Rapid and Facile Access to Indeno[1,2-*d*]imidazoles *via* a Tandem Addition–Cyclization Reaction

by **Abdolali Alizadeh***, **Ameneh Zarei**, and **Atieh Rezvanian**

Department of Chemistry, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Iran (phone: +98-21-88006631; fax: +98-21-88006544; e-mail: aalizadeh@modares.ac.ir, abdol_alizad@yahoo.com)

A novel and tandem synthesis of highly functionalized tetrahydroindeno[1,2-*d*]imidazole is described. A one-pot reaction between a primary amine, an aryl isothiocyanate, and ninhydrin leads to highly substituted indeno[1,2-*d*]imidazoles under solvent-free conditions in excellent yields (*Scheme*). Their structures were corroborated spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and by elemental analyses.

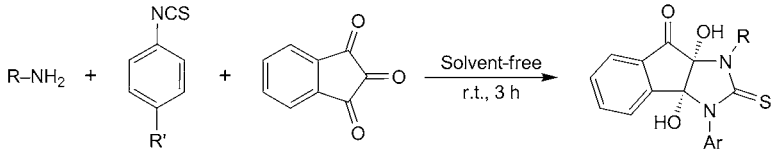
Introduction. – 2-Substituted dihydroimidazoles are of increasing interest because of their applications [1] as disinfectants, pharmaceuticals, and also because of their applications in supramolecular-chemistry preparation of molecular tectonics [2]. Especially, imidazole-2-thiones and their derivatives have received attention because of their bioactivities and application for pharmaceutical synthesis. Thus, the presence of an imidazole ring in natural products and pharmacologically active compounds has instituted a diverse array of synthetic approaches to these heterocycles [3].

Results and Discussion. – As far as we know, only a few general methods are known for the construction of tetrasubstituted indeno[1,2-*d*]imidazoles by formation of three bonds with various substituents directly from readily available building blocks. Considering the important biological properties of these fused tricyclic compounds, we are continuing our efforts in the development of multicomponent reactions for the synthesis of potential biologically active fused polycyclic heterocyclic compounds [4]. Here, we describe a one-pot, multicomponent, and solvent-free preparation of highly substituted indeno[1,2-*d*]imidazoles utilizing primary amines, aryl isothiocyanate, and ninhydrin.

The reaction of primary amines **1** and aryl isothiocyanates **2** in the presence of ninhydrin under solvent-free conditions at ambient temperature afforded tetrahydroindeno[1,2-*d*]imidazoles **3a**–**3h** within 3 h in yields of 65–75% (*Table*). We have shown that the use of a wide range of primary amines **1** and aryl isothiocyanates **2** in this there-component reaction permits the synthesis of libraries of **3** under almost identical conditions. Two substituents in the products can be varied independently of each other. The results are compiled in the *Table*.

The structures of compounds **3a**–**3h** were elucidated from their elemental analysis, IR and high-field ^{1}H- and ^{13}C-NMR, and mass spectra as described for **3a**. The IR

Table. *(3a*R*,8a*R*)-1-Alkyl-3-aryl-2,3,3a,8a-tetrahydro-3a,8a-dihydroxy-2-thioxoindeno[1,2-*d*]imidazol-8(1*H*)-ones by Three Component Reaction*



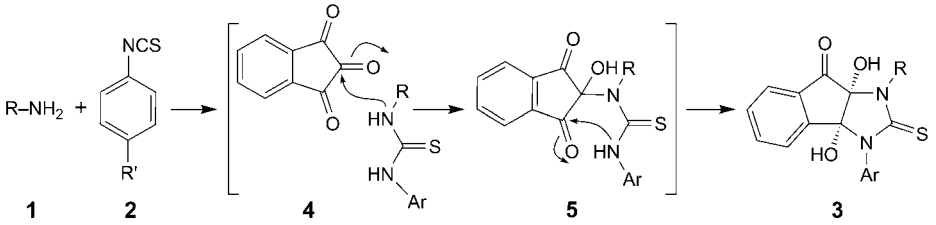
1 **2** **3**

Entry	R	R′	Product	Yield [%]
1	Pr	H	**3a**	71
2	Pr	Me	**3b**	68
3	Pr	Cl	**3c**	65
4	^{i}Bu	H	**3d**	70
5	^{i}Bu	Me	**3e**	67
6	Bn	H	**3f**	70
7	Bn	Me	**3g**	73
8	4-Me–$C_6H_4CH_2$	H	**3h**	75

spectrum (KBr) of **3a** showed absorption bands due to the OH stretching frequency at 3415 and 3200 cm^{-1}. Absorption bands at 1720 and 1369 cm^{-1} are due to the C=O and C=S groups. The ^{1}H-NMR spectrum ($CDCl_3$) of **3a** exihibted signals for the Pr group (δ(H) 0.94 (*t*, *J* = 7.4, *Me*CH_2CH_2), 1.80 – 1.86 and 3.73 – 3.80 (2*m*, MeCH_2CH_2)), two broad signals for the two OH groups (δ(H) 1.65 and 4.60), and the aromatic moieties gave rise to *multiplet*s at δ(H) 6.83 – 7.91. The ^{1}H-decoupled ^{13}C-NMR spectrum of **3a** showed 17 distinct resonances in agreement with the suggested structure.

Although we have not established the mechanism of the reaction experimentally, a proposal is presented in the *Scheme*. At first, the primary amine **1** readily reacts with aryl isothiocyanate **2** to produce arylthiourea **4**, which is converted to intermediate **5** in the presence of ninhydrin. Finally, intermediate **5** can undergo cyclization by addition of the arylthioamido group to the CO group, leading to the product **3**.

Scheme. *Proposed Mechanism of the Formation of Indeno[1,2-*d*]imidazoles*



1 **2** **4** **5** **3**

In summary, we developed a novel and efficient method for the synthesis of tetrahydroindeno[1,2-*d*]imidazoles. This one-pot reaction includes some important aspects like the ease of workup, high atom economy, and high diversity *via* various functional groups, yields in the range of 65 to 76%, and neutral and solvent-free reaction conditions.

Experimental Part

General. The primary amines, aryl isothiocyanate, and ninhydrin were obtained from *Fluka* (CH-Buchs) and used without further purification. Column chromatography (CC): silica gel (SiO_2; 230–240 mesh; *Merck*). M.p.: *Electrothermal 9100* apparatus. IR Spectra: *Shimadzu IR-460* spectrometer, in KBr. ^{1}H- and ^{13}C-NMR spectra: at 500 and 125 MHz, resp., on a *Bruker DRX 500-AVANCE* FT-NMR instrument with $CDCl_3$ as solvent. MS: *Finnigan-MAT 8430* mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N: *Heraeus CHN-O-Rapid* analyzer.

General Procedure. Formation of **3f**. To a magnetically stirred 5-ml flat-bottom flask containing $PhCH_2NH_2$ (**1f**; 0.11 g, 1 mmol), was added PhNCS (**2a**; 0.13 g, 1 mmol). After 30 min, ninhydrin (0.16 g, 1 mmol) was added to the mixture. The mixture was stirred for 2.5 h, followed by purification of the crude product by CC (hexane/AcOEt 7:1) to yield **3f**.

*(3a*R*,8a*R*)-2,3,3a,8a-Tetrahydro-3a,8a-dihydroxy-3-phenyl-1-propyl-2-thioxoindeno[1,2-*d*]imidazol-8(1*H*)-one* (**3a**). Yield: 250 mg (71%). Yellow oil. IR: 3415 (OH), 3200 (OH), 1720 (C=O), 1369 (C=S). ^{1}H-NMR: 0.94 (*t*, *J* = 7.4, 3 H); 1.80–1.86 (*m*, 2 H); 1.65 (br., 1 H); 3.73–3.80 (*m*, 2 H); 4.60 (br., 1 H); 6.83–7.91 (*m*, 9 H). ^{13}C-NMR: 11.4; 21.8; 45.4; 89.2; 91.3; 125.0; 125.4; 128.7; 128.8; 130.8; 131.1; 132.5; 136.1; 136.8; 147.8; 180.5; 194.6. EI-MS (70 eV): 190 (99), 175 (61), 135 (100), 77 (55), 51 (15). Anal. calc. for $C_{19}H_{18}N_2O_3S$ (354.42): C 64.39, H 5.12, N 7.90; found: C 64.33, H 5.10, N 7.91.

*(3a*R*,8a*R*)-2,3,3a,8a-Tetrahydro-3a,8a-dihydroxy-3-(4-methylphenyl)-1-propyl-2-thioxoindeno[1,2-*d*]imidazol-8(1*H*)-one* (**3b**). Yield: 250 mg (68%). Yellow oil. IR: 3414 (OH), 3220 (OH), 1722 (C=O), 1363 (C=S). ^{1}H-NMR: 1.03 (*t*, *J* = 7.3, 3 H); 1.07 (br. *s*, 1 H); 1.24–1.27 (*m*, 2 H); 2.37 (*s*, 3 H); 3.72–3.78 (*m*, 1 H); 4.00–4.06 (*m*, 1 H); 4.42 (br. *s*, 1 H); 6.80–7.93 (*m*, 6 H). ^{13}C-NMR: 10.86; 21.3; 21.8; 45.3; 124.1; 124.8; 129.0; 129.4; 129.78; 130.0; 130.5; 130.7; 132.2; 136.27; 136.9; 138.6; 147.6; 179.9; 193.34. EI-MS: 189 (53), 149 (99), 91 (70), 46 (99), 204 (100). Anal. calc. for $C_{20}H_{20}N_2O_3S$ (368.44): C 65.20, H, 5.47, N 7.60; found: C 65.21, H 5.45, N 7.57.

*(3a*R*,8a*R*)-3-(4-Chlorophenyl)-2,3,3a,8a-tetrahydro-3a,8a-dihydroxy-1-propyl-2-thioxoindeno[1,2-*d*]imidazol-8(1*H*)-one* (**3c**). Yield: 245 mg (65%). Yellow oil. IR: 3416 (OH), 3240 (OH), 1719 (C=O), 1379 (C=S). ^{1}H-NMR: 1.04 (*t*, *J* = 6.1, 3 H); 1.31–1.44 (*m*, 2 H); 1.45 (br., 1 H); 3.65–3.79 (*m*, 1 H); 3.65–3.79 (*m*, 1 H); 3.98–4.04 (*m*, 1 H); 4.40 (br., 1 H); 6.94–7.94 (*m*, 8 H). ^{13}C-NMR: 10.8; 21.0; 45.6; 88.85; 91.1; 124.2; 124.8; 128.2; 128.9; 130.3; 130.8; 131.3; 134.5; 135.0; 137.0; 147.6; 179.5; 193.1. EI-MS: 226 (66), 197 (58), 184 (100), 169 (98), 135 (100), 127 (30). Anal. calc. for $C_{19}H_{17}N_2O_3S$ (388.86): C 58.69, H 4.40, N 7.20; found: C 58.67, H 4.41, N 7.18.

*(3a*R*,8a*R*)-2,3,3a,8a-Tetrahydro-3a,8a-dihydroxy-1-(2-methylpropyl)-3-phenyl-2-thioxoindeno[1,2-*d*]imidazol-8(1*H*)-one* (**3d**). Yield: 250 mg (70%). Yellow oil. IR: 3424 (OH), 3223 (OH), 1722 (C=O), 1355 (C=S). ^{1}H-NMR: 1.06 (*d*, *J* = 6.5, 6 H); 1.08 (*d*, *J* = 6.5, 6 H); 1.42 (br., 1 H); 2.73–2.76 (*m*, 1 H); 3.50–3.54 (*m*, 1 H); 4.03–4.07 (*m*, 1 H); 4.43 (br. *s*, 1 H); 7.19–7.91 (*m*, 9 H). ^{13}C-NMR: 20.1; 20.2; 27.0; 51.1; 89.1; 91.4; 124.7; 124.9; 125.2; 129.1; 130.5; 130.8; 131.1; 131.2; 132.6; 137.4; 147.8; 180.9; 193.9. EI-MS: 198 (99), 118 (98), 105 (28), 77 (55). Anal. calc. for $C_{20}H_{20}N_2O_3S$ (368.48): C 65.20, H 5.47, N 7.6; found: C 65.21, H 5.46, N 7.59.

*(3a*R*,8a*R*)-2,3,3a,8a-Tetrahydro-3a,8a-dihydroxy-3-(4-methylphenyl)-1-(2-methylpropyl)-2-thioxoindeno[1,2-*d*]imidazol-8(1*H*)-one* (**3e**). Yield: 270 mg (67%). Yellow oil. IR: 3423 (OH), 3230 (OH), 1723 (C=O), 1338 (C=S). ^{1}H-NMR: 1.06 (*t*, *J* = 6.7, 3 H); 1.08 (*t*, *J* = 6.7, 3 H); 1.59 (br., 1 H); 2.37 (*s*, 3 H); 2.72–2.79 (*m*, 1 H); 3.50–3.55 (*m*, 2 H); 4.04–4.07 (*m*, 2 H); 3.90 (br., 1 H); 7.06–7.93 (*m*, 8 H). ^{13}C-NMR: 20.2; 20.3; 21.3; 27.0; 51.1; 89.0; 91.3; 124.7; 124.9; 130.2; 130.5; 131.1; 131.2; 132.6; 137.3; 139.1; 147.8; 181.0; 193.9. EI-MS: 149 (99), 126 (100), 106 (33), 91 (69), 81 (94). Anal. calc. for $C_{21}H_{22}N_2O_3S$ (382.47): C 65.95, H 5.80, N 7.32; found: C 65.93, H 5.81, N 7.33.

*(3a*R*,8a*R*)-1-Benzyl-2,3,3a,8a-tetrahydro-3a,8a-dihydroxy-3-phenyl-2-thioxoindeno[1,2-*d*]imidazol-8(1*H*)-one* (**3f**). Yield: 290 mg (72%). Yellow oil. IR: 3453 (OH), 3222 (OH), 1733 (C=O), 3374 (C=S). ^{1}H-NMR: 1.62 (br. *s*, 1 H); 5.31–5.34 (*m*, 1 H); 5.35–5.37 (*m*, 1 H); 4.41 (br., 1 H); 6.87–7.89 (*m*, 14 H). ^{13}C-NMR: 46.5; 89.14; 91.5; 124.5; 124.9; 126.8; 127.0; 127.9; 128.3; 128.6; 130.0; 130.3; 130.7; 132.0; 135.1; 136.3; 137.2; 181.1; 193.1. EI-MS: 194 (38), 126 (90), 91 (99), 77 (55), 63 (78). Anal. calc. for: $C_{23}H_{18}N_2O_3S$ (354.42): C 68.64, H 4.51, N 6.96; found: C 68.63, H 4.53, N 6.94.

*(3a*R*,8a*R*)-1-Benzyl-2,3,3a,8a-tetrahydro-3a,8a-dihydroxy-3-(4-methylphenyl)-2-thioxoindeno[1,2-*d*]imidazol-8(1*H*)-one* (**3g**). Yield: 300 mg (73%). Yellow oil. IR: 3372 (OH), 3233 (OH), 1723 (C=O), 1362 (C=S). ^{1}H-NMR: 2.45 (*s*, 3 H); 1.54 (br., 1 H); 4.12 (br., 1 H); 4.85–4.96 (*m*, 1 H); 5.22–5.42 (*m*, 1 H); 4.96 (*s*, 1 H); 5.30 (*s*, 1 H); 6.90–7.89 (*m*, 13 H). ^{13}C-NMR: 20.8; 46.8; 86.6; 89.0; 124.9; 125.5; 127.5; 127.5; 127.6; 127.7; 128.0; 128.5; 129.6; 130.5, 130.9; 131.1; 132.5; 133.3; 136.8; 137.6; 138.8; 147.7; 181.4; 193.9. EI-MS: 194 (40), 149 (100), 117 (15), 91 (70). Anal. calc. for $C_{24}H_{20}N_2O_3S$ (416.49): C 69.21, H 4.84, N 6.73; found: C 69.22, H 4.81, N 6.70.

*(3a*R*,8a*R*)-2,3,3a,8a-Tetrahydro-3a,8a-dihydroxy-1-(4-methylbenzyl)-3-phenyl-2-thioxoindeno[1,2-*d*]imidazol-8(1*H*)-one* (**3h**). Yield: 300 mg (75%). Yellow oil. IR: 3432 (OH), 3250 (OH), 1728 (C=O), 1358 (C=S). ^{1}H-NMR: 1.38 (br., 1 H); 2.33 (*s*, 3 H); 4.20–4.23 (*m*, 2 H); 4.70 (*s*, 1 H); 7.12–7.72 (*m*, 13 H). ^{13}C-NMR: 22.6; 46.7; 89.1; 91.4; 124.9; 128.7; 128.9; 129.0; 129.0; 130.4; 130.7; 132.7; 134.7; 135.9; 136.4; 136.8; 136.8; 147.8; 167.6; 181.3. EI-MS: 194 (99), 167 (37), 149 (100), 135 (980), 77 (55). Anal. calc. for $C_{24}H_{20}N_2O_3S$ (416.49): C 69.21, H 4.84, N 6.73; found: C 69.23, H 4.85, N 6.76.

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