**, *38*, 499.
(21) Qiao, L.; Kozikowski, A. P.; Olivera, A.; Spiegel, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 711.
(22) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597.
(23) Gordon, K.; Bolger, M.; Khan, N.; Balasubramanian, S. *Tetrahedron Lett.* **2000**, *41*, 8621.
(24) Before the introduction of the dibenzoyl-hemi(L)tartaric acid salt isolation for the precursor **2**, on discovery chemistry stage, the aminoalcohol **1** was made via a different process (data not shown), hence the lower ee for **1**.

Scheme 3. **TBTU-coupling of diaminoalcohol 1 with acid 3**



Scheme 4. **Synthesis of cinnamic thioester 5**



the quality of **4** to the desired level. It became clear that for further scale-up, a higher-yielding, more selective and robust coupling method was urgently needed.

Mercaptobenzothiazolyl-2-thioesters of substituted acetic acids have been used very successfully for *N*-acylations of not only sensitive API intermediates, mostly in the area of β-lactam antibiotics[26−28] but also for ACE inhibitors,[29] β-lactones,[30] and quinolone antibiotics.[31] However, thioesters of α,β-unsaturated acids such as *N*-acylating agents have not been reported,[15] perhaps because it was felt that 1,4-addition of the liberated thiol to the unsaturated carbonyl group would be a side reaction difficult to overcome in those systems.[32] We wanted to investigate the mercaptobenzothiazolyl-2-thioester of the cinnamic acid **3** as a potentially more selective[36] reaction partner for the aminoalcohol **1**. In the event, synthesis of the desired thioester was best accomplished by reaction of **3** with bis(2-mercaptobenzothiazolyl)disulfide[37] [$(BThS)_2$] in the presence of triphenylphosphine and *N*-methylmorpholine (Scheme 4).[26]

The cinnamic thioester **5**[10,40] conveniently precipitated as a stable, crystalline solid from the reaction mixture and was isolated by a simple filtration step in good yield and excellent purity in the pilot plant without any trace of the 1,4-addition product. Since α,β-unsaturated acids obtained via transition metal-catalyzed cross-coupling reactions often contain trace metal impurities, this sequence is especially gratifying since the 2-mercaptobenzothiazole liberated in situ acts as a transition/heavy metal scavenger.[41]

Considering that thiazolidin-2-thione is known to react with activated carboxylic acids to a thionoamide instead of a thioester[42,43] and 2-mercaptobenzothiazole has been reported to give a mixture of thionoamide and thioester with

(25) All attempts to selectively hydrolyse the *N*,*O*-diacyl product back to the desired *N*-acyl product were unsuccessful and led to decomposition.
(26) Defossa, E.; Fischer, G.; Gerlach, U.; Hoerlein, R.; Isert, D.; Krass, N.; Lattrell, R.; Stache, U.; Wollmann, T.; *Liebigs Ann. Chem*. **1996**, 1743.
(27) Wei, C. C.; Bartkovitz, D.; West, K. F. *J. Org. Chem.* **1992**, *57*, 4027.
(28) Tsubouchi, H.; Tsuji, K.; Yasumura, K.; Tada, N.; Nishitani, S.; Minamikawa, J.; Ishikawa, H. *Tetrahedron: Asymmetry* **1994**, *5*, 441.
(29) Prasad, K. K.; Chen, K. M. U.S. Patent 4,847,384, 1989.
(30) Rao, M. N.; Holkar, A. G.; Ayyangar, N. R. *Chem. Commun*. **1991**, 1007.
(31) Li, J.; Lu, R.; Yang, A.; Zhang, J. *Heterocycl. Commun.* **2004**, *10*, 447.
(32) High yielding 1,4-additions of 2-mercaptobenzothiazole to Michael acceptors such as 4-vinylpyridines,[33] *S*-vinyl-sulfimines,[34] and acrylates/acrylamide[35] have been reported.
(33) Katritzky, A. R.; Takahashi, I.; Marson, C. M. *J. Org. Chem.* **1986**, *51*, 4914.
(34) Yamamoto, T.; Okawara, M. *Chem. Lett*. **1975**, 581.
(35) Anan'eva, K. V.; Rozhkova, N. K. *Khim. Geterotsikl. Soedin*. **1986**, 554.
(36) *S*-Benzoyl-2-mercaptobenzothiazole has been reported to give exclusively the *N*-benzoylation product with 2-amino-1-propanol: Lee, J. H.; Kim, J. D. *Bull. Korean Chem. Soc.* **1997**, *18*, 442.
(37) Mercaptobis(benzothiazolyl)disulfide (CAS Reg. No. 120-78-5) is a very cheap bulk chemical produced on a multiton scale (used as vulcanization additive in the rubber industry[38]). For the use of this disulfide in the in situ generation of a mercaptobenzothiazol-2-yl-thioester-*Ti*-enolate en route to β-lactams, see ref 39.
(38) Freytag, H.; Kempermann, T.; Fromandi, G. French Patent FR 1455518, 1966.
(39) Sharma, S. D.; Kanwar, S. *Synlett* **2004**, 2824.
(40) Prior to our study, only a single account on the preparation of a 2-mercaptobenzothiazolylcinnamic acid thioester via a different method appeared in the literature: Moharram and Assad reported the synthesis of the 4-nitro- and 4-chlorocinnamic thioesters of 2-mercaptobenzothiazole in 45 and 60% yield, respectively, by reacting the corresponding cinnamic acid chloride with the sodium salt of 2-mercaptobenzothiazole in benzene (only elemental analysis and mp given; no NMR, IR, or crystal structure data reported; hence thione structure can not be excluded): Moharram, H. H.; Asaad, F. M. *Egypt. J. Chem.* **1989**, *32*, 367.

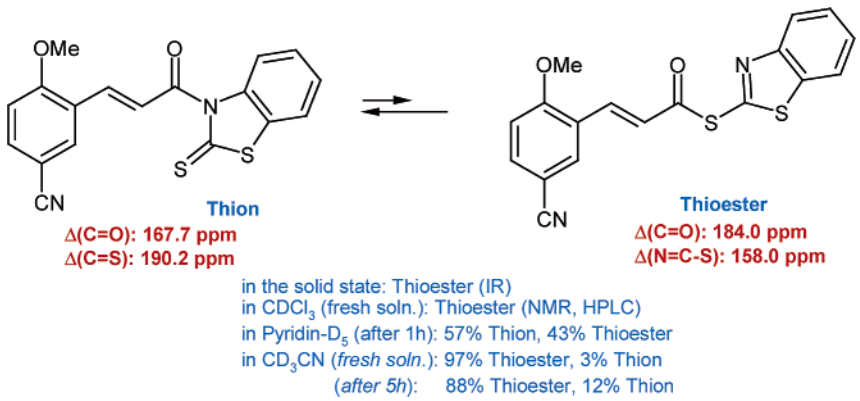


Figure 2. **Thioester−thion equilibrium of 5.**

acetic anhydride,[44] we characterized thioester **5** carefully. In the solid state, **5** exists exclusively as the thioester, whereas, in solution, a slow equilibration toward the thermodynamically more stable[44] thionoamide takes place (Figure 2).[45]

Not surprisingly,[48] this equilibrium did not have any bearing on the subsequent *N*-acylation process (vide infra). While a solution of the thioester **5** in EtOH (rt and 40 °C) failed to show any signs of transacylation to ethanol up to 48 h of reaction time, a solvent screening for the coupling reaction revealed a puzzling finding: even with this relatively unreactive and usually *N*-selective[36] thioester, considerable amounts of the *N*,*O*-diacyl product **4b** were formed; in ethyl acetate and pyridine, exclusive formation of **4b** was observed (Table 1)!

At this point we suspected that our results, taken with the equally disappointing (18−41%) yields in the few examples known (vide supra, Scheme 1[12−14]), pointed to an intramolecular *N*-acceptor hydrogen bond in these systems, which would be expected to greatly enhance the nucleophilicity of the primary hydroxyl group and favor the formation of the *N*,*O*-diacyl side product **4b** (Figure 3).

Intramolecular hydrogen bonding has been recognized[62] as the dominating noncovalent interaction in 1,2-,[59] 1,3-,[60] and 1,4-[61] aminoalcohols. While the impact of this phenomenon on enzyme mechanisms is well recognized in biology (Serine esterase model),[63] surprisingly few reports probe the practical consequences for synthetic organic transformations: an early study of Yoshida et al. from 1972[64] on the *O*-benzoylation of 2-dimethyl- and 2-diethylamino-1-ethanols

Table 1. **Solvent screening coupling 1 + 5**

solvent	thioester (equiv)	base (equiv)	*T* [°C]/*t* [h][a]	**4** [A% HPLC]	**4b** [A% HPLC]
EtOAc	1.1	NMM (2.0)	2−25, 7		21.6
THF	1.1	NMM (2.0)	25−43, 17	82	11.5
pyridine	1.3	(none)	0−2, 3.5		8.7
DMSO	1.4	NMM (1.5)	25, 120	91.9	1.3

[a] Reaction stopped after time given in table and analyzed by HPLC.

(41) 2-Mercaptobenzothiazole readily forms complexes with many transition metals; see: Wang, B.; Ma, H.; Yang, S. *Transition Met. Chem.* (London) **1995**, *20*, 391. A 2-mercaptobenzothiazole clay (a) and poly(vinylene) polymer (b) have been proposed as matrices for sorption of heavy metals: (a) Dias Filho, N. L.; Gushikem, Y.; Polito, W. L. *Anal. Chim. Acta* **1995**, *306*, 167. (b) Antokolskaya, I. I.; Volf, L. A.; Danilova, E. Y.; Emets, L. V.; Myasoedova, G. V.; Naumenko, E. A.; Sawin, S. B.; Trutneva, L. M.; Shvoeva, O. P.; Shcherbinina, N. I. Russian Patent SU 1015651, 1992.

(42) Nagao, Y.; Kawabata, K.; Seno, K.; Fujita, E. *J. Chem. Soc., Perkin Trans. I* **1980**, 2470.

(43) Nagao, Y.; Inoue, T.; Fujita, E.; Terada, S.; Shiro, M. *J. Org. Chem.* **1983**, *48*, 132.

(44) Nishio, T.; Shiwa, K. *Heterocycles* **2004**, *62*, 313.

(45) By the same token, the α-amino acid benzothiazole thioesters reported by Singh et al.[46] were most likely the corresponding thione isomers by virtue of the reported ^{13}C NMR data (δ 203−204 ppm more characteristic of thiocarbonyl than of thioester- or ester-carbonyl[47]). The thioester is the kinetic product, and the thione, the thermodynamic product[44]; we observed that the rate of equilibration increases with the solvent polarity (fastest in pyridine, slowest in chloroform).

(46) Singh, G. P.; Godbole, H. M.; Nehate, S. P.; Mahajan, P. R. *Synth. Commun.* **2005**, *35*, 243.

(47) Pretsch, E.; Simon, W.; Seibl, J.; Clerc, T. *Spectral Data for Structure Determination of Organic Compounds*, 2nd ed.; Springer-Verlag: Berlin, 1989; C203.

(48) *N*-Acylthiazolidin-2-thiones have been reported to undergo facile transamidation with primary and secondary amines; see: (a) Nagao, Y.; Seno, K.; Miyasaka, T.; Fujita, E. *Chem. Lett.* **1980**, 159. (b) Joyeau, R.; Brown, E. *Bull. Soc. Chim. Fr.* **1982**, 391.

(49) Mulla, S. T.; Jose, C. I.; *J. Chem. Soc., Faraday Trans. I* **1986**, *82*, 691.

(50) Prabhumirashi, L. S.; Jose, C. I. *J. Chem. Soc., Faraday Trans. II* **1975**, *71*, 1545.

(51) Chitale, S. M.; Jose, C. I. *J. Chem. Soc., Faraday Trans. I* **1986**, *82*, 663.

(52) In polar solvents such as alcohols or DMSO, intramolecular hydrogen bonds usually collapse or are much weaker, as hydrogen bonds to the solvent dominate; see: (a) Singelenberg, F. A. J.; Lutz, E. T. G.; van der Maas, J. H.; Jalsovszky, G. J. *Mol. Structure* **1991**, *245*, 173. (b) Kramer, R.; Lang, R.; Brzezinski, B.; Zundel, G. *J. Chem. Soc. Faraday Trans. I* **1990**, *86*, 627. (c) Sasanuma, Y.; Hattori, S.; Imazu, S.; Ikeda, S.; Kaizuka, T.; Iijima, T.; Sawanobori, M.; Azam, M. A.; Law, R. V.; Steinke, J. H. G. *Macromolecules* **2004**, *37*, 9169.

(53) On a relative price scale, the coupling reagent pair PPh_3/$(BThS)_2$ ranges among the most economic choices (chloroformates/imidoyl chlorides/carbodiimides):

Reagent	*Price Base*	*Approx. price in CHF / mol [status: 2002]*
DCC	Ton scale	7
EDCI	Ton scale	96
PROPSAL	Ton scale	40
CDMT	Ton scale	12
TBTU	Ton scale	84
PyBOP	100-200kg	520
CDI	Ton scale	23
Isobutyl chloroformate	Ton scale	2
Vilsmeyer reagent	Ton scale	6
PPh_3/$(BThS)_2$	Ton scale	6

(54) Above 240 °C, an exothermic decomposition sets in from the melt liberating ~ −115 kJ/kg. In the wetcake, a dynamic DSC reveals that exothermic decomposition may set in earlier (−175 kJ/kg, at ~160 °C).

(55) In an experiment where the cinnamic acid was added all in one portion, the observed ΔT_{max} was ≤15 °C.

(56) At ~200 °C, the melt exhibits exothermic decomposition (−255 ± 15 kJ/kg), most likely related to acrylic polymerization since the cinnamic acid **3** shows the same type of behavior in the dynamic DSC above the melting point (226−228 °C): decomposition around ~250 °C, −274 kJ/kg.

(57) In more polar solvents, such as DMSO and pyridine, a gradual equilibration to the thione sets in (slow emergence of second set of signals).

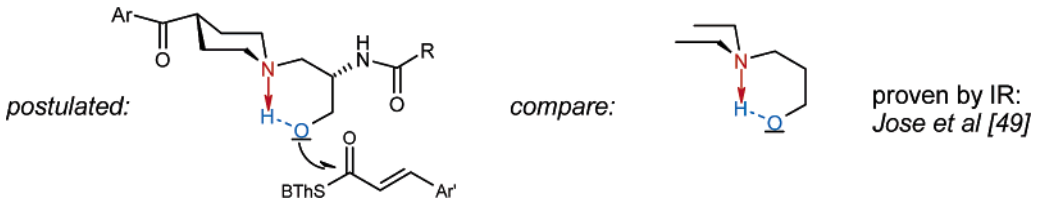


Figure 3. **Postulated intramolecular hydrogen bond in 4.**

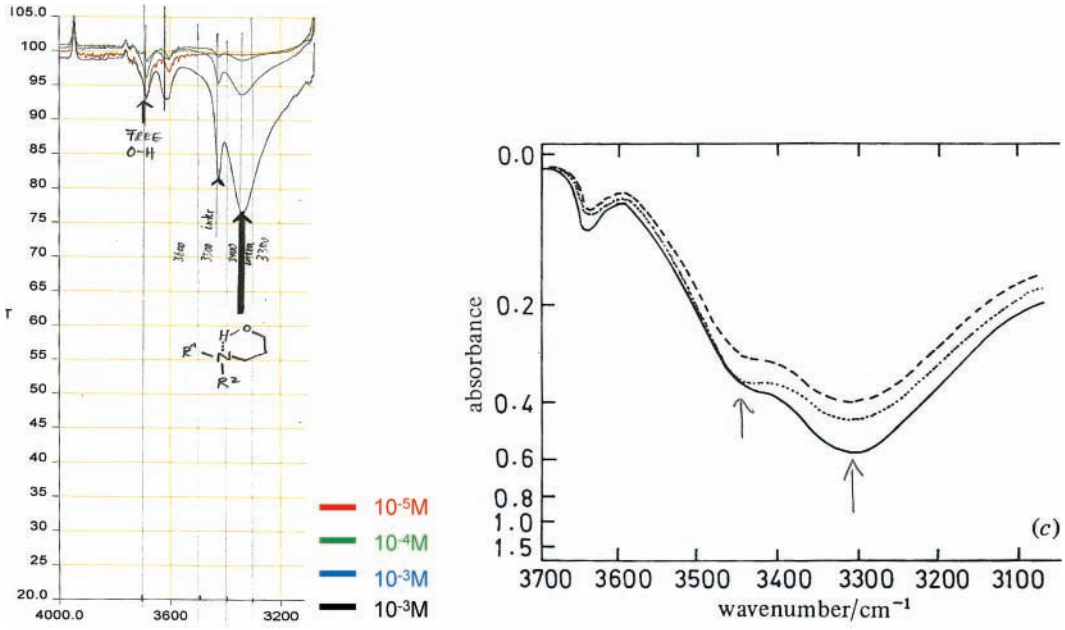


Figure 4. **IR (CH_2Cl_2) of 4 (left, in CH_2Cl_2) and of 3-diethylamino-1-propanol (right, in C_2Cl_4)[49] in the O−H stretching region.**

found significant rate increases in cases where intramolecar hydrogen bonding was strong; similar observations were later reported for the *O*-acylation rates of dimethylaminoalcohols of varying chain lengths with *N*-acetylimidazole (De Clercq et al.[65]) and hexanoic acid (Bach et al.[66]), whereas Hine et al.[67,68] investigated *o*-(dimethylaminomethyl)benzyl alcohol as a serine esterase model and demonstrated its effectiveness as a nucleophilic catalyst for the hydrolysis of *p*-nitrophenyl acetate.

In fact, dilute solution IR spectra of the aminoalcohol **4** (free base) confirmed our hypothesis (Figure 4). In keeping with the findings of Jose and Mulla[49] on the hydrogen bonding behavior of 3-diethylamino-1-propanol and similar aminoalcohols, the relative population of intramolecularly hydrogen-bonded species versus free species in **4** was found to be much larger as typically observed for β-alkoxy[50] or β-halogeno[51] alcohols (cf. Figures 3 and 4).

Based on this finding, we decided to further investigate the coupling reaction in a hydrogen bond donor solvent, i.e., an alcohol.[52] Furthermore, we speculated that, by only partially neutralizing the acid in the aminoalcohol dihydrochloride **1**, the crucial *N*-acceptor hydrogen bond believed to be responsible for hydroxyl group activation should collapse both in the starting material and in the product (Figure 5), thereby minimizing the formation of the unwanted *N*,*O*-diacylated side product **4b**.

Table 2 summarizes the experiments that confirmed our hypothesis; in the finalized coupling process (Table 2, entry 5), only 1 equiv of base was used (Scheme 5).

The coupling scaled up very well in the pilot plant; after salt formation and the final polish recrystallization from

(58) Above 170 °C, a slow exothermic decomposition sets in from the melt, liberating ~ −110 kJ/kg.
(59) For 2-aminoalcohols, see: (a) Casy, A. F.; Hassan, M. M. A. *Can. J. Chem.* **1969**, *47*, 1587. (b) De Roos, A. M.; Bakker, G. A. *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 219. (c) Shergina, N. I.; Kashik, T. V.; Kositsyna, É. I.; Dmitrieva, Z. T.; Trofimov, B. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1969**, 2703. (d) Houriet, R.; Rüfenacht, H.; Carrupt, P.-A.; Vogel, P.; Tichy, M. *J. Am. Chem. Soc.* **1983**, *105*, 3417. (e) Máté-Divó, M.; Barcza, L. *ACH-Models in Chemistry* **1994**, *131*, 769.
(60) For 3-aminoalcohols, see: (a) De Roos, A. M.; Bakker, G. A. *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 219. (b) Máté-Divó, M.; Barcza, L. *ACH-Models in Chemistry* **1994**, *131*, 769. (c) Przeslawska, M.; Melikowa, S. M.; Lipkowski, P.; Koll, A. *Vib. Spectrosc.* **1999**, *20*, 69. (d) Bartoli, G.; Grilli, S.; Lunazzi, L.; Massaccesi, M.; Mazzanti, A.; Rinaldi, S. *J. Org. Chem.* **2002**, *67*, 2659. (e) Koll, A.; Karpfen, A.; Wolschann, P. *J. Mol. Struct.* **2006**, *790*, 55.
(61) For 4-aminoalcohols, see: (a) De Roos, A. M.; Bakker, G. A. *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 219. (b) Delacroix, O.; Andriamihaja, B.; Picart-Goetgheluck, S.; Brocard, J. *Tetrahedron* **2004**, *60*, 1549.
(62) Bergmann et al. were the first to recognize this intramolecular interaction during their study of *N*-alkyl-substituted 2-aminoalkanols: Bergmann, E. D.; Gil-Av, E.; Pinchas, S. *J. Am. Chem. Soc.* **1953**, *75*, 68.
(63) In several key metabolic enzymes (including acetylcholine esterase and α-chymotrypsin), the enzyme mechanism involves attack onto a substrate carbonyl by a serine hydroxyl group activated by a hydrogen bond to an imidazole from a histidine residue; see: (a) Hartely, B. S. *Annu. Rev. Biochem.* **1960**, *29*, 45. (b) Zeffren, E., Hall, P. L., Eds. *The study of enzyme mechanisms*; Wiley-Interscience: New York, 1973; Chapter 9. (c) Scheiner, S.; Lipscomb, W. N. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 432. (d) Naray-Szabo, G. *THEOCHEM* **2000**, *500*, 157.
(64) Yoshida, J.; Ichimura, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3215.
(65) Madder, A.; De Clercq, P. J.; Maskill, H. *J. Chem. Soc., Perkin Trans. II* **1997**, 851.
(66) Breitenlechner, S.; Bach, T. *Z. Naturforsch.* **2006**, *61b*, 583.
(67) Hine, J.; Khan, M. N. *J. Am. Chem. Soc.* **1977**, *99*, 3847.
(68) Hine, J.; Khan, M. N. *Indian J. Chem.* **1992**, *31B*, 427.

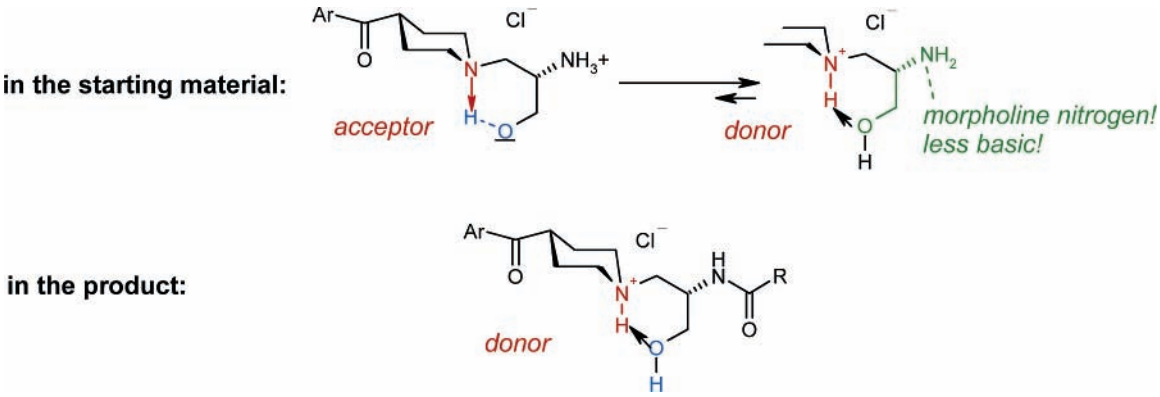


Figure 5. **Monohydrochloride reverses the crucial N−H−O hydrogen bond in starting material and product: from acceptor to donor.**

Table 2. **Screening of base amount**

solvent	thioester (equiv)	base (equiv)	*T* [°C]/ *t* [h][a]	**4** [A% HPLC]	*N*,*O*-diacyl [A% HPLC]
*i*PrOH	1.1	NMM (2.0)	2−25, 8	73.1	0.9 (+16.5% **1**)
EtOH	1.1	NMM (4.0)	50, 8	92.1	4.7
EtOH	1.1	NMM (2.0)	36, 24	94.4	2.4
EtOH	1.1	NMM (1.25)	45, 27	96.0	0.9
EtOH	1.05	NMM (1.0)	45, 24	97.7	0.3

[a] Reaction stopped after time given in table and analyzed by HPLC.

ethanol, we obtained 3.8 kg (76% overall yield [lab: 79%] from **1**) of the tartrate **4** in previously unattainable purity (>98% HPLC **4b**: <0.2%, >99% ee), effectively more than tripling the overall yield of the discovery route and eliminating all chromatographic purifications. The thioester activation *in combination* with the alcoholic solvent and substoichiometric (0.5 equiv) base proved crucial for success. Attempts to extend these coupling conditions to other activation methods (acid chloride, CDI, DIC) met with failure due to increased side product formation with these coupling agents in alcoholic solvents.

Conclusions

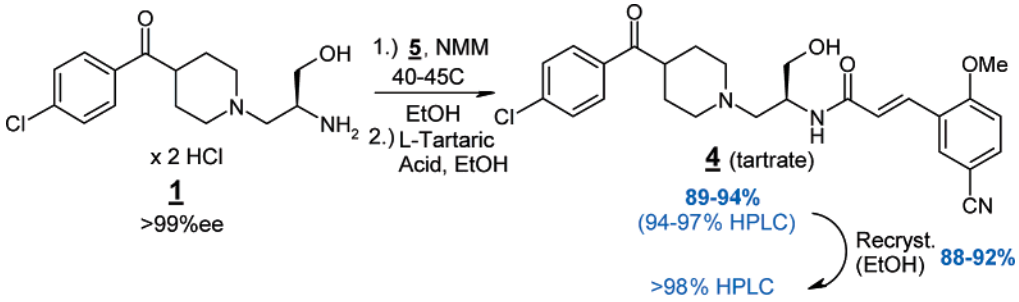
The first robust, selective, and high-yielding process for kilogram-scale, chromatography-free preparation of an α-*N*-acyl-α,*β*-diaminoalcohol (**4**) has been developed. We propose this novel and economic[53] coupling procedure using the *S*-2-mercaptobenzothiazolylester in an alcoholic solvent with half-stoichiometric base as a selective and efficient *N*-acylation method for α-aminoalcohols with an alkylamino substituent in the *β*-position, as in those systems the activation of the hydroxyl group by intramolecular *N*-acceptor-hydrogen bonding is expected to be a general phenomenon.[49,60,64−66] Furthermore, we demonstrated the first use of a *S*-mercaptobenzothiazolyl thioester of an α,*β*-unsaturated (cinnamic) ester as *N*-acylating agent and found that 1,4-addition of the liberated mercaptane is not a limiting side reaction for this coupling system.

Experimental Section

Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without further purification. All the melting points are uncorrected and determined on a Büchi apparatus. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz on a Bruker DPX 400/500 instrument. Assignments were confirmed by the appropriate 2D NMR experiments. IR spectra were measured on a Bruker IFS660 spectrometer. Exact mass determinations were performed on a Micromass QtoF Ultima API instrument (a soln of 0.1% caffeine was used for lock mass correction). For reaction monitoring, a Hewlett-Packard Series 1050 HPLC system with either a SymmetryShield RP-18 or YMC ODS-AQ column (150 mm × 3 mm, 3 μm particle size) was used (0.01 M $(NH_4)_2HPO_4$ or KH_2PO_4−CH_3CN gradient). The enantiomeric purities of **1**, **2**, and **4** were determined at λ = 245 nm on a Hewlett-Packard Series 1050 or 1100 HPLC system using a Chiralpak AD column (Daicel, 250 mm × 4.6 mm, 10 μm particle size); mobile phase: *n*-hexane/isopropanol/diethylamine 20:80:0.1, isocratic.

(2*S*)-2-Amino-3-(4-(4′-chlorobenzoyl)piperidin-1-yl)-1-propanol Dihydrochloride (1).[10] To a suspension of the dibenzoyl-hemi(L)tartrate **2**[10] (75.0 g, 60.86 mmol) in *n*-butylacetate (750 mL) was slowly added concd aq (32%) hydrochloric acid (35.8 mL, 0.3645 mol) at 20−22 °C. The resulting thin white suspension was stirred at 20−25 °C for an additional 2.5 h, when HPLC showed completeness of the deprotection reaction. The suspension was cooled to 0−2 °C, stirred at this temperature for 90 min, and filtered. The filter cake was washed with ice-cold *n*-butyl acetate (4 × 50 mL), and the colorless filtercake was dried at 45−50 °C under a vacuum overnight to give **1** as a white, crystalline solid (44.8 g, 99% yield) [Pilot Plant: 6.3 kg, 93%]. HPLC [265 nm] 98.1% [Pilot Plant: 98.8%], 97% ee [Pilot Plant: >99% ee], mp (DSC) 239−240 °C, DSC [dry product] (dynamic): no exotherm up to 235 °C,[54] DSC (isotherm, 100 °C, 24 h): no exotherm observed [dynamic DSC of stressed sample: no significant changes vs DSC of fresh sample]. ^{1}H NMR (400 MHz, DMSO) δ 1.95−2.12 (m, 4 H, 2 × N−CH_2−CH_2 (piperidine)), 3.05−3.90 (br m, 10 H, 3 × N−CH_2 (piperidine), H_3N^+−CH, HO−CH_2, CH−C=O), 5.62 (br s, 1 H, O−*H*, *exch. with NaOD*), 7.62/8.03 (AA′BB′, 4 H, 4-Cl−Ph), 8.65 (br s, 3 H, H_3N^+, *exch. with NaOD*), 10.78 (br s, 1 H, HN^+ (piperidine), *exch. with NaOD*). ^{13}C NMR (100 MHz, DMSO) δ: 26.3, 26.4, 41.0, 48.5, 52.4, 53.9, 57.0, 60.4, 129.9, 131.2, 134.6, 139.3, 200.8.

Scheme 5. **Optimized coupling of diaminoalcohol 1 with thioester 5**



IR (neat, FT−IR microscope, cm^{-1}): 3543m, 3314s, 2981s, 2956s, 2933s, 2888s, 2759m, 2676sh, 2623m/s, 2496s, 2411sh, 1681ss, 1589m/s, 1464m/s, 1434m, 1308m, 1281m, 1217m, 1153w, 1093m, 1052m, 1012w, 939m, 846m. Elemental analysis calcd. for $C_{15}H_{23}Cl_3N_2O_2$ (369.72): C, 48.73%; H, 6.27%; N, 7.58%. Found: C, 48.85%; H, 6.11%; N, 7.57%.

(*E*)-3-(5-Cyano-2-methoxyphenyl)thioacrylic Acid *S*-Benzothiazol-2-yl-thioester (5).[10] A suspension of triphenylphosphine (28.4 g, 0.108 mol) and bis(2,2′-benzothiazolyl)-disulfide (36.0 g, 0.108 mol) in methylene chloride (540 mL) was stirred vigorously under a nitrogen atmosphere for 1.5 h at 20−22 °C. To the resulting thin, caramel suspension was added 5-cyano-2-methoxyphenylacrylic acid **3**[10] (20.0 g, 98.4 mmol, [46 ppm Pd]) in four equal portions over a 1 h 20 min period. Under these conditions, the reaction is nearly addition controlled and only very weakly exothermic (temp rises by ∼3−4 °C after each addition and then drops back to ambient temp over an ∼20 min period).[55] After the last addition, the yellow suspension was stirred for an additional 45 min. *N*-Methylmorpholine (10.82 mL, 98.4 mmol) was added, and stirring was continued for another hour, when HPLC showed ≥99%. The suspension was cooled to 0−4 °C, stirred for 30 min at 0−4 °C, and filtered. The filter cake was washed with ice-cold methylene chloride (1 × 60 mL), and the yellowish filtercake was dried at 35 °C under a vacuum overnight to afford **5** as a slightly yellowish, crystalline solid (26.95 g, 78% yield) [Pilot Plant: 3.0 kg, 68%], HPLC [265 nm]: 97.3% [Pilot Plant: 95.3%], Pd ≤ 1 ppm, mp 183−185 °C. DSC [dry product] (dynamic): no exotherm up to 185 °C.[56] DSC (isotherm, 100 °C, 24 h): no exotherm observed [dynamic DSC of stressed sample: no significant changes vs DSC of fresh sample]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 3 H, OC*H*$_3$), 7.0 (d, 1 H, C*H*═, $^3J_{trans}$ = 16.0 Hz), 7.06 (d, 1 H, C*H*$_{arom}$ [OMe(CN)Ph], ^3J = 8.4 Hz), 7.48−7.58 (m, 2 H, C*H*$_{arom}$ [BTh]), 7.73 (d, 1 H, C*H*$_{arom}$ [OMe(CN)Ph], ^3J = 8.4 Hz), 7.88 (s, 1 H, C*H*$_{arom}$ [OMe(CN)Ph]), 7.95−8.12 (m, 2 H, C*H*$_{arom}$ [BTh]), 8.03 (d, 1 H, C*H*═, $^3J_{trans}$ = 16.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.7, 105.3, 112.5, 118.6, 121.6, 123.6, 124.1, 126.0, 126.1, 126.8, 127.8, 133.9, 136.5, 137.3, 139.7, 151.9, 158.2 (*N*═*C*—S), 162.1, 185.1 (*C*═O).[57] Elemental analysis calcd. for $C_{18}H_{12}N_2O_2S_2$ (352.43): C, 61.34%; H, 3.43%; N, 7.95%; S, 18.20%. Found: C, 61.12%; H, 3.65%; N, 7.63%; S, 17.87%.

(*E*)-*N*-{(*S*)-1-[4-(4-Chlorobenzoyl)-piperidin-1-yl-methyl]-2-hydroxyethyl}-3-(5-cyano-2-methoxyphenyl)acrylamide (L)-Tartrate (4).[10] To a suspension of the dihydrochloride **1** (9.24 g, 25 mmol) in ethanol abs (250 mL) at 20−22 °C was added *N*-methylmorpholine (2.76 mL, 25 mmol). Under vigorous stirring, the temperature of the white suspension was slowly increased to 45 °C over a 30 min period. The first aliquot of thioester **5** (4.40 g, 12.5 mmol) was added (washed powder addition funnel with 20 mL ethanol abs). The yellow, thin suspension was stirred vigorously at 45 °C. In process, controls were taken in 2.5 h intervals. As soon as the HPLC showed no more increase in **4**, the second aliquot of the thioester **5** was added (4.40 g, 12.5 mmol), and stirring was continued until HPLC indicated ≥98% conversion of **1** (typically after 22−24 h). The yellowish suspension was then cooled to 20−22 °C, *N*-methylmorpholine (2.76 mL, 25 mmol) was added, and the mixture was filtered over a glass frit (medium porosity). The filter residue was washed with ethanol abs (15 mL), and the yellowish filtrate was evaporated to a small volume. After a solvent switch to methylene chloride, the clear solution (300 mL) was washed at 20−22 °C with 10% aq sodium carbonate (2 × 100 mL), 10% aq sodium chloride (100 mL), and water (100 mL). The acidity of the combined aq phases was adjusted to pH 11 by addition of solid sodium carbonate, and the aq phases were extracted with methylene chloride (100 mL). The combined organic phases were filtered over celite and reduced to a small volume. After a solvent switch to ethanol, the clear solution (130 mL) was heated to 55 °C. Under vigorous stirring, a solution of (L)-tartaric acid (4.50 g, 30 mmol) in ethanol abs (100 mL) was added over a 15 min period. The mixture was quickly heated to 70 °C and stirred until a clear, homogeneous solution formed (∼30 min). Over a 1.5 h period, the solution was slowly cooled to 0 °C and stirred at this temperature for 45 min. The solid was filtered off and washed with cold ethanol abs (20 mL). The wetcake was suspended in ethanol abs (200 mL) and heated to reflux under stirring. More ethanol abs was slowly added until a clear solution formed (total volume: 610 mL). The hot solution was filtered, and the clear, yellowish filtrate was concentrated under reduced pressure (300 mbar, 65−67 °C) to 60% of the original volume. The concentrate was cooled to 30 °C over a 1.5 h period (seeded with 100 mg of **4** at 60 °C) and then to 0 °C over a 2 h period and stirred at 0−2 °C for 1.5 h. The suspension was filtered, and the filter cake was washed with ice-cold ethanol abs (20 mL) and dried at 45−50 °C under a vacuum overnight to afford recrystallized **4** as an off-white, crystalline solid (12.43 g, 79% yield from **1**) [Pilot Plant:

3.85 kg, 77%], HPLC [245 nm]: 98% [Pilot Plant: 98%] (residual *N*,*O*-diacyl product: <0.3% [245 nm], residual 2-mercaptobenzothiazole: <60 ppm), >99% ee [Pilot Plant: >99% ee]. Mp 165−166 °C. DSC (dynamic): no exotherm up to 160 °C;[58] DSC (isotherm, 130 °C, 12 h): no exotherm observed [dynamic DSC of stressed sample: no significant changes vs DSC of fresh sample]. Salt stoichiometry titrations (NaOH + $HClO_4$): 1:1 salt (tartrate). For NMR-spectrum analysis, a small sample was freebased (10% Na_2CO_3/CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO) [free base] δ ^{1}H NMR (400 MHz, DMSO) δ 1.50−1.82 (m, 4 H, 2 × N−CH_2−CH_2 (piperidine)), 2.11−2.23 and 2.89−3.01 (2 m, 4 H, 2 × N−CH_2 (piperidine), 2.40, 2.50 (2 dd, 2 H, N−CH_2−CH−N, J = 7.0 Hz, J = 12.5 Hz), 3.35−3.41 (m, 1 H, C*H*−C═O), 3.45−3.53 (br m, 2 H, CH_2−OH, collapses to AB-system with D_2O), 3.98 (s, 3 H, OCH_3), 3.98−4.08 (m, 1 H, HN−C*H*), 4.82 (br s, 1 H, O−*H*, exchanged with D_2O), 6.88 (d, 1 H, *H*−C═C, J_{trans} = 15.9 Hz), 7.27 (d, 1 H, *H*−C_{arom}, J = 8.7 Hz), 7.56 (d, 1 H, *H*−C═C, J_{trans} = 15.9 Hz), 7.61 (AA′-system, 2 H, *H*−C_{arom} [chlorophenyl]), 7.83−7.90 (m, 2 H, *H*−C_{arom} + *H*−N−C═O, collapses to a simpler m [1 H] with D_2O), 7.96−8.03 (m, 3 H, *H*−C_{arom}). ^{13}C NMR (100 MHz, DMSO) [free base] δ 29.3 (N−CH_2−*C*H_2 (piperidine)), 43.6 (*C*H−C═O), 49.5 (HN−*C*H), 53.78/53.84 (2 × N−*C*H_2 (piperidine)), 57.2 (N−CH_2−*C*H), 59.9 (O*C*H_3), 62.9 (*C*H_2−OH), 104.1 (C_{ipso} arom. (cyanophenyl)), 113.7 (*C*H_{arom}), 119.7 (*C*≡N), 125.7 (═C−C_{ipso} arom.), 126.6 (O═C−*C*═), 129.8 (2 × *C*H_{arom} (chlorophenyl)), 131.0 (2 × *C*H_{arom} (chlorophenyl)), 132.5 (═*C*−C_{ipso}), 133.0 (*C*H_{arom}), 135.2, 135.5 (2 × C_{ipso} (chlorophenyl), 138.9 (*C*H_{arom}), 161.5 (C_{ipso} (methoxyphenyl)), 165.4 (HN−*C*═O), 202.5 (4-ClPh−*C*═O). IR [free base] (KBr, cm^{-1}) 3433w/br, 3387m, 3354m, 2945w, 2926w, 2225m, 1664ss, 1623m, 1601s, 1588m, 1527s, 1495s, 1462w, 1267ss, 1208w, 1092m, 1015w, 974m/s, 821m. HR−MS [free base]: exact mass calculated for $C_{26}H_{28}ClN_3O_4 \times H^+$, 482.1841; found, 482.1842.

Acknowledgment

We are grateful to Mr. Michael Haller for skillful technical assistance and to Dr. Jacques Wiss for DSC measurements. Drs. Thomas Allmendinger and Ching-Pong Mak are thanked for their continued support and encouragement.

Received for review July 23, 2006.

OP0601464