JOC*Note*

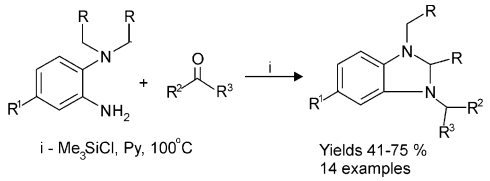
One-Pot Synthesis of 2,3-Dihydro-1*H*-benzimidazoles

Sergey V. Ryabukhin,[†,‡] Andrey S. Plaskon,[†,‡] Dmitry M. Volochnyuk,*[,†,§] Alexander N. Shivanyuk,[‡] and Andrey A. Tolmachev[‡]

Enamine Ltd., 23 A. Matrosova st., 01103 Kyiv, Ukraine, National Taras Shevchenko University, 62 Volodymyrska st., 01103 Kyiv, Ukraine, and Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Murmanska st., 02094 Kyiv-94, Ukraine

d.volochnyuk@enamine.net

Received June 12, 2007



A convenient one-pot method for the synthesis of 2,3-dihydro-1*H*-benzimidazoles has been elaborated. A set of 2,3-dihydro-1*H*-benzimidazoles was prepared from various *ortho*-dialkylaminoanilines and aldehydes using Me_3SiCl as a condensation agent and pyridine as a basic medium.

2,3-Dihydro-1*H*-benzimidazoles are potential CH hydride donors whose reactivity is facilitated by the formation of aromatic benzimidazolium cations. They attracted considerable research interest as biologically active compounds, mimetics of redox enzymes, and reduced electron carriers such as NADH and $FADH_2$.[1,2]

2,3-Dihydro-1*H*-benzimidazoles can be obtained through condensation of 1,2-disubstituted phenylenediamines[2] with aldehydes[3] or the Mannich reaction with formaldehyde and benzotriazole.[4] Another synthetic methodology is based on reduction of benzimidazolium salts.[5,6]

The use of t-amino effect[7] in the synthesis of 2,3-dihydro-1*H*-benzimidazoles from azomethines of *ortho*-phenylenediamines is impeded by the acid-catalyzed disproportionation leading to equimolar mixtures of 2,3-dihydro-1*H*-benzimidazolium salts and *ortho*-phenylenediamines.[8] Only in the case of the pyrrolidine derivatives of *ortho*-phenylenediamine were the 2,3-dihydro-1*H*-benzimidazoles obtained in preparative yields, most probably due to steric hindrances of the intermolecular hydride transfer. In our search of efficient preparative methods for the synthesis of 2,3-dihydro-1*H*-benzimidazoles from *ortho*-phenylenediamines and carbonyl compounds, we chose pyridine as a proton-accepting solvent which might prevent the undesirable disproportionation of target compounds and TMSCl as promoter,[9] which is known to mediate various condensation reactions.[10]

Condensation of *ortho*-pyrrolidinyl-, *ortho*-perhydroazepinyl-, *ortho*-diethylamino-, and *ortho*-dipropylamino anilines with aldehydes **2** in pyridine at 100 °C in the presence of 3 mol of chlorotrimethylsilane led to 2,3-dihydro-1*H*-benzimidazoles **3** in 41−75% yields (Scheme 1), whereas no trace of the azomethines was detected in the reaction mixtures. Apparently, pyridine neutralizes HCl formed and prevents the disproportionation of compounds **3** into 2,3-dihydro-1*H*-benzimidazolium salts **4** and *ortho*-phenylenediamines **5** (Scheme 2). Compounds **3** are white crystalline compounds well soluble in $CHCl_3$, CH_2Cl_2, MeOH, EtOH, and DMF and insoluble in hexane. ^{1}H NMR spectroscopy revealed that 2,3-dihydro-1*H*-benzimidazoles are easily oxidized by DMSO in solution.

Cyclohexanone and acetophenone also react with diamine **1a** to give stable 2,3-dihydro-1*H*-benzimidazoles **3f** and **3g** in preparative yields. ^{1}H NMR spectroscopy revealed that two possible diastereomers of compound **3g** are formed in a 2:3 molar ratio. Lower reactivity of ketones compared to that of aldehydes required longer reaction times and resulted in somewhat lower yields of 2,3-dihydro-1*H*-benzimidazoles **3f** and **3g**. 2,3-Dihydro-1*H*-benzimidazoles based on N-methylization and alloxan were reported to rearrange into spirotetrahy-

[†] Enamine Ltd.
[‡] National Taras Shevchenko University.
[§] National Academy of Sciences of Ukraine.

(1) (a) Kuecuekbay, H.; Cetinkaya, E.; Cetinkaya, B.; Lappert, M. F. *Synth. Commun.* **1997**, *27*, 4059−4066. (b) Ramos, S. M.; Tarazi, M.; Wuest, J. D. *J. Org. Chem.* **1987**, *52*, 5437−5442.

(2) (a) Hasegawa, E.; Chiba, N.; Takahashi, T.; Takizawa, S.; Kitayama, T.; Suzuki, T. *Chem. Lett.* **2004**, *33*, 18−19. (b) Brunet, P.; Wuest, J. D. *Can. J. Chem.* **1996**, *74*, 689−696. (c) Suslov, A. N.; Chernoivanov, V. A.; Dubonosov, A. D.; Kozina, O. A.; Bren', V. A.; Minkin, V. I. *Russ. J. Org. Chem.* **1995**, *31*, 1146−1147. (d) Morkovnik, A. S.; Suslov, A. N.; Klimov, E. S.; Morkovnik, Z. S.; Okhlobystin, Yu, O. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1995**, *31*, 563−566.

(3) (a) Kalyanam, N.; Manjunatha, S. G. *Heterocycles* **1991**, *32*, 1131−1136. (b) Harper, N. J.; Sprake, J. M. *J. Chem. Soc. C* **1969**, 882−886. (c) Hayward, R. J.; Meth-Cohn, O. *J. Chem. Soc., Perkin Trans. 1* **1975**, 212−218. (d) Saunders, A.; Sprake, J. M. *J. Chem. Soc. C* **1970**, 1161−1165.

(4) Katritzky, A. R.; Suzuki, K.; He, H.-J. *J. Org. Chem.* **2002**, *67*, 3109−3114.

(5) (a) Lee, I.-S. H.; Jeoung, E. H. *J. Org. Chem.* **1998**, *63*, 7275−7279. (b) Hasegawa, E.; Chiba, N.; Nakajima, A.; Suzuki, K.; Yoneoka, A.; Iwaya, K. *Synthesis* **2001**, 1248−1252. (c) Lee, I.-S. H.; Jeoung, E. H.; Kreevoy, M. M. *J. Am. Chem. Soc.* **1997**, *119*, 2722−2728. (d) Katritzky, A. R.; Aslan, D. C.; Oniciu, D. C. *Tetrahedron: Asymmetry* **1998**, *9*, 2245−2252. (e) Craig, J. C.; Ekwuribe, N. N.; Fu, C. C.; Walker, K. A. M. *Synthesis* **1981**, 303−305.

(6) Shi, Z.; Gu, H. *Synth. Commun.* **1996**, *26*, 4175−4179.

(7) (a) Meth-Cohn, O.; Suschitzky, H. *Adv. Heterocycl. Chem.* **1972**, *14*, 211−278. (b) Meth-Cohn, O. *Adv. Heterocycl. Chem.* **1996**, *65*, 1−37. (c) Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 311−324.

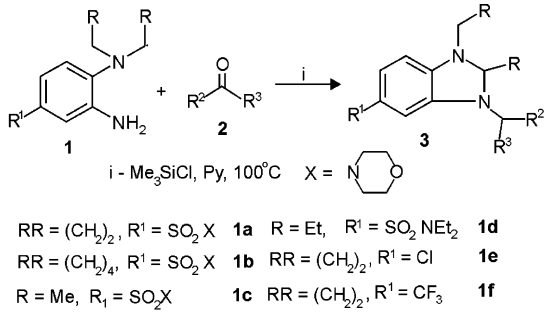
(8) (a) Meth-Cohn, Smalley, R. K.; O. Suschitzky, H. *J. Chem. Soc.* **1963**, 1666−1669. (b) Grantham, R. K.; Meth-Cohn, O. *Chem. Commun.* **1968**, 500−502. (c) Grantham, R. K. Meth-Cohn, O.; Naqui, M. A. *J. Chem. Soc. C* **1969**, 1438−1443. (d) Grantham, R. K.; Meth-Cohn, O. *J. Chem. Soc. C* **1969**, 1444−1448. (e) Clark-Lewis, J. W.; Moody, K.; Thompson, M. J. *Aust. J. Chem.* **1970**, *23*, 1249−1273. (f) Krasnov, K. A.; Kartsev, V. G.; Khrustalev, V. N. *Mendeleev Commun.* **2006**, *16*, 52−54.

(9) (a) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2006**, 3715−3726. (b) Ryabukhin, S. V.; Plaskon, A. S.; Ostapchuk, E. N.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2007**, 417−427. (c) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Tolmachev, A. A. *Synlett* **2004**, 2287−2290. (d) Ryabukhin, S. V.; Plaskon, A. S.; Tverdokhlebov, A. V.; Tolmachev, A. A. *Synth. Commun.* **2004**, *34*, 1483−1487.

(10) (a) Saidi, M. R.; Azizi, N. *Tetrahedron: Asymmetry* **2002**, *13*, 2523−2528. (b) Saidi, M. R.; Azizi, N. *Synlett* **2002**, 1347−1349. (c) Bolognesi, M. L.; Andrisano, V.; Bartolini, M.; Minarini, A.; Rosini, M.; Tumiatti, V.; Melchiorre, C. *J. Med. Chem.* **2001**, *44*, 105−109.

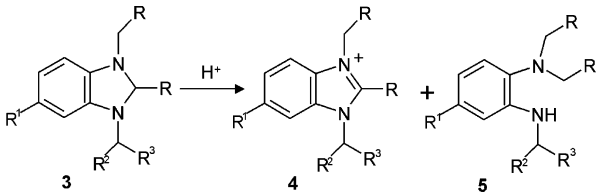
10.1021/jo0712087 CCC: $37.00
Published on Web 08/23/2007

SCHEME 1. One-Pot Synthesis of 2,3-Dihydro-1*H*-benzimidazoles from *ortho*-Dialkylaminoanilines and Aldehydes



N	R or RR	R^1	R^2	R^3	Yield %
3a	$(CH_2)_2$	SO_2X	H	Ph	72
3b	$(CH_2)_2$	SO_2X	H	*p*-$MeOC_6H_4$	70
3c	$(CH_2)_2$	SO_2X	H	*p*-ClC_6H_4	75
3d	$(CH_2)_2$	SO_2X	H	5-Me-2-thienyl	68
3e	$(CH_2)_2$	SO_2X	H	1,5-Me_2-2-CN-4-pyrrolyl	65
3f	$(CH_2)_2$	SO_2X		cyclohexyl	54
3g	$(CH_2)_2$	SO_2X	Me	Ph	41
3h	$(CH_2)_4$	SO_2X	H	Ph	45
3i	Me	SO_2X	H	*p*-$MeOC_6H_4$	64
3j	Me	SO_2X	H	1,5-Me_2-2-CN-4-pyrrolyl	63
3k	Et	SO_2NEt_2	H	*p*-ClC_6H_4	68
3l	$(CH_2)_2$	Cl	H	*p*-ClC_6H_4	61
3m	$(CH_2)_2$	CF_3	H	5-Me-2-thienyl	46
3n	$(CH_2)_2$	CF_3	H	1,5-Me_2-2-CN-4-pyrrolyl	60

SCHEME 2. Disproportionation of 2,3-Dihydro-1*H*-benzimidazoles into Benzimidazolium Salts and Phenylenediamines



droquinoxaline and tetrahydroquinoxalinespiropyrimidine-2,4,6-trione, respectively.

The reactions of *p*-dimethylaminobenzaldehyde or 2,3,4-trimethoxybenzaldehyde with compounds **1** resulted in a mixture of 2,3-dihydro-1*H*-benzimidazolium salt **4** and the corresponding phenylenediamine **5** (Scheme 2). Apparently, these compounds

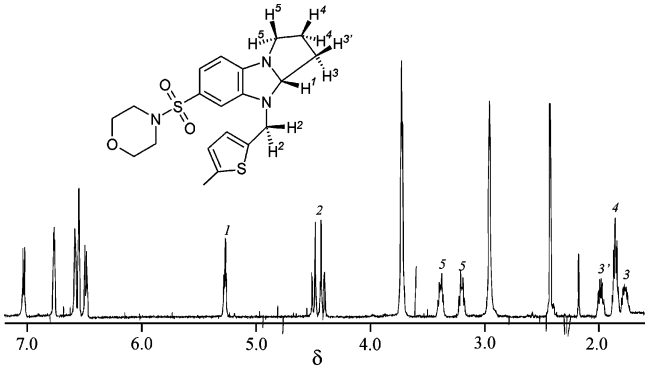


FIGURE 1. The ^{1}H NMR spectrum of compound **3d** (500 MHz, $CDCl_3$, 295 K). COSY correlations: H^1-H^3, $H^1-H^{3'}$, H^3-H^4, H^4-H^5; NOESY correlations: H^1-H^2, $H^1-H^{3'}$, H^3-H^4, H^4-H^5. $H^1-H^{3'}$ NOESY correlation is not observed.

are formed in the acid-catalyzed disproportionation of the corresponding 2,3-dihydro-1*H*-benzimidazoles **3**.

The structure and composition of compounds **3** were proved by 1D ^{1}H and ^{13}C NMR spectroscopy, COSY, NOESY, ^{1}H−^{13}C HMBC 2D NMR techniques, elemental analysis, and mass spectrometry. The ^{1}H NMR spectrum of compound **3d** measured in $CDCl_3$ at 295 K is sharp (Figure 1) and contains a characteristic triplet (*1*) for the methine proton H^1 in position 2 of the dihydroimidazole ring and a well-resolved AB quartet for diastereotopic methylene protons H^2. Diastereotopic protons of the pyrrolidine ring emerge as pairs of well-separated signals (H^3 and H^5), whereas a compact multiplet corresponds to protons H^4.

In order to reveal the role of TMSCl in the formation of compounds **3**, a series of model experiments was carried out. Diamines **1** do not react with carbonyl compounds **2** without TMSCl in pure pyridine or in the presence of pyridine hydrochloride. The model reaction of azomethine **6a** (RR = $(CH_2)_2$, $R^1 = R^2 = H$, R^3 = *p*-$MeOC_6H_4$)[11] with TMSCl (pyridine, 100 °C) resulted in complex mixtures containing about 20−30% of 2,3-dihydro-1*H*-benzimidazoles **3**, whereas in the absence of TMSCl, no reaction occurs. These results suggest that the azomethines are not intermediates in the one-pot synthesis.

It seems likely that the reaction of compounds **1**, **2**, and TMSCl may result in silylated product **A** (Scheme 3) in which the trimethylsilyl group is coordinated to the oxygen atom of the trimethylsiloxy fragment. The hydride transfer to the positively charged carbon atom seems likely to give intermediate **B**, which after elimination of hexamethyldisiloxane and intramolecular N-alkylation results in compound **3**. Addition of TMSCl to the C=N bond of azomethines **6** is anticipated to give intermediate **C** that can transform into compound **B** through hydride transfer. Subsequent elimination of TMSCl and intramolecular N-alkylation seems likely to result in target compound **3**. This hypothesis is in keeping with observations described above and the fact that the yields of compounds **3** are different in the one-pot and stepwise procedures.

The PM3[12] energy optimization of intermediate structure **A** (Figure 2a,b) predicted rather strong intramolecular interaction between trimethylsilyl and trimethylsiloxy fragments (Si−O distance of 0.29 nm), resulting in polarization and activation of

(11) Compound **6a** was obtained by MW-assisted condensation of the corresponding diamine and aldehyde.

(12) *Hyperchem*, release 7; Hypercube Inc., 2002.

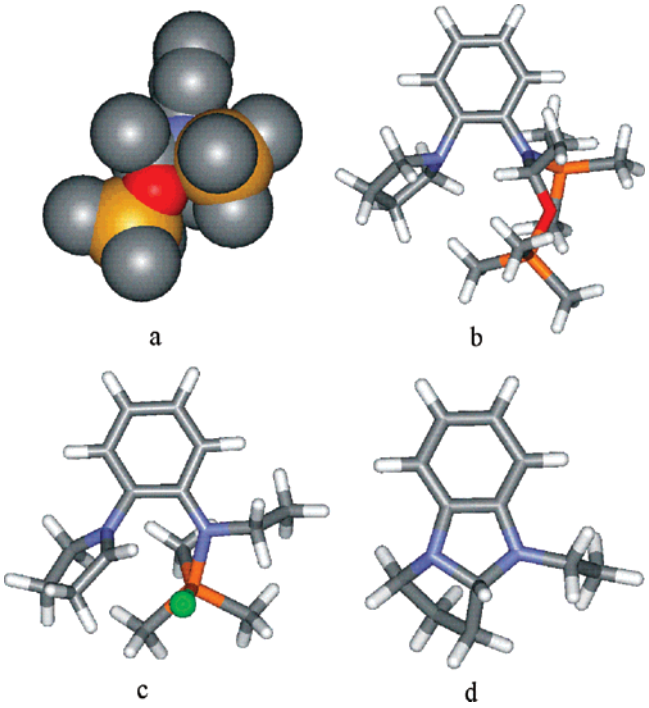
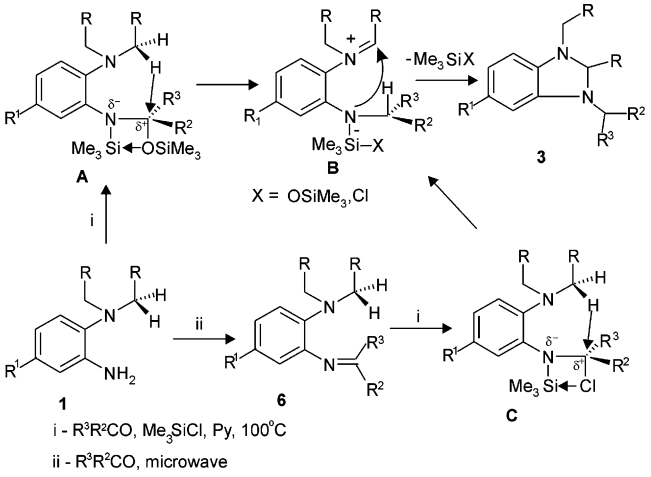


FIGURE 2. Energy optimized structure (PM3) of intermediates **A** (a, b), **B** (c, group X is shown as a green sphere of arbitrary radius), and the cyclic core of compounds **3a**−**g** and **3l**−**n**. R_1 = H for the sake of simplicity.

SCHEME 3. Proposed Mechanism for the Formation of Compounds 3 in the One Pot and Stepwise Procedure



the C−N bond. In the optimized conformation of intermediate **A**, one NCH_2 group is situated in a suitable position for the intramolecular hydride transfer. Apparently, the elimination of hexamethyldisiloxane from the intermediates **A** without hydride transfer should lead to the corresponding azomethines.

In the optimized structures of intermediates **B**, the pyrrolidine rings are coplanar apparently due to the requirements of electronic conjugation stabilizing the positive charge (Figure 2c). The arrangement of the oppositely charged groups in intermediates **B** appears to be suitable for the intramolecular C−N bond formation resulting in 2,3-dihydro-1*H*-benzimidazoles **3** (Figure 2d).

In the energy optimized structures of the intermediates **B** containing *o*-piperidinylaniline and *o*-morpholinoaniline fragments, the six-membered heterocycles are distorted due to the planarity of the positively charged C=N fragment. Such a distortion may destabilize the intermediate **B** and hamper the formation of the corresponding 2,3-dihydro-1*H*-benzimidazoles.

Reaction of *o*-piperidinylaniline and *o*-morpholinoaniline with aldehydes **2** (Me_3SiCl, Py, 100 °C) led to the corresponding azomethines **6b** (RR = $(CH_2)_3$, R^1 = $SO_2N(CH_2CH_2)_2O$, R^2 = H, R^3 = *p*-$HF_2COC_6H_4$) and **6c** (RR = CH_2OCH_2, R^1 = $SO_2N(CH_2CH_2)_2O$, R^2 = H, R^3 = *p*-ClC_6H_4) in 60% yield, whereas dihydro-1*H*-benzimidazoles were not detected in the reaction mixtures.

In conclusion, a convenient method has been elaborated for one-pot synthesis of 2,3-dihydro-1*H*-benzimidazoles from *ortho*-dialkylaminoanilines and carbonyl compounds. Using TMSCl as a promoter and pyridine as a basic solvent results in stabilization and good yields of the target compounds. This methodology is applicable to various starting materials and apparently allows one to obtain 2,3-dihydro-1*H*-benzimidazoles of high structural and functional diversity.

Experimental Section

To a solution of amine **1** (2 mmol) and aldehyde **2** (2 mmol) in dry pyridine (1−2 mL) was added chlorotrimethylsilane (6 mmol) was added dropwise. The pressure tube was thoroughly sealed and heated in a water bath for 2−8 h with magnetic stirring. After cooling, the tube was opened (*Caution! Excessive pressure inside*) and triethylamine (6.6 mmol) was added dropwise, and the solution was sonicated for 1 h at rt. The crude product was precipitated by water (10 mL), and the suspension obtained was sonicated for 1 h. The precipitate formed was filtered off, washed with *i*-PrOH or Et_2O, and recrystallized.

Spectral data for compound **3d**: yield 68%; mp 128−129 °C; ^{1}H NNR (500 MHz, $CDCl_3$) δ = 1.77 (1H, m, CH), 1.85 (m, CH), 1.98 (m, 1H), 2.43 (3H, s, CH_3), 2.95 (4H, m, CH), 3.20 (1H, m, CH), 3.38 (1H, m, CH), 3.72 (4H, m, CH), 4.46 (2H, $^2J_{HH}$ = 15.8 Hz, NCH_2), 5.27 (1H, t, $^3J_{HH}$ = 5.2 Hz, CH), 6.49 (1H, d, $^3J_{HH}$ = 7.9 Hz, CH), 6.55 (1H, s, CH), 6.58 (1H, d, $^3J_{HH}$ = 2.8 Hz, CH), 6.76 (1H, d, $^3J_{HH}$ = 2.8 Hz, CH), 7.03 (1H, dd, $^3J_{HH}$ = 7.9 Hz, CH); ^{13}C NNR (125 MHz, $CDCl_3$) δ = 15.4, 23.9, 32.0, 45.4, 46.1, 52.8, 66.2, 86.7, 103.3, 108.6, 120.7, 124.7, 125.9, 126.1, 137.3, 140.1, 143.5, 148.6. Anal. Calcd for $C_{20}H_{25}N_3O_3S_2$: C, 57.25; H, 6.01; N, 10.02; S, 15.29. Found: C, 57.29; H, 5.99; N, 10.05; S, 15.33.

Acknowledgment. The authors acknowledge V. V. Polovinko for spectral measurements, and Dr. A. N. Kostyuk for helpful discussions and suggestions.

Supporting Information Available: Experimental procedures and characterization data for the compounds obtained. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0712087