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ANIONIC [3,3] REARRANGEMENTS OF CYCLIC HYDRAZINE DIACYLATES TO MEDIUM-SIZE CYCLIC DIAMIDES AND THEIR STRUCTURES.

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Abstract- The anionic rearrangement of *N,N'*-dimethyl-*N,N'*-diacylhydrazines to 1,2-disubstituted succinamides proceeds in the presence of a ajacent enolate-stabilizing substituent such as a phenyl group. However, a substituent that poorly stabilizes the α-carbanion results in an extremely low yield of the products. The [3,3] sigmatropic rearrangement generally requires a chair form for the cyclic six-centered transition state. When the dienolates of *N,N'*-diacylhydrazines have favorable steric factors for the cyclic transition state, the rearrangement seems to proceed smoothly. The diacylates of 5- to 8-membered cyclic hydrazine which readily adopt a favorable conformation for the [3,3] rearrangement readily rearrange to 9- to 12-membered cyclic diamides.

The 3,4-diaza [3,3] sigmatropic rearrangement[1] is important in the fields of synthetic and mechanistic organic chemistry.[2] An example of the aromatic version of the rearrangement is the first step in the conversion of *N*-aryl-*N'*-enylhydrazines to indoles.[3] We previously reported an aliphatic version of anionic rearrangements of *N,N'*-diacylhydrazines[4] and *N*-acyl-*N'*-enylhydrazines.[5] The C-C bond-forming rearrangement can be rationalized in terms of hetero [3,3] sigmatropic shifts of dienolated precursors. These investigations indicated that the carboxamide enolate can be employed as a component of [3,3] rearrangement precursors. When the dienolates of *N,N'*-diacylhydrazines are stable enough to form the cyclic six-centered structure required in the [3,3] sigmatropic shifts transition state, the rearrangement proceeds smoothly to give 1,2-disubstituted succinamides in up to 50 % yield. However, the rearrangement of *N,N'*-diacylhydrazines without a substituent stabilizing the adjacent enolate, such as a phenyl group does not proceed effectively.[4] When the enolates are not stable enough to proceed the rearrangement, restriction to a favorable conformational state for the cyclic transition state can be employed to advantage in the rearrangements. For example, in the case of similar [3,3] rearrangement of *N,O*-diacylhydroxylamines, a bulky substituent on the nitrogen was effective for the C-C bond-forming rearrangement. *N,O*-Diacyl-*N*-*tert*-butylhydroxylamine rearranged to the succinic acid

derivatives in 68% yield, although the substrate does not have an α-stabilizing group.[6] However, introduction of a *tert*-butyl group on the nitrogen of the *N,N'*-diacylhydrazines did not improve the result. In this paper, we wish to report the [3,3] rearrangement of diacylates of cyclic hydrazines which are conformationally restricted to a favorable conformation for the rearrangement in terms of methylene linkage to give cyclic diamides.

The 5- to 8-membered cyclic hydrazines (tetrahydropyrazole, hexahydropyridazine, hexahydro-1,2-diazepine, octahydro-1,2-diazocine) were prepared as reported,[7] and were readily converted into *N,N'*-diacyl cyclic hydrazines. Treatment of *N,N'*-diacetyl-5- and 6-membered cyclic hydrazines (**1a** (n= 3) and **1b** (n= 4)) with 5.0 eq of lithium diisopropylamide (LDA) in THF at -78°C, then 20°C for 2 h and 50°C for 15 h did not give the expected cyclic diamides (**2a** and **2b**). In contrast, *N,N'*-diacetyl-7- and 8-membered cyclic hydrazines (**1c** (n= 5) and **1d** (n= 6)) rearranged under the same conditions to 11- and 12-membered cyclic diamides (**2c** and **2d**) in low yields.[8] Although a rate-acceleration effect of a dimethyl substituent on the reaction sites of the [3,3] rearrangement was reported,[9] acyclic *N,N'*-isobutyryl-*N,N'*-dimethylhydrazine did not give the [3,3] rearranged product.[10] *N,N'*-Diisobutyryl 5- to 8-membered cyclic hydrazines (**1e**-**1h** (n= 3- 6)) rearranged upon treatment with 5.0 eq of LDA in THF at 20°C for 2 h to afford 9- to 12-membered cyclic diamides (**2e**-**2h**) in 5-79% yields.

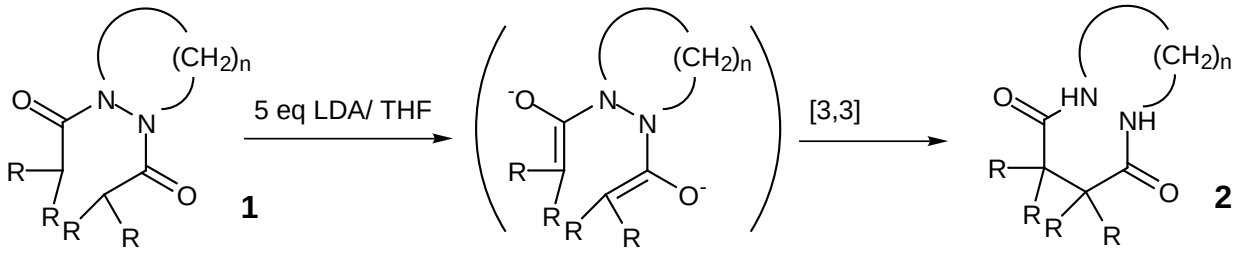

Table 1. [3,3] Rearrangement of *N,N'*-Diacyl Cyclic Hydrazines

Compound	n	R	Yield (%) of Cyclic Diamide[a]
a	3	H	0
b	4	H	0
c	5	H	13
d	6	H	12
e	3	CH_3	5
f	4	CH_3	62
g	5	CH_3	79
h	6	CH_3	20

[a] Yields are isolated yields. All starting materials were enolized with 5.0 eq of LDA at -78°C in THF and the temperature was allowed to rise from -78°C to 20°C over 30 min. It was held at 20°C for 2 h, then raised to 50°C for 5 h for **1a**-**1d**; it was just held at 20°C for 2 h for **1e**-**1h**.

Rearrangements of *N,N'*-diacyl cyclic hydrazines with a phenyl group stabilizing the α-carbanion proceed smoothly, compared with the acyclic case.[4] *N,N'*-Diphenylacetyl 5- to 8-membered cyclic hydrazines,

(**3a**-**3d** (n= 3- 6)) also rearranged upon treatment with 3.0 eq of LDA in THF at 20°C for 2 h, then at 50°C for 3.5 h to give the 9- to 12-membered cyclic diamides (**4** and **5**) in 66-91% yields. Although the conformation of 5- and 8-membered cyclic hydrazides are not favorable for the rearrangement (Table 1), stabilization effect by phenyl group seems to compensate the disadvantage.

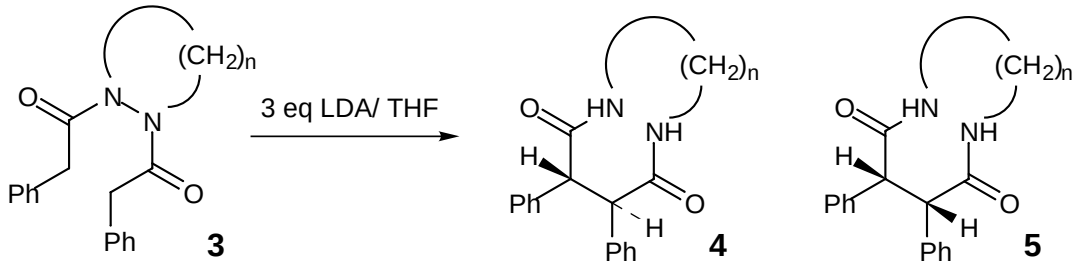

Table 2. [3,3] Rearrangement of *N,N'*-Diacyl Cyclic Hydrazines with a Phenyl Group

Compound	n	Yield (%)[a]	*dl* : *meso*
a	3	66	0 : 100
b	4	74	83 : 17
c	5	91	92 : 8
d	6	87	45 : 55

[a] Yields are isolated yields. All starting materials were enolized with 3.0 eq of LDA at -78°C in THF and the temperature was allowed to rise from -78°C to 20°C over 30 min, then held at 20°C for 2 h and raised to 50°C for 3.5 h.

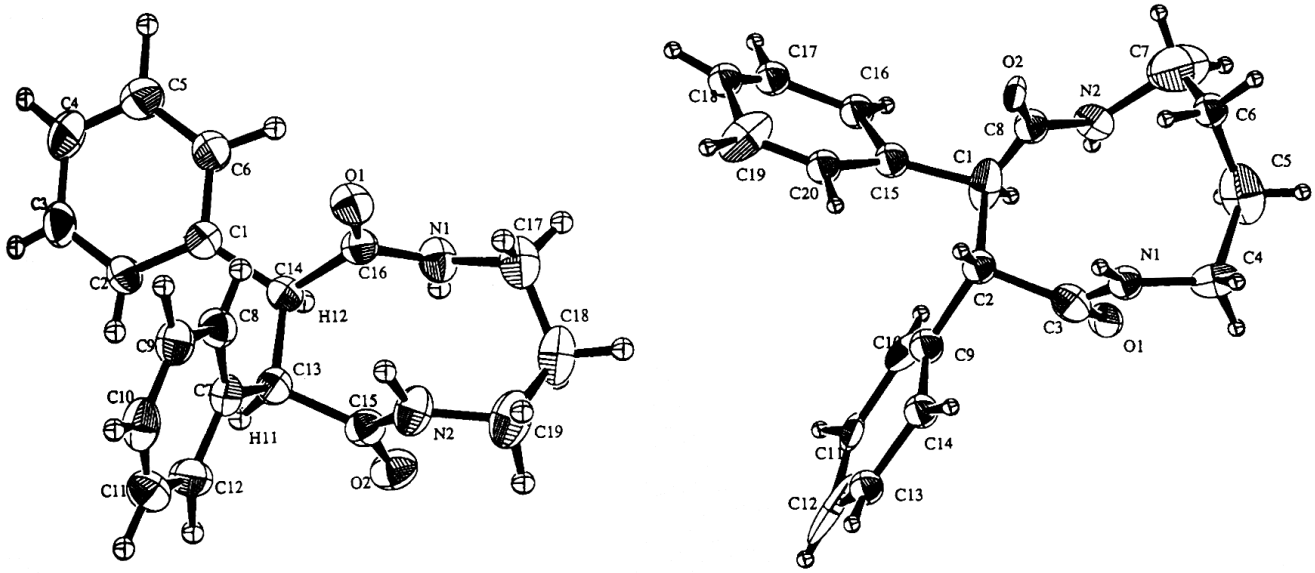

Figure 1. ORTEP drawing of the 9-membered (**5a**, left) and 10-membered diamides (**4b**, right)

The reaction of *N,N'*-diphenylacetyltetrahydropyrazole (**3a**) gavethe 9-membered compound (**5a**) as the sole product. The ^{1}H-NMR spectrum of **5a** indicates that the conformational structure lacks symmetry,

and is distinct from those of the other cyclic products (**4b**-**4d**, **5b**-**5d**). The structure of **5a** was determined by X-Ray crystallography. The crystal of **5a** belongs to triclinic space group P1, with cell constant *a*= 9.475(1), *b*= 10.382(2), *c*= 9.271(1) Å, *Z*= 2, and the final *R*-value was 0.056. The ORTEP drawing of the structure of **5a** is shown in Figure 1. Unexpectedly, both of the amide bonds of **5a** were *trans* in spite of the strain in the 9-membered ring system.

In the rearrangements of **3b**-**3d**, the *dl*-products (**4b**-**4d**) and the *meso*-products (**5b**-**5d**) are formed. Their ^{1}H-NMR spectra showed similar tendencies for the two isomers and indicate that the conformational states have symmetry. If both of the isomers have symmetrical conformation, the *dl*-product has C2 symmetry, and the *meso* product has a symmetrical plane. From these results and examination of molecular models, the structures of the isomers were deduced. Our conclusion was confirmed by an X-Ray study on **4b**, the crystal of which belongs to monoclinic space group Cc, with cell constant *a*= 17.47(2), *b*= 10.468(4), *c*= 9.707(4) Å, *Z*= 4, and the final *R*-value was 0.100. The ORTEP drawing of the structure of **4b** is shown in Figure 2. The stereochemistry of the rearranged products depends on the ring size of the cyclic hydrazine. Because of the relatively high temperature and strongly basic condition, the *dl:meso* ratios of products are assumed to reflect the thermodynamic stability.

Conformational analyses of simple lactams have been conducted by using several kinds of measurements.[11] These studies clearly indicate that 5- to 8-membered lactams have the *cis* conformation and 10-membered and larger lactams have the *trans* conformation. The 9-membered lactam, azacyclononanone, exists as an equilibrium mixture of *cis* and *trans* conformers, the relative amounts of which depend on the solvent.[12] The *cis*- and *trans*- structures and interconversion of amide bonds play important roles in specifying the conformational behavior of peptides as well as low-molecular-weight biologically active substances. For example, we have reported that tumor-promoting teleocidins, which have a 9-membered lactam structure including an indole ring, exist in an equilibrium of two conformational states in solution owing to *cis-trans* isomerization.[13] We have also reported the determination of the active conformation of teleocidins by the design and synthesis of conformationally restricted teleocidin mimics, benzolactams, which have an 8-membered lactam structure including a benzene ring.[14] On the other hand, conformational structures of medium-size cyclic diamides have been investigated in connection with partial structures of peptides. An 8-membered cyclic diamide, 1,5-diazaoctane-2,6-dione, exists as a two *cis* amide structure.[15] A 10-membered cyclic diamide, 1,6-diazacyclodecane-2,7-dione, exists as a two *trans* amide structure in solution and in the crystalline state.[16] In the present study, we found that a 9-membered cyclic diamide, *cis*-7,8-diphenyl-1,5-diazacyclononane-6,9-dione (**5a**) and a 10-membered cyclic diamide, *trans*-3,4-diphenyl-1,6-diazacyclononane-2,5-dione (**4b**) have two *trans* amides in the crystalline state. The present synthetic method for cyclic diamides employing anionic [3,3] rearrangement should be useful for the preparation of 9- to 12-membered cyclic diamides and for further investigation of conformational behaviors and transannular interactions in these compounds.

EXPERIMENTAL

General Remarks. Melting points were obtained on a Yanagimoto micro hot stage without correction. ^{1}H-NMR spectra were recorded with a JEOL JMN-FX-400 spectrometer (400 MHz), with tetramethylsilane (TMS) as an internal standard and chemical shifts are given in ppm as δ values from TMS. MS spectra were recorded on a JEOL JMS-D-300 for DI-MS. Column chromatography was performed on silica gel (Merck 7734 or 9385 (flash chromatography)).

***N,N′*-Diacyl Cyclic Hydrazine (1 and 3); Typical Procedure for *N,N′*-Diphenylacetyltetrahydropyrazole (3a)** A solution of phenylacetyl chloride (1.39 g, 9.0 mmol) in THF (3 mL) was added dropwise to a stirred solution of tetrahydropyrazole hydrochloride (326 mg, 3.0 mmol) and K_2CO_3 (912 mg, 2.2 mmol) in THF-H_2O (1:1, 10 mL) at rt. The mixture was stirred for 10 h, then sat. $NaHCO_3$ aqueous solution (30 mL) was added to it, and the mixture was extracted with ethyl acetate (4 x 50 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The product was purified by silica gel column chromatography using CH_2Cl_2/ethyl acetate as the eluent to give **3a** (795 mg, 86%). Spectral data of the products are as follows.

1a: colorless syrup, ^{1}H-NMR ($CDCl_3$) 2.05 (m, 2H), 2.15 (s, 6H), 2.97 (m, 2H), 4.32 (m, 2H); HR-MS Calcd for $C_7H_{12}N_2O_2$: 156.0899. Found: 156.0893.

1b: mp 57-59°C (ether/*n*-hexane), ^{1}H-NMR ($CDCl_3$) 1.71 (m, 4H), 2.09 (m, 6H), 2.70 (m, 2H), 4.63 (m, 2H); Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45, H, 8.29, N, 16.46. Found: C, 56.16, H, 8.47, N, 16.40.

1c: mp 65-66°C (ether/*n*-hexane), ^{1}H-NMR ($CDCl_3$) 1.53 (m, 2H), 1.70 (m, 2H), 1.84 (m, 2H), 2.03 (s, 6H), 3.06 (m, 2H), 4.27 (m, 2H); Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67, H, 8.75, N, 15.20. Found: C, 58.97, H, 8.57, N, 15.50.

1d: mp 43°C (ether/*n*-hexane/ethyl acetate), ^{1}H-NMR ($CDCl_3$) 1.61 (m, 6H), 1.78 (m, 2H), 2.02 (s, 6H), 3.08 (m, 2H), 4.26 (m, 2H); HR-MS Calcd for $C_{10}H_{18}N_2O_2$: 198.1368. Found: 198.1384.

1e: pale brown syrup, ^{1}H-NMR ($CDCl_3$) 1.06-1.22 (m, 12H), 2.04 (m, 2H), 2.91 (m, 2H), 3.03 (m, 2H), 4.29 (m, 2H); HR-MS Calcd for $C_{11}H_{20}N_2O_2$: 212.1522. Found: 212.1539.

1f: colorless syrup, ^{1}H-NMR ($CDCl_3$) 1.11 (d, 12H, J = 6.6 Hz), 1.70 (m, 4H), 2.71 (m, 2H), 2.94 (m, 2H), 4.68 (m, 2H); HR-MS Calcd for $C_{12}H_{22}N_2O_2$: 226.1681. Found: 226.1687.

1g: mp 53-54°C (*n*-hexane), ^{1}H-NMR ($CDCl_3$) 1.11-1.13 (m, 12H), 1.57 (m, 2H), 1.68 (m, 2H), 1.83 (m, 2H), 2.77 (m, 2H), 3.04 (m, 2H), 4.34 (m, 2H); Anal. Calcd for $C_{13}H_{24}N_2O_2$: C, 64.96, H, 10.07, N, 11.66. Found: C, 64.91, H, 9.83, N, 11.89.

1h: mp 64-65°C (CH_2Cl_2/*n*-hexane), ^{1}H-NMR ($CDCl_3$) 1.03-1.16 (m, 12H), 1.42-1.75 (m, 6H), 2.63 (m, 1H), 2.79 (m, 1H), 3.01 (m, 1H), 3.35 (m, 1H), 4.00 (m, 1H), 4.35 (m, 1H); HR-MS Calcd for $C_{14}H_{26}N_2O_2$: 254.1994. Found: 254.2001.

3a: mp 78-79°C (ethyl acetate), ^{1}H-NMR ($CDCl_3$) 1.80 (m, 2H), 2.50 (m, 2H), 3.59 (d, 2H, J = 14.7Hz), 3.67 (d, 2H, J = 14.7Hz), 4.15 (m, 2H), 7.22-7.52 (m, 10H); HR-MS Calcd for $C_{15}H_{20}N_2O_2$: 308.1525. Found: 308.1523.

3b: mp 118-120°C (CH_2Cl_2/*n*-hexane), ^{1}H-NMR ($CDCl_3$) 1.57 (m, 4H), 2.36 (m, 2H), 3.45 (d, 2H, J = 14.3 Hz), 3.53 (d, 2H, J = 14.3 Hz), 4.52 (m, 2H), 7.20-7.34 (m, 10H); Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.50, H, 6.88, N, 8.69. Found: C, 74.32, H, 6.73, N, 8.97.

3c: mp 74-75°C (CH_2Cl_2/*n*-hexane), ^{1}H-NMR ($CDCl_3$) 1.43 (m, 2H), 1.61 (m, 2H), 1.80 (m, 2H), 3.02 (m, 2H), 3.27 (d, 2H, *J* = 14.7 Hz), 3.45 (d, 2H, *J* = 14.7 Hz), 4.23 (m, 2H), 7.17-7.41 (m, 10H); Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97, H, 7.19, N, 8.33. Found: C, 74.93, H, 7.06, N, 8.48.

3d: mp 75-77°C (CH_2Cl_2/*n*-hexane), ^{1}H-NMR ($CDCl_3$) 1.48 (m, 6H), 1.76 (m, 2H), 3.09 (m, 2H), 3.22 (d, 2H, *J* = 15.0 Hz), 3.46 (d, 2H, *J* = 15.0 Hz), 4.35 (m, 2H), 7.05-7.39 (m, 10H); Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.39, H, 7.48, N, 7.99. Found: C, 75.46, H, 7.56, N, 8.21.

Rearrangements of 1 and 3: General Procedure: A solution of freshly distilled diisopropylamine (0.70 mL, 5.0 mmol for **1a**-**1h**, 0.42 mL, 3.0 mmol for **3a**-**3d**) in THF (3 mL) was treated with 1.6 M *n*-BuLi in hexane (3.12 mL, 5.0 mmol for **1a**-**1h**, 1.87 mL, 3.0 mmol for **3a**-**3d**) at –20 °C under Ar. After having been stirred for 15 min at 0°C, the LDA solution was cooled to -78°C, and a solution of **1** (2 mmol) in THF (4 mL) was added at -78°C with stirring. The reaction mixture required an additional 30 min for the temperature to rise from -78°C to 20°C. It was held at 20°C for 2 h, then raised to 50°C for 1.5 h for **1a**-**1d**, to 50°C for 3.5 h for **3a**-**3d**, or not raised for **1e**-**1h**. Stirring was continued during the periods described above, then the reaction was quenched by the addition of saturated NH_4Cl aqueous solution (5 mL). The mixture was diluted with brine (30 mL) and extracted with ethyl acetate (4 x 100 mL). The organic layer was washed with 5% HCl (80 mL), saturated $NaHCO_3$ aqueous solution (80 mL) and brine (80 mL), dried over $MgSO_4$, filtered and concentrated. The residue was crystallized from CH_2Cl_2/*n*-hexane to give a major product. The filtrate was concentrated and chromatographed on silica gel using CH_2Cl_2/ethyl acetate to give the rearranged C-C products (**2**) from **1**, and (**4**) and (**5**) from **3**. Spectral data of the products are as follows.

2c: colorless amorphous powder, ^{1}H-NMR (DMSO-d_6, 70°C) 1.41 (m, 6H), 2.27 (s, 4H), 3.15 (m, 4H), 7.36 (br s, 2H); HR-MS Calcd for $C_9H_{16}N_2O_2$: 184.1212. Found: 184.1210.

2d: colorless amorphous powder, ^{1}H-NMR (DMSO-d_6, 70°C) 1.25 (m, 4H), 1.46 (m, 4H), 2.29 (s, 4H), 3.15 (m, 4H), 7.29 (br s, 2H); HR-MS Calcd for $C_{10}H_{18}N_2O_2$: 198.1368. Found: 198.1396.

2e: colorless amorphous powder, ^{1}H-NMR (DMSO-d_6, 70°C) 1.01 (s, 12H), 1.67 (m, 2H), 2.84 (m, 2H), 3.52 (m, 2H), 6.31 (br s, 2H); HR-MS Calcd for $C_{11}H_{20}N_2O_2$: 212.1525. Found: 212.1521.

2f: mp 178-180°C (ethyl acetate), ^{1}H-NMR (DMSO-d_6, 70°C) 1.12 (s, 12H), 1.55 (m, 4H), 2.97 (m, 4H), 6.83 (br s, 2H); Anal. Calcd for $C_{12}H_{22}N_2O_2$: C, 63.68, H, 9.80, N, 12.38. Found: C, 63.81, H, 9.65, N, 12.34.

2g: mp 184-186°C (ethyl acetate/*n*-hexane), ^{1}H-NMR (DMSO-d_6, 70°C) 1.14 (s, 12H), 1.43 (m, 2H), 1.50 (m, 4H), 3.11 (m, 4H), 6.82 (br s, 2H); Anal. Calcd for $C_{13}H_{24}N_2O_2$: C, 64.96, H, 10.07, N, 11.66. Found: C, 64.66, H, 10.09, N, 11.46.

2h: mp 185-187°C (ethyl acetate), ^{1}H-NMR (DMSO-d_6, 70°C) 1.18 (s, 12H), 1.25 (m, 4H), 1.50 (m, 4H), 3.18 (m, 4H), 6.62 (br s, 2H); Anal. Calcd for $C_{14}H_{26}N_2O_2$: C, 66.10, H, 10.30, N, 11.01. Found: C, 66.13, H, 10.17, N, 11.07.

5a: mp 177-180°C (ethyl acetate), ^{1}H-NMR (DMSO-d_6, 70°C) 1.78 (m, 2H), 2.92 (m, 2H), 3.56 (m, 1H), 3.73 (m, 1H), 4.30 (d, 1H, *J* = 7.7 Hz), 4.40 (d, 1H, *J* = 7.7 Hz), 5.79 (m, 1H), 7.04-7.34 (m, 6H), 7.37 (d, 2H, *J* = 7.0 Hz), 7.52 (m, 1H), 7.65 (d, 2H, *J* = 7.0 Hz); Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.06, H, 6.54, N, 9.08. Found: C, 74.11, H, 6.67, N, 9.08.

4b: mp 176-177°C (ethyl acetate), ^{1}H-NMR (DMSO-d_6, 70°C) 1.65 (m, 4H), 2.94 (m, 2H), 3.20 (m, 2H), 4.36 (s, 2H), 7.07 (t, 2H, *J* = 7.3 Hz), 7.13 (t, 4H, *J* = 7.3 Hz), 7.25 (br s, 1H), 7.47 (d, 4H, *J* = 7.3 Hz); Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.50, H, 6.88, N, 8.69. Found: C, 74.49, H, 6.93, N, 8.81.

5b: mp 136-138°C (ethanol), ^{1}H-NMR (DMSO-d_6, 70°C) 1.51 (m, 2H), 1.79 (m, 2H), 2.60 (m, 2H), 3.39 (m, 2H), 4.20 (s, 2H), 7.05 (t, 2H, *J* = 7.3Hz), 7.13 (t, 4H, *J* = 7.3Hz), 7.28 (d, 2H, *J* = 7.3Hz), 7.95 (br s, 1H); Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.50, H, 6.88, N, 8.69. Found: C, 74.39, H, 6.93, N, 8.76.

4c: mp 224-227°C (ethyl acetate), ^{1}H-NMR (DMSO-d_6, 70°C) 1.38 (m, 2H), 1.51 (m, 2H), 1.65 (m, 2H), 2.64 (m, 2H), 3.62 (m, 2H), 4.25 (s, 2H), 7.09-7.15 (m, 6H), 7.21 (br s, 1H), 7.41 (dd, 4H, *J* = 2.5, 8.1Hz); Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97, H, 7.19, N, 8.33. Found: C, 74.76, H, 7.04, N, 8.41.

5c: not isolated, ^{1}H-NMR (DMSO-d_6, 70°C) 1.51 (m, 6H), 3.11 (m, 2H), 3.33 (m, 2H), 4.31 (s, 2H), 7.01 (t, 2H, *J* = 7.3 Hz), 7.03-7.43 (m, 8H), 7.88 (m, 1H).

4d: mp >300°C (ethyl acetate), ^{1}H-NMR (DMSO-d_6, 70°C) 1.35-1.70 (m, 8H), 3.11 (m, 2H), 3.35 (m, 2H), 4.29 (s, 2H), 7.07-7.28 (m, 8H), 7.31 (dd, 4H, *J* = 1.8, 7.3 Hz); Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.39, H, 7.48, N, 7.99. Found: C, 75.26, H, 7.66, N, 8.19.

5d: mp >300°C (ethanol), ^{1}H-NMR (DMSO-d_6, 70°C) 1.08 (m, 2H), 1.47 (m, 2H), 1.63 (m, 4H), 2.64 (m, 2H), 4.32 (s, 2H), 3.35 (m, 2H), 4.29 (s, 2H), 7.01 (t, 2H, *J* = 7.3 Hz), 7.08 (t, 4H, *J* = 7.3 Hz), 7.27 (d, 2H, *J* = 7.3 Hz), 7.87 (d, 2H, *J* = 8.8 Hz); Anal. Calcd for $C_{22}H_{26}N_2O$: C, 75.39, H, 7.48, N, 7.99. Found: C, 75.45, H, 7.74, N, 8.11.

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