JOC*Note*

An Unexpected Three-Component Condensation Leading to Amino-(3-oxo-2,3-dihydro-1*H*-isoindol-1-ylidene)-acetonitriles

Till Opatz* and Dorota Ferenc

Institut für Organische Chemie, Universität Mainz, Duesbergweg 10-14, 55128 Mainz, Germany

opatz@uni-mainz.de

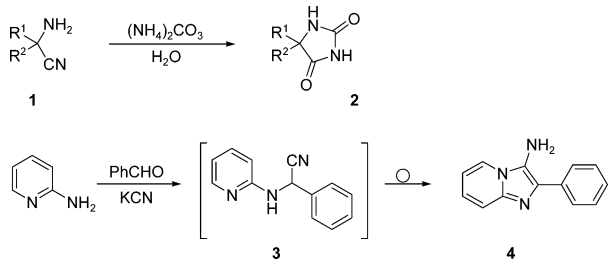
Received July 30, 2004

Abstract: The reaction of 2-carboxybenzaldehyde with primary amines in the presence of cyanide leads to the formation of 2-substituted amino(3-oxo-2,3-dihydro-1*H*-isoindol-1-ylidene)acetonitriles. These compounds originate from the condensation of 2-carboxybenzaldehyde with the amine and two molecules of hydrogen cyanide and represent a novel class of isoindolinones.

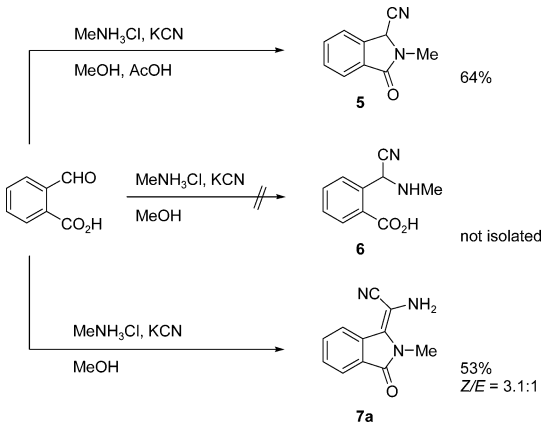
The Strecker reaction between an aldehyde, an amine, and hydrogen cyanide is widely regarded as the first multicomponent reaction (MCR).[1] Its reliability, the ready availability of the starting materials, and the versatility of the resulting products make it a very important process for the large-scale production of amino acids, herbicides, and chelating agents, such as NTA and EDTA. Although the Strecker reaction can be performed on a wide variety of substrates, the presence of neighboring groups may lead to the formation of products other than α-aminonitriles. In particular, the nitrile carbon is susceptible to intra- or intermolecular nucleophilic attack. Examples are the Bucherer−Bergs reaction[2−4] and the analogous formation of dithiohydantoins from α-aminonitriles and carbon disulfide,[5] the ketone-mediated hydration of α-aminonitriles,[6] and the preparation of 2-phenylimidazo[1,2-*a*]pyridin-3-amine (**4**) from 2-aminopyridine, benzaldehyde, and cyanide (Scheme 1).[7,8]

During an attempt to prepare aminonitrile **6** from 2-carboxybenzaldehyde, methylamine hydrochloride, and potassium cyanide in aqueous methanol, a yellow crystalline solid precipitated from the reaction mixture when left to stand overnight at room temperature. Structural elucidation by ^{1}H and ^{13}C NMR spectroscopy revealed this precipitate to be a mixture of (2*E*)- and (2*Z*)-amino-(2-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-ylidene)acetonitrile (**7a**). Experiments showed that elevated reaction temperatures promote the formation of **7a**, and that the course of the reaction critically depends on the pH of the medium. If the reaction medium was acidified by the addition of acetic acid, 2-methyl-3-oxoisoindoline-1-carbonitrile **5** was obtained instead (Scheme 2).

SCHEME 1. Consecutive Reactions of Strecker Products via a Nucleophilic Attack on the Nitrile Carbon



SCHEME 2. Preparation of Compounds 5 and 7a

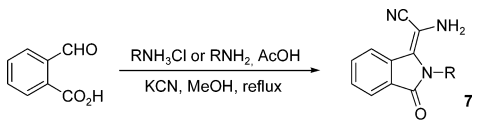


In contrast to the formation of **5**, which results from cyclodehydration of the Strecker product **6**,[9,10] the formation of **7a** is less easy to understand. Formally, this product results from the nucleophilic addition of a molecule of HCN to the nitrile carbon of **6** and subsequent cyclodehydration. The similar dimerization of HCN to the highly reactive iminoacetonitrile has been proposed to be the initial step in the formation of diaminomaleonitrile, the stable tetramer of HCN.[11,12] In the case of the addition of HCN to an α-aryl-substituted aminonitrile, the resulting α-cyanoimine could tautomerize to the thermodynamically more favorable 2,3-diaminocinnamonitrile, although this would not explain the importance of the *ortho*-carboxy group. An alternative for the formation of **7a** is via the initial formation of **5**, which, either directly or after tautomerization to the ketenimine, is nucleophilically attacked by a second cyanide ion. Indeed, **5** does react with KCN and acetic acid in methanol to form **7a** when heated; however, the conversion is poor, and the reaction is too slow to account for the formation

(1) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27−45.
(2) Bergs, H. German Patent 566094, 1929; *Chem. Abstr.* **1933**, *27*, 1001.
(3) Bucherer, H. T.; Brandt, W. *J. Prakt. Chem.* **1934**, *140*, 129−150.
(4) Bucherer, H. T.; Steiner, W. *J. Prakt. Chem.* **1934**, *140*, 291−316.
(5) Chubb, F. L.; Edward, J. T. *Can. J. Chem.* **1981**, *59*, 2724−2728.
(6) Lagriffoul, P.-H.; Tadros, Z.; Taillades, J.; Commeyras, A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1279−1285.
(7) Astik, R. R.; Thaker, K. A. *J. Indian Chem. Soc.* **1981**, *58*, 1013−1014.
(8) Schmitt, M.; Bourguignon, J.-J.; Barlin, G. B.; Davies, L. P. *Aust. J. Chem.* **1997**, *50*, 719−725.
(9) Welch, W. M. *J. Org. Chem.* **1982**, *47*, 886−888.
(10) Baum, J. S.; Staveski, M. M. *Synth. Commun.* **1989**, *19*, 2283−2292.
(11) Ferris, J. P.; Bonner, D. B.; Lotz, W. *J. Am. Chem. Soc.* **1972**, *94*, 6968−6974.
(12) Evans, R. A.; Lorencak, P.; Ha, T.-K.; Wentrup, C. *J. Am. Chem. Soc.* **1991**, *113*, 7261−7276.

10.1021/jo0486802 CCC: $27.50
Published on Web 10/26/2004

TABLE 1. Preparation of Amino(2-alkyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-ylidene)acetonitriles



entry	product	R	method[a]	yield (%)	*Z*/*E*
1	**7a**	Me	A	53	3.1:1
2	**7b**	Et	A	29 (*Z*), 9 (*E*)	3.2:1
3	**7c**	*n*-Bu	B	21	4.6:1
4	**7d**	*i*-Pent	B	29	4.5:1
5	**7e**	*i*-Pr	B		
6	**7f**	Bn	B	44 (*Z*)	
7	**7g**	3-pyr−CH_2−	B	37 (*Z*), 9 (*E*)	4.0:1
8	**7h**	$PhCH_2CH_2$−	B	40	5.2:1

[a] Method A: 2 equiv of amine hydrochloride and 2.2 equiv of KCN. Method B: 2 equiv of amine, 2 equiv of AcOH, and 2.2 equiv of KCN.

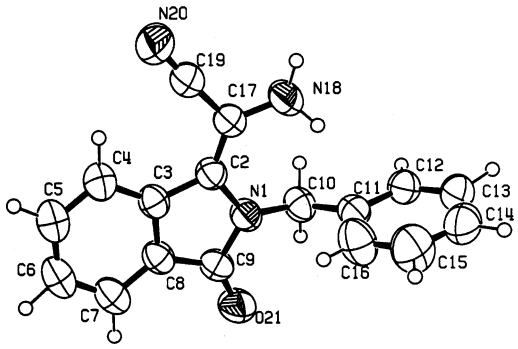


FIGURE 1. Crystal structure of (*Z*)-**7f** with the atomic numbering scheme. Thermal ellipsoids are drawn at 50% probability.

of **7a** under the original experimental conditions. In addition, lactam **5** could not be detected if the reaction proceeded in a neutral or an alkaline medium. To explore the scope of the reaction, a set of α-unbranched primary amines were subjected to the reaction. In all cases, compounds of **7** were obtained in moderate yield (Table 1).

The best yield of compounds **7a** and **7b** could be obtained if the amine hydrochloride was used (method A), whereas the longer-chain amines were most suitably employed in combination with acetic acid (method B). For instance, the preparation of **7b**, according to method B, resulted in a yield of only 24%, and method A gave only 13% of **7h**. Sterically more demanding α-branched primary amines, such as isopropylamine, gave only trace amounts of the corresponding products, which are probably destabilized by unfavorable interactions between the amine side chains, the oxygen, and the amino or cyano group. To investigate the structural features of the unusual heterocyclic core of compounds **7**, an X-ray crystallographic analysis of the *N*-benzyl derivative, (*Z*)-**7f**, was performed (Figure 1).

The steric repulsion between the hydrogens at C(4) and C(19) results in a slight twist of the exocyclic aminoacetonitrile moiety against the plane of the bicyclic π-system by an angle of 6°, whereas the length of the exocyclic double bond is normal (1.353 Å). This value, as well as the bond distances and angles in the aminoacetonitrile moiety (Table 2), is in good accordance with the corresponding values found in *N*-(2-amino-1,2-dicyanovinyl)-acetamide by Booth et al.[13]

TABLE 2. Selected Bond Lengths (Å) and Angles (deg) for (*Z*)-7f

N(1)−C(2)	1.412	C(19)−N(20)	1.143
C(2)−C(17)	1.353	C(2)−C(3)	1.467
C(17)−N(18)	1.375	N(1)−C(9)	1.373
C(17)−C(19)	1.428	C(9)−O(21)	1.226
N(1)−C(2)−C(3)	105.73	C(2)−C(17)−N(18)	127.67
N(1)−C(2)−C(17)	125.42	C(2)−C(17)−C(19)	118.74

In all of the experiments, minor amounts of the (*E*)-isomers were formed, as well. In the case of compounds **7b** and **7g**, both isomers were separated and purified by column chromatography and crystallization. Not surprisingly, the NMR signal of the proton at C(4) in (*E*)-**7g** showed a very strong NOE enhancement of 28% upon irradiation of the amino protons. The small distance between the amino group and the aromatic *ortho*-hydrogen in the (*E*)-isomer also accounts for the predominant formation of the sterically less-demanding (*Z*)-product. When the pure isomers (*E*)-**7b** and (*Z*)-**7b** were heated to 90 °C in DMSO-d_6, the slow equilibration of the double-bond geometry could be observed in both cases, resulting in a 3.8:1 mixture in favor of the (*Z*)-isomer. Whether the mechanism of this reaction involves a tautomerization to the α-cyanoimine or an addition−elimination sequence remains to be investigated. Although the relative mobility of the (*E*)-isomers on TLC is always slightly higher, the best way to distinguish between the isomers is the ^{1}H chemical shift of the amino group in DMSO-d_6; the NH_2 protons of the (*Z*)-isomers constantly resonate at ∼0.20 ppm downfield.

In summary, a three-component condensation leading to a novel class of isoindolinones has been found. Although the yield of the reactions was only moderate, the synthesis from readily available 2-carboxybenzaldehyde is simple and makes these remarkable amino(alkylidene)-acetonitriles interesting starting materials for the preparation of more complex heterocycles.

Experimental Section

2-Methyl-3-oxoisoindoline-1-carbonitrile (5). To a stirred solution of 2-carboxybenzaldehyde (3.0 g, 20 mmol) in methanol (50 mL) were added methylamine hydrochloride (2.70 g, 40 mmol), potassium cyanide (1.69 g, 26 mmol), and acetic acid (2.28 mL, 40 mmol). The reaction mixture was heated to reflux for 3 h, and after it cooled, the mixture was partitioned between water and CH_2Cl_2; the organic layer was separated, washed with aqueous $NaHCO_3$, and dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by flash chromatography (cyclohexane/ethyl acetate, 1:1) to yield **5** as colorless crystals (2.19 g, 64%): mp 108−110 °C; IR (KBr) ν 3433 (br), 2891, 1698, 1472, 1427, 1386, 1320, 1058, 747, 691 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.13 (s, 3H, CH_3), 6.00 (s, 1H, CHN), 7.64 (pseudo-t, J = 7.4 Hz, 1H), 7.71−7.79 (m, 2H), 7.86 (pseudo-d, J = 7.4 Hz, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 27.7 (CH_3), 51.2 (C1), 115.9 (CN), 123.3 (d), 123.6 (d), 130.1 (d), 130.7 (s), 132.7 (d), 137.4 (s), 166.3 (CO); FD-MS (*m*/*z*) M$^+$ 172.1

(13) Al-Azmi, A.; Booth, B. L.; Pritchard, R. G.; Proença, F. J. R. P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 485−486.

(100). Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.55; H, 4.62; N, 16.15.

Amino(2-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-ylidene)acetonitrile (7a). To a stirred solution of 2-carboxybenzaldehyde (1.5 g, 10 mmol) and methylamine hydrochloride (1.35 g, 20 mmol) in methanol (25 mL) was added potassium cyanide (1.43 g, 22 mmol), and the mixture was heated to reflux for 3.5 h. After 2.5 h, the formation of yellow crystals could be observed. The yellow suspension was poured onto ice, and the yellow solid was collected by filtration to yield **7a** (967 mg, 49%) as a mixture of isomers. The filtrate was extracted with ether; the organic layer was separated and dried over Na_2SO_4, and the solvent was removed in vacuo to yield another portion of **7a** (93 mg, 4.7%): R_f (cyclohexane/EtOAc, 3:2) = 0.15 (*Z*), 0.31 (*E*); IR (KBr) ν 3442, 3313, 3209, 2214, 1706, 1632, 1474, 1428, 1312, 1268, 1090, 767, 692 cm^{-1}; FD-MS (*m/z*) M^+ 199.1 (100). Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.42; H, 4.35; N, 21.09. For NMR spectroscopic analysis, the (*Z*)-isomer was purified by recrystallization (EtOAc/petroleum ether): ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ 3.51 (s, 3H, CH_3), 5.80 (br s, 2H, NH_2), 7.46 (dt, J_t = 7.4 Hz, J_d = 0.9 Hz, 1H, H5), 7.65 (ddd, J = 8.2, 7.4, 1.3 Hz, 1H, H6), 7.74 (ddd, J = 7.4, 1.3, 0.9 Hz, 1H, H4), 8.14 (dt, J_d = 8.2 Hz, J_t = 0.9 Hz, 1H, H7); ^{13}C NMR, HMQC, HMBC (100.6 MHz, DMSO-d_6) δ 28.8 (CH_3), 101.2 (C−NH_2), 117.7 (CN), 120.0 (C7), 123.0 (C4), 123.9 (C1), 126.8 (C3a), 127.8 (C5), 132.1 (C6), 133.8 (C7a), 165.4 (CO). Signals of the (*E*)-isomer (from the spectrum of the *E*/*Z* mixture): ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.45 (s, 3H, CH_3), 5.65 (br s, 2H, NH_2), 7.51 (dt, J_t = 7.4 Hz, J_d = 0.9 Hz, 1H, H5), 7.67 (ddd, J = 7.9, 7.4, 1.3 Hz, 1H, H6), 7.77 (ddd, J = 7.4, 1.3, 0.9 Hz, 1H, H4), 8.14 (dt, J_d = 7.9 Hz, J_t = 0.9 Hz, 1H, H7); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 28.0 (CH_3), 101.6 (C−NH_2), 117.0 (CN), 122.8 (C4), 124.1 (C7), 127.2, 127.9 (C1, C3a), 128.7 (C5), 132.1 (C6), 133.5 (C7a), 164.9 (CO).

Amino(2-ethyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-ylidene)acetonitrile (7b). To a stirred solution of 2-carboxybenzaldehyde (1.5 g, 10 mmol) and ethylamine hydrochloride (1.63 g, 20 mmol) in methanol (25 mL) was added potassium cyanide (1.43 g, 22 mmol), and the mixture was heated to reflux for 4.5 h. After the reaction mixture was cooled, it was partitioned between water and CH_2Cl_2; the organic layer was separated, washed with aqueous $NaHCO_3$, and dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by flash chromatography (cyclohexane/ethyl acetate/CH_2Cl_2, 1:1:2) to yield the (*Z*)-isomer (609 mg, 29%, yellow crystals) and the (*E*)-isomer (188 mg, 9%, yellow crystals). (*Z*)-Isomer: mp 143 °C dec; R_f (cyclohexane/EtOAc, 1:1) = 0.49; IR (KBr) ν 3391, 3339, 3245, 2983, 2216, 1685, 1627, 1475, 1316, 1093, 762, 696 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.12 (t, J = 7.2 Hz, 3H, CH_3), 4.10 (q, J = 7.2 Hz, 2H, CH_2), 5.81 (br s, 2H, NH_2), 7.49 (dt, J_t = 7.4 Hz, J_d = 0.9 Hz, 1H, H5), 7.69 (ddd, J = 8.1, 7.4, 1.3 Hz, 1H, H6), 7.76 (ddd, J = 7.4, 1.3, 0.9 Hz, 1H, H4), 8.21 (dt, J_d = 8.1 Hz, J_t = 0.9 Hz, 1H, H7); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 15.0 (CH_3), 35.5 (CH_2), 100.6 (C−NH_2), 117.9 (CN), 120.2 (C7), 123.1 (C4), 123.4 (C1), 126.9 (C3a), 127.9 (C5), 132.3 (C6), 134.4 (C7a), 165.3 (CO); FD-MS (*m/z*) M^+ 213.1 (100). Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.84; H, 5.20; N, 19.50. (*E*)-Isomer: mp 124 °C dec; R_f (cyclohexane/EtOAc, 1:1) = 0.55; IR (KBr) ν 3440 (br), 3382, 3300, 3207, 2211, 1682, 1397, 1364, 1098, 771, 699 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.21 (t, J = 7.2 Hz, 3H, CH_3), 4.07 (q, J = 7.2 Hz, 2H, CH_2), 5.61 (br s, 2H, NH_2), 7.54 (dt, J_t = 7.4 Hz, J_d = 0.9 Hz, 1H, H5), 7.70 (ddd, J = 7.9, 7.4, 1.3 Hz, 1H, H6), 7.79 (ddd, J = 7.4, 1.3, 0.9 Hz, 1H, H4), 8.19 (dt, J_d = 7.9 Hz, J_t = 0.9 Hz, 1H, H7); ^{13}C NMR, HMQC, HMBC (100.6 MHz, DMSO-d_6) δ 14.6 (CH_3), 34.8 (CH_2), 101.0 (C−NH_2), 116.8 (CN), 122.8 (C4), 124.6 (C7), 126.8 (C1), 127.2 (C3a), 128.8 (C5), 132.2 (C6), 133.9 (C7a), 164.8 (CO); FD-MS (*m/z*) M^+ 213.3 (100). Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.58; H, 5.21; N, 19.57.

Amino(2-butyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-ylidene)acetonitrile (7c). To a stirred solution of 2-carboxybenzaldehyde (1.5 g, 10 mmol) in methanol (25 mL) were added *n*-butylamine (1.98 mL, 20 mmol), potassium cyanide (1.43 g, 22 mmol), and acetic acid (1.14 mL, 20 mmol). The reaction mixture was heated to reflux for 4 h, and after it was cooled, the mixture was partitioned between water and CH_2Cl_2; the organic layer was separated, washed with aqueous $NaHCO_3$, and dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by flash chromatography (cyclohexane/ethyl acetate/CH_2Cl_2, 2:1:4) to yield a 4.6:1 mixture of (*Z*)- and (*E*)-**7c** (515 mg, 21%) as yellow crystals: R_f (cyclohexane/EtOAc, 2:1) = 0.39 (*E*,*Z*); IR (KBr) ν 3422 (br), 3330, 3222, 2960, 2206, 1671, 1629, 1473, 1312, 1096, 765, 699 cm^{-1}. Signals of the (*Z*)-isomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.84 (t, J = 7.3 Hz, 3H, CH_3), 1.16 (sextet, J = 7.3 Hz, 2H, γ-CH_2), 1.51, (quintet, J = 7.3 Hz, 2H, β-CH_2), 4.07 (t, J = 7.3 Hz, 2H, NCH_2), 5.80 (br s, 2H, NH_2), 7.48 (dt, J_t = 7.4 Hz, J_d = 0.9 Hz, 1H, H5), 7.68 (ddd, J = 8.2, 7.4, 1.3 Hz, 1H, H6), 7.76 (ddd, J = 7.4, 1.3, 0.9 Hz, 1H, H4), 8.21 (dt, J_d = 8.2 Hz, J_t = 0.9 Hz, 1H, H7); ^{13}C NMR, DEPT (75.5 MHz, DMSO-d_6) δ 13.5 (CH_3), 19.1 (γ-CH_2), 31.4 (β-CH_2), 40.0 (NCH_2), 100.7 (C−NH_2), 117.9 (CN), 120.2 (C7), 123.2 (C4), 123.5 (C1), 126.8 (C3a), 128.0 (C5), 132.4 (C6), 134.4 (C7a), 165.7 (CO). Signals of the (*E*)-isomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.89 (t, J = 7.3 Hz, 3H, CH_3), 1.28 (sextet, J = 7.3 Hz, 2H, γ-CH_2), 1.60 (quintet, J = 7.3 Hz, 2H, β-CH_2), 4.01 (t, J = 7.3 Hz, 2H, NCH_2), 5.59 (br s, 2H, NH_2), 7.53 (dt, J_t = 7.4 Hz, J_d = 0.9 Hz, 1H, H5), 7.78 (ddd, J = 7.4, 1.3, 0.9 Hz, 1H, H4), 8.18 (dt, J_t = 0.9 Hz, 1H, H7). The signal of H6 was completely obscured by the corresponding signal of the (*Z*)-isomer; $J_{6,7}$ could not be determined from the signal of H7 due to a partial overlap with the H7 resonance of the (*Z*)-isomer: ^{13}C NMR, DEPT (75.5 MHz, DMSO-d_6) δ 13.5 (CH_3), 19.1 (γ-CH_2), 30.9 (β-CH_2), 39.5 (NCH_2), 101.1 (C−NH_2), 116.8 (CN), 122.8 (C4), 124.6 (C7), 126.97 (C1, C3a), 127.04 (C3a, C1), 128.8 (C5), 132.2 (C6), 133.8 (C7a), 165.0 (CO); FD-MS (*m/z*) M^+ 241.2 (100). Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.55; H, 6.29; N, 17.25.

Amino[2-(3-methylbutyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-ylidene]acetonitrile (7d). The preparation of **7d** was carried out in the manner described for **7c** using isopentylamine (2.32 mL) as the amine component. The eluent for flash chromatography was cyclohexane/ethyl acetate/CH_2Cl_2, 2:1:2. Yellow crystals of **7d** (733 mg, 29%) were obtained as a 4.5:1 mixture of diastereomers (*Z*/*E*): R_f (cyclohexane/EtOAc, 1:1) = 0.69 (*Z*), 0.79 (*E*); IR (KBr) ν 3410 (br), 3334, 3231, 2957, 2206, 1673, 1625, 1474, 1371, 1311, 1281, 1098, 766, 698 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (d, J = 6.4 Hz, 6H, $CH_3{}^Z$), 0.91 (d, J = 6.4 Hz, 1.3H, $CH_3{}^E$), 1.34−1.63 (m, 3.7H, γ-CH^{E+Z}, β-$CH_2{}^{E+Z}$), 4.04 (t, J = 7.7 Hz, 0.5H, $NCH_2{}^E$), 4.09 (t, J = 7.2 Hz, 2H, $NCH_2{}^Z$), 5.58 (br s, 0.4H, $NH_2{}^E$), 5.79 (br s, 2H, $NH_2{}^Z$), 7.48 (dt, J_t = 7.4 Hz, J_d = 0.9 Hz, 1H, H5^Z), 7.53 (dt, J_t = 7.4 Hz, J_d = 0.9 Hz, 0.2H, H5^E), 7.63−7.71 (m, 1.2 H, H6^{E+Z}), contained in this multiplet, 7.67 (ddd, J = 8.2, 7.4, 1.3 Hz, 1H, H6^Z), 7.76 (ddd, J = 7.4, 1.3, 0.9 Hz, 1H, H4^Z), 7.77 (ddd, J = 7.4, 1.3, 0.9 Hz, 0.2H, H4^E), 8.18 (dt, J_d = 7.9 Hz, J_t = 0.9 Hz, 0.2H, H7^E), 8.21 (dt, J_d = 8.2 Hz, J_t = 0.9 Hz, 1H, H7^Z); ^{13}C NMR, DEPT (75.5 MHz, DMSO-d_6) (signals of (*Z*)-isomer) δ 22.3 (CH_3), 25.2 (γ-CH), 38.2, 38.8 (β-CH_2, NCH_2), 100.7 (C−NH_2), 117.9 (CN), 120.2 (C7), 123.2 (C4), 123.6 (C1), 126.8 (C3a), 128.0 (C5), 132.4 (C6), 134.4 (C7a), 165.6 (CO); ^{13}C NMR, DEPT (75.5 MHz, DMSO-d_6) (signals of (*E*)-isomer) δ 22.3 (CH_3), 25.5 (γ-CH), 37.6, 38.4 (β-CH_2, NCH_2), 101.2 (C−NH_2), 116.9 (CN), 122.8 (C4), 124.6 (C7), 126.9, 127.1 (C1, C3a), 128.8 (C5), 132.2 (C6), 133.9 (C7a), 165.0 (CO); FD-MS (*m/z*) M^+ 255.2 (100), $[2M]^+$ 510.8 (4). Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.50; H, 6.79; N, 16.22. (Note, the superscripts *E* and *Z* denote signals of the corresponding isomers.) The (*Z*)-isomer could be purified by recrystallization from ethyl acetate/petroleum ether. Yellow crystals were obtained: mp 131.5−132.5 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.34−1.46 (m, 3H, γ-CH, β-CH_2). For all other signals, see the ^{1}H NMR spectrum of the isomeric mixture: FD-MS (*m/z*) M^+ 255.4 (100), $[2M]^+$ 510.9 (8).

Amino(2-benzyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-ylidene)acetonitrile (7f). The preparation of **7f** was carried out in the manner described for **7c** using benzylamine (2.2 mL) as the amine component. The eluent for flash chromatography was cyclohexane/ethyl acetate/CH_2Cl_2, 3:1:1. (*Z*)-**7f** (1.20 g, 44%) was

obtained as yellow crystals: mp 138 °C dec; R_f (cyclohexane/EtOAc, 3:2) = 0.64; IR (KBr) ν 3444, 3335, 3219, 2214, 1696, 1685, 1636, 1612, 1473, 1342, 1313, 1294, 1175, 1159, 984, 764, 743, 710 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 5.34 (br s, 2H, CH_2), 5.76 (br s, 2H, NH_2), 7.11 (pseudo-d, J = 7.2 Hz, 2H, *o*-Ph), 7.19−7.34 (m, 3H, *m*/*p*-Ph), 7.53 (dt, J_t = 7.4 Hz, J_d = 0.9 Hz, 1H, H5), 7.72 (ddd, J = 8.2, 7.4, 1.3 Hz, 1H, H6), 7.85 (ddd, J = 7.4, 1.3, 0.9 Hz, 1H, H4), 8.21 (dt, J_d = 8.2 Hz, J_t = 0.9 Hz, 1H, H7); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 43.7 (CH_2), 101.2 (C−NH_2), 117.6 (CN), 120.3 (C7), 122.9 (C1), 123.5 (C4), 126.1 (*o*-Ph), 126.4 (C3a), 127.1 (*p*-Ph), 128.1 (C5), 128.5 (*m*-Ph), 132.7 (C6), 134.5 (C7a), 137.6 (*i*-Ph), 166.0 (CO); FD-MS (*m*/*z*) M^+ 275.4 (100). Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.28; H, 4.87; N, 15.18.

Amino[3-oxo-2-(pyridin-3-ylmethyl)-2,3-dihydro-1*H*-isoindol-1-ylidene]acetonitrile (7g). The preparation of **7g** was carried out in the manner described for **7c** using 3-picolylamine (2.04 mL) as the amine component. The eluent for flash chromatography was cyclohexane/ethyl acetate, 6:1. (*Z*)-**7g** (1.01 g, 37%) and (*E*)-**7g** (251 mg, 9%) were obtained as yellow crystals. (*Z*)-Isomer: mp 133 °C dec; R_f (EtOAc) = 0.42; IR (KBr) ν 3348, 3133 (br), 2206, 1684, 1635, 1611, 1478, 1431, 1344, 1319, 1281, 1159, 983, 768, 710 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 5.39 (br s, 2H, CH_2), 5.85 (br s, 2H, NH_2), 7.31 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H, H5′), 7.44 (ddd, J = 7.9, 2.4, 1.7 Hz, 1H, H4′), 7.53 (dt, J_t = 7.4 Hz, J_d = 0.9 Hz, 1H, H5), 7.72 (ddd, J = 8.1, 7.4, 1.3 Hz, 1H, H6), 7.85 (ddd, J = 7.4, 1.3, 0.9 Hz, 1H, H4), 8.21 (dt, J_d = 8.1 Hz, J_t = 0.9 Hz, 1H, H7), 8.42 (dd, J = 2.4, 0.9 Hz, 1H, H2′), 8.44 (dd, J = 4.8, 1.7 Hz, 1H, H6′); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 41.5 (CH_2), 101.2 (C−NH_2), 117.5 (CN), 120.3 (C7), 123.1 (C1), 123.5 (C4, C5′), 126.3 (C3a), 128.2 (C5), 132.8 (C6), 133.2 (C3′), 134.0 (C4′), 134.5 (C7a), 147.9, 148.4 (C2′, C6′), 166.0 (CO); ESI-MS (*m*/*z*) $[M + H]^+$ 277.3 (100). Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.65; H, 4.40; N, 20.20. (*E*)-Isomer: mp 128 °C dec; R_f (EtOAc) = 0.54; IR (KBr) ν 3407, 3329, 3221, 2214, 1673, 1645, 1472, 1436, 1428, 1392, 1345, 1276, 781, 764, 713, 698 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 5.34 (br s, 2H, CH_2), 5.69 (br s, 2H, NH_2), 7.35 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H, H5′), 7.45 (ddd, J = 7.9, 2.4, 1.7 Hz, 1H, H4′), 7.60 (dt, J_t = 7.4 Hz, J_d = 0.9 Hz, 1H, H5), 7.75 (ddd, J = 7.9, 7.4, 1.3 Hz, 1H, H6), 7.89 (ddd, J = 7.4, 1.3, 0.9 Hz, 1H, H4), 8.20 (dt, J_d = 7.9 Hz, J_t = 0.9 Hz, 1H, H7), 8.37 (dd, J = 2.4, 0.9 Hz, 1H, H2′), 8.47 (dd, J = 4.8, 1.7 Hz, 1H, H6′). Irradiation (transient NOE) at 5.69 ppm (NH_2) enhanced the signal at 8.20 ppm (H7) by 28%. Irradiation at 5.34 ppm (CH_2) enhanced the signals at 8.37 (H2′, 10%) and 7.45 ppm (H4′, 7%): ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 41.1 (CH_2), 102.2 (C−NH_2), 116.6 (CN), 123.2, 123.5 (C4, C5′), 124.5 (C7), 125.9, 126.6 (C1, C3a), 129.0 (C5), 132.6 (C6), 132.8 (C3′), 133.8 (C4′), 134.0 (C7a), 147.6, 148.2 (C2′, C6′), 165.5 (CO); ESI-MS (*m*/*z*) $[M + H]^+$ 277.3 (100). Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.53; H, 4.34; N, 20.12.

(2*Z*)-Amino[3-oxo-2-(2-phenylethyl)-2,3-dihydro-1*H*-isoindol-1-ylidene]acetonitrile (7h). The preparation of **7h** was carried out in the manner described for **7c** using 2-phenethylamine (2.52 mL) as the amine component. The eluent for flash chromatography was cyclohexane/ethyl acetate/CH_2Cl_2, 3:2:2. Yellow crystals of **7h** (1.16 g, 40%) were obtained as a 5.2:1 mixture of diastereomers (*Z*/*E*): R_f (cyclohexane/EtOAc, 1:1) = 0.67 (*Z*), 0.77 (*E*); FD-MS (*m*/*z*) M^+ 289.3 (100), $[2M]^+$ 578.8 (27). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.49; H, 5.24; N, 14.30. The pure (*Z*)-isomer could be obtained by recrystallization from ethyl acetate/petroleum ether: mp 150 °C dec; IR (KBr) ν 3382, 3325, 3251, 2209, 1694, 1684, 1650, 1632, 1615, 1474, 1343, 1314, 1249, 1149, 762, 750, 698 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.83 (pseudo-t, J = 7.5 Hz, 2H, $PhCH_2$), 4.31 (pseudo-t, J = 7.5 Hz, 2H, NCH_2), 5.87 (br s, 2H, NH_2), 7.11−7.26 (m, 5H, Ph), 7.48 (dt, J_t = 7.4 Hz, J_d = 0.9 Hz, 1H, H5), 7.68 (ddd, J = 8.1, 7.4, 1.3 Hz, 1H, H6), 7.71 (ddd, J = 7.4, 1.3, 0.9 Hz, 1H, H4), 8.23 (dt, J_d = 8.1 Hz, J_t = 0.9 Hz, 1H, H7); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 35.3 ($PhCH_2$), 41.8 (NCH_2), 100.6 (C−NH_2), 117.9 (CN), 120.3 (C7), 123.2 (C4), 124.4 (C1), 126.2 (*p*-Ph), 126.8 (C3a), 128.1 (C5), 128.2, 128.6 (*o*/*m*-Ph), 132.4 (C6), 134.4 (C7a), 138.2 (*i*-Ph), 165.6 (CO).

Acknowledgment. This work was supported by the Fonds der Chemischen Industrie. The help of Dr. D. Schollmeyer (crystallographic analysis of compound (*Z*)-**7f**) and H. Kolshorn (NMR experiments and chemical shift simulations) is gratefully acknowledged.

Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **5**, **7a**−**d**, and **7f**−**h**, as well as the X-ray crystallographic data of (*Z*)-**7f**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0486802