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Electrophilic Amination of Hydrazones: A New Synthetic Route to Protected α-Hydrazino- and α-Aminoketones

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Abstract: *N*-BOC protected α-hydrazinoketones **4** and *N*-tris protected α-aminoketones **6** were synthesized in good overall yields by deprotonation and electrophilic amination of the corresponding ketone-*N,N*-dimethylhydrazones **2** and subsequent oxidative cleavage of the resulting product hydrazones **3** and **5** by ozonolysis.
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The electrophilic amination of carbon nucleophiles is an important *C-N* connective process in organic synthesis.[1] In this context, a variety of synthetic equivalents of the $NH_2^{\oplus}$-synthon (a^1-synthon, Umpolung) have been developed over the years, among them hydroxylamine derivatives,[2] sulfonylazides,[3] di-*tert*-butylazodicarboxylate (DBAD),[4] oxaziridines[5] and 1-chloro-1-nitroso reagents.[6] In addition, asymmetric electrophilic amination procedures, especially of carbonyl compounds, have been reported in recent years.[7]

α-Aminoketones have found wide application as precursors of physiologically important ethanolamine derivatives and as intermediates for the synthesis of a large variety of heterocyclic systems.[8] Different synthetic routes to α-aminoketones have been well reviewed,[9] but nevertheless, there is still a need for new, efficient syntheses of these compounds. Herein we describe the use of metalated *N,N*-dimethylhydrazones (DMH's) in the formation of *C-N* bonds α to the carbonyl group thus establishing a general procedure for the synthesis of the title compounds. The versatility and usefulness of *N,N*-dimethylhydrazones in a variety of other electrophilic substitutions is well established.[10] The aminating reagents used in our study were DBAD and triisopropylbenzenesulfonylazide (trisN3). DBAD was purchased commercially and trisylazide was prepared using the literature procedure.[3]

The intial step in the synthesis of α-aminoketones is the transformation of the ketones **1** into the corresponding DMH derivatives **2**, followed by metalation with lithium diisopropylamide (LDA) at 0 °C to give the azaenolates, which are trapped by the aminating reagent (DBAD or trisN3) at −78 °C. Subsequent oxidative cleavage of the product hydrazones **3** and **5** by ozone leads to the corresponding α-aminoketones **4** and **6** as outlined in Scheme 1 and 2.

We selected cyclohexanone-*N,N*-dimethylhydrazone (**2c**) as the standard substrate and found in the case of both of the aminating reagents DBAD and trisN3 acceptable yields of the α-aminated hydrazones, when the azaenolate was treated with 1.3 equivalents of the

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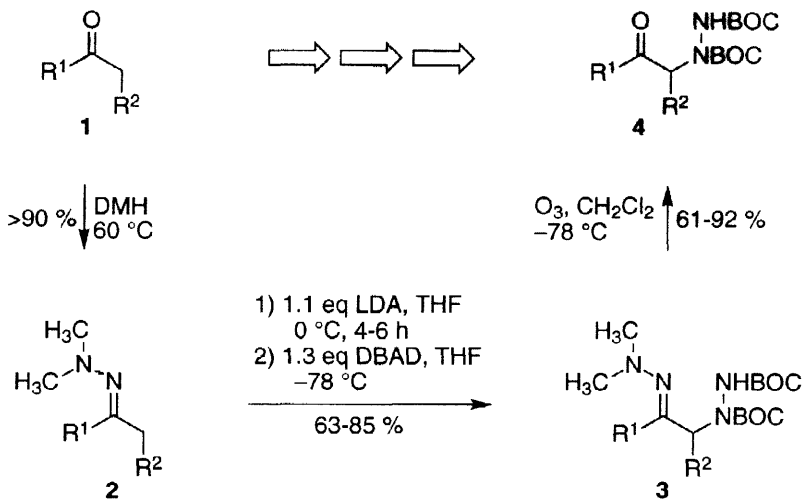
aminating reagent at −78 °C in THF. In order to examine the generality of the present methodology, reactions were carried out on several hydrazones including cyclic, acyclic and aromatic ones. The scope of these electrophilic aminations is evident from the data provided in Table 1 and 2.



Scheme-1

Table 1: Electrophilic amination of dimethylhydrazones using DBAD

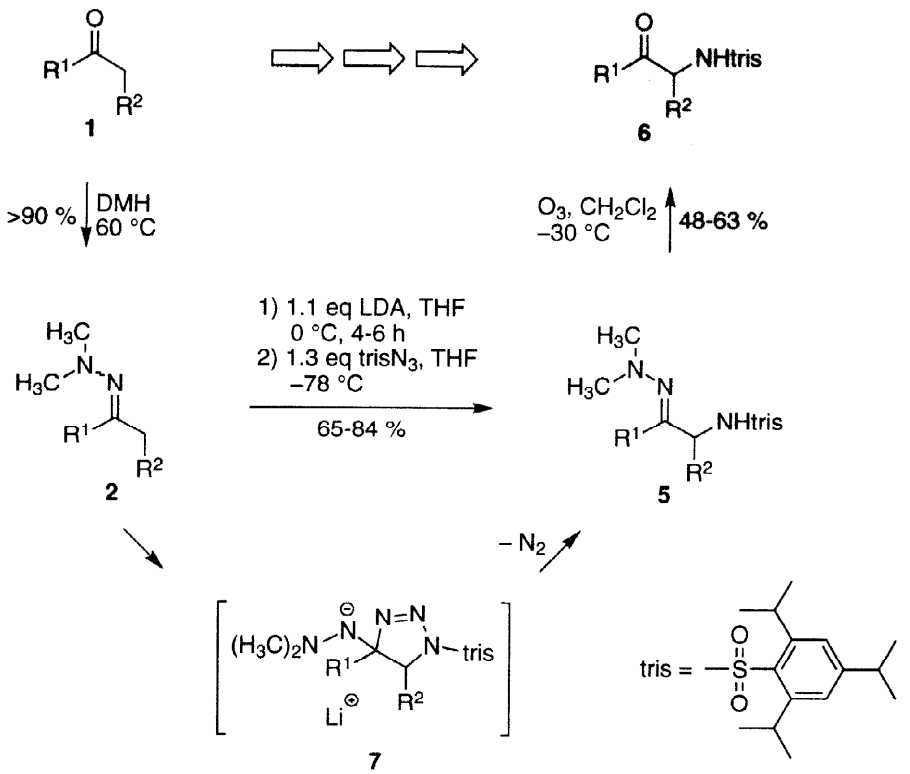
R^1	R^2	product	yield (%)[a]	product	yield (%)[a]
Et	Me	**3a**	85	**4a**	92
n-Pr	Et	**3b**	74	**4b**	85
-$(CH_2)_4$-		**3c**	78	**4c**	78
Ph	CH_3	**3d**	66	**4d**	65
Bn	Ph	**3e**	63	**4e**	61

[a] Yield of isolated product after column chromatography

In all instances the DMH-azaenolates reacted virtually instantaneously with DBAD and trisN3 at −78°C. In a typical experiment, a cooled (−78 °C) solution of the lithiated hydrazone was treated with a precooled solution of 1.3 equivalents of DBAD or trisN3 via syringe. After 2-5 min, the reaction was quenched with aqueous NH_4Cl solution and an extractive workup followed by chromatographic purification afforded the aminated hydrazones **3** and **5** in good yields. In the case of amination with trisN3 the isolated product was not an expected α-azidohydrazone but an α-sulfonamidohydrazone under the NH_4Cl quench condition. A possible mechanistic pathway as depicted in Scheme 2 would be the 1,3-dipolar cycloaddition of the azide dipole moiety with the enolate in an opposite regioselectivity as proposed by Evans *et al*,[1d] to form the triazoline, which upon loss of nitrogen and quenching with NH_4Cl leads to the stable sulfonamide **5**.

Finally, the product hydrazones were oxidatively cleaved to yield the target α-aminoketones. Whereas ozonolysis at −78 °C worked well with the *N*-BOC protected hydrazinohydrazones **3**

to give the corresponding *N*-BOC protected α-hydrazinoketones **4**, oxidative cleavage of the trisyl-protected α-aminohydrazones **5** turned out to be not an easy task and the yields of the



Scheme-2

Table 2: Electrophilic amination of dimethylhydrazones using trisylazide

R^1	R^2	product	yield (%)[a]	product	yield (%)[a]
Et	Me	**5a**	84	**6a**	63
n-Pr	Et	**5b**	78	**6b**	60
-$(CH_2)_4$-		**5c**	66	**6c**	55
Ph	CH_3	**5d**	69	**6d**	48
Bn	Ph	**5e**	65	**6e**	49

[a] Yield of isolated product after column chromatography

corresponding ketones **6** were low (≤20 %). Different cleavage conditions such as $MoOCl_3$,[11] CoF_3,[12] hydroxytosyloxyiodobenzene,[13] $CuCl_2$,[13] $Cu(OAc)_2$,[14] $NaIO_4$,[10d] $Pd(OAc)_4/SnCl_2$,[15] $CeCl_3 \cdot 7H_2O$,[16] and MMPP[17] were tried, but in all cases the cleavage was not satisfactory. However, ozonolysis at –30 °C worked in moderate yields. The reason for the lack of reactivity in the case of **5** could be steric demand of the bulky trisyl protecting group.

In conclusion, the new α-amination described allows a general access to protected α-hydrazino- and α-aminoketones. The advantage of this *C-N* connective approach is the easy availability of simple ketones as starting materials. An analogous reaction sequence is now

being investigated in our laboratories on ketone SAMP hydrazones to obtain enantiomerically enriched α-aminoketones.

Experimental

The melting points (Büchi apparatus system Dr. Tottoli) are uncorrected. IR spectra: Perkin Elmer FT 1750 spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR spectra (75 MHz): Varian VXR 300 and Gemini 300 (δ in ppm, TMS as internal standard). Mass spectra were recorded on a varian MAT 212 (70eV) spectrometer with DEI ionisation and are represented as *m/z* (%). Microanalyses were obtained using a Heraeus CHN-O-Rapid element analyser. Ozonolysis: Fischer ozone generator type 502.

Chemicals: All reactions were carried out under argon. The reagents were of commercial quality from freshly opened containers or purified prior to use. *n*-BuLi (1.6N in hexane) was purchased from Merck, Darmstadt. Tetrahydrofuran was freshly distilled from potassium under argon. Dichloromethane was distilled from calcium hydride. Flash column chromatography was carried out using Merck silica gel-60. Reactions were monitored by TLC using Merck plates (silica gel F_{254}) and visualised using 5 % phosphomolybdic acid solution in ethanol. *N,N*-Dimethylhydrazones **2** were prepared following standard literature procedures.[10]

General procedure for amination with DBAD:

In a typical reaction procedure, a cooled (−78 °C) solution of the lithium aza-enolate of the hydrazone (formed by the reaction of 1 eq of the hydrazone **2a** (0.128 g) in 2 ml THF with 1.1 eq of LDA at 0 °C for 4-6 h) was treated with a precooled solution of 1.3 eq DBAD (0.299 g) in 2 ml THF via cannula. After 2-5 min, the reaction was quenched with saturated aqueous NH_4Cl solution. An extractive workup, followed by column chromatography (pentane/ether 2:1) affords the aminated product **3a** in 85 % yield (0.304 g).

Di-(tert-butyl) 1-{2[(E)-N,N-dimethylhydrazono]-1-methylbutyl}-1,2-hydrazinecarboxylate **(3a)**: Yield: 85 %. Viscous liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.06 (t, J = 7.2 Hz, 3H, CH_3), 1.54 (s, br, 18H, $2C(CH_3)_3$), 1.57 (m, 3H, CH_3), 2.36 (s, 6H, $N(CH_3)_2$), 2.69 (m, 2H, CH_2), 4.98 (m, 1H, CHN), 6.88 (br, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.43, 16.66, 23.00, 28.20, 28.30, 47.55, 52.63, 80.01, 80.63, 155.86, 173.28 ppm. FT-IR (in $CHCl_3$, cm^{-1}): 3310, 2990, 2940, 2860, 1720, 1650, 1450, 1400, 1340, 1290, 1150, 1100, 1050, 1020, 900, 850, 790. MS (70 eV, 80 °C) *m/z* (%): 359 (M^+ +1) (8), 358 (32), 302 (8), 242 (8), 229 (12), 201 (8), 158 (32), 142 (52), 99 (24), 72 (12), 57 (100). $C_{17}H_{34}N_4O_4$ (358.4): Calcd. C 56.98, H 9.49, N 15.64. Found C 57.01, H 9.45, N 15.62.

Di-(tert-butyl) 1-{2[(E)-N,N-dimethylhydrazono]-1-ethylpentyl}-1,2-hydrazinecarboxylate **(3b)**: Yield : 74 %. Viscous liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.80 (t, J = 7.0 Hz, 3H, CH_3), 0.96 (t, J = 7.1, 3H, CH_3), 1.15- 1.17 (m, 2H, CH_2) 1.45 (s, 18H, $2C(CH_3)_3$), 1.97- 2.08 (m, 2H, CH_2), 2.35 (s, 6H, $N(CH_3)_2$), 2.54 (m, 2H, CH_2), 4.74 (m, 1H, CHN), 6.48 (br, 1H, NH) ppm.^{13}C NMR ($CDCl_3$, 75 MHz): δ = 10.03, 14.23, 21.56, 25.10, 28.25, 33.22, 46.46, 63.39, 47.55, 81.01, 155.86, 171.86 ppm. FT-IR (in $CHCl_3$, cm^{-1}): 3300, 2990, 2940, 2860, 1760, 1640, 1400, 1340, 1290, 1100, 1050, 1020, 950, 900, 760, 650. MS (70 eV, 80 °C) *m/z* (%):

386 (M^+) (20), 330 (10), 270 (15), 251 (18), 186 (32), 155 (52), 142 (20), 112 (28), 86 (16), 70 (24), 57 (100). $C_{19}H_{38}N_4O_4$ (386.5): Calcd. C 59.06, H 9.84, N 14.50. Found C 58.96, H 9.86, N 14.55.

Di-(tert-butyl) 1-{2[(E)-N,N-dimethylhydrazono]cyclohexyl}-1,2-hydrazinecarboxylate **(3c)**:

Yield : 78 %. Viscous liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.43 (s, 18H, $2C(CH_3)_3$), 1.54-2.32 (m, 8H, $CH_2CH_2CH_2CH_2$), 2.39 (s, 6H, $N(CH_3)_2$), 4.42 (m, 1H, CHN), 6.45 (br, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.02, 27.79, 28.62, 28.72, 30.33, 39.07, 47.61, 57.16, 80.60, 155.26, 160.23 ppm. FT-IR (in $CHCl_3$, cm^{-1}): 3390, 2890, 2980, 2920, 2860, 1740, 1680, 1420, 1380, 1340, 1300, 1250, 1150, 1050, 980, 900, 850, 740. MS (70 eV, 80 °C) *m/z* (%): 370 (M^+) (24), 314 (8), 270 (4), 258 (12), 241 (12), 213 (12), 172 (8), 170 (64), 139 (48), 110 (36), 96 (32), 73 (10), 57 (100). $C_{18}H_{34}N_4O_4$ (370.4): Calcd. C 58.37, H 9.18, N 15.13. Found C 58.28, H 9.11, N 15.10.

Di-(tert-butyl) 1-{2[(E)-N,N-dimethylhydrazono]1-methyl-2-phenylethyl}-1,2-hydrazinecarboxylate **(3d)**:

Yield : 66 %. Viscous liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.46 (d, J = 7.0 Hz, 3H, CH_3), 1.5 (s, 18H, $2C(CH_3)_3$), 2.55 (s, 6H, $N(CH_3)_2$), 5.88 (m, 1H, CHN), 6.59 (br, 1H, NH), 7.2-7.8 (m, 5H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.43, 28.10, 28.17, 47.95, 51.49, 80.70, 81.60, 128.20, 133.48, 134.96, 155.41, 169.50 ppm. FT- IR (in $CHCl_3$, cm^{-1}): 3320, 2980, 2940, 2860, 1720, 1650, 1480, 1450, 1400, 1340, 1250, 1200, 1050, 1020, 920, 850, 780, 650. MS (70 eV, 80 °C) *m/z* (%): 406 (M^+) (20), 362 (4), 350 (8), 290 (8), 206 (24), 190 (32), 175 (44), 132 (32), 104 (16), 74 (52), 57 (100). $C_{21}H_{34}N_4O_4$ (406.5): Calcd. C 62.06; H 8.37, N 13.79. Found C 62.80, H 8.38, N 13.83.

Di-(tert-butyl) 1-{2[(E)-N,N-dimethylhydrazono]1,3-diphenylpropyl}-1,2-hydrazinecarboxylate **(3e)**:

Yield : 63 %. Viscous liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.40 (s, 18H, $2C(CH_3)_3$), 2.65 (s, 6H, $N(CH_3)_2$), 3.72 (s, 2H, CH_2), 5.97 (s, 1H, CHN), 6.54 (br, NH), 7.08-7.40 (m, 10H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 28.19, 37.73, 47.65, 60.49, 80.90, 81.70, 125.76, 125.81, 127.85, 127.98, 128.35, 128.56, 136.72, 137.29, 154.99, 165.54 ppm. FT-IR (in $CHCl_3$, cm^{-1}): 3320, 3029, 2980, 2820, 1790, 1700, 1600, 1490, 1460, 1380, 1360, 1340, 1250, 1150, 1050, 1030, 1010, 900, 800, 750. MS (70 eV, 80 °C) *m/z* (%): 482 (M^+) (100), 474 (10), 457 (12), 455 (44), 443 (40), 441 (16), 428 (6), 415 (4), 386 (4), 366 (4), 350 (4), 331 (24), 267 (14), 252 (100), 230 (64), 219 (10), 206 (70), 176 (4), 161 (4), 132 (10), 103 (6), 85 (2), 76 (6), 59 (8), 57 (100). $C_{27}H_{38}N_4O_4$(482.6): Calcd. C 67.21, H 7.88, N 11.61. Found C 68.02, H 7.62, N 11.63

General procedure for ozonolysis:

In a typical reaction procedure the compound **3a** (0.358 g, 1 mmol) in dry dichloromethane was subjected to ozonolysis at −78 °C. The completion of the reaction was monitored by TLC. The excess of ozone was removed by flushing in argon . The crude product obtained by evaporation of the solvent was purified by column chromatography (pentane/ether 4:1) to afford the *N*-BOC-protected α- hydrazinoketones **4a** in 92 % yield (0.290 g).

Di-(tert-butyl)-1-(1-methyl-2-oxobutyl)-1,2-hydrazinedicarboxylate(**4a**):

Yield: 92 %. Viscous liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.06 (t, J = 7.2 Hz, 3H, CH_3), 1.38 (d, J = 7.4 Hz, 3H, CH_3), 1.48 (s, 18H, $2C(CH_3)_3$), 2.51 (m, 2H, CH_2), 4.4-4.9 (br, 1H, CHN), 6.2-6.5 (br, 1H, NH) ppm.^{13}C NMR ($CDCl_3$, 75 MHz): δ = 7.54, 13.80, 28.18, 32.31, 61.09, 81.69, 155.39, 210.05 ppm. FT-IR (in $CHCl_3$, cm^{-1}): 3279, 2979, 2937, 2879, 2835, 1708, 1698, 1478, 1458, 1405, 1362, 1317, 1255, 1101, 1049, 1024, 965, 760. MS (70 eV, 80 °C) *m/z* (%): 316 (M^+) (0.4), 259 (5), 159 (10), 103 (100), 85 (8), 59 (21), 57 (89). $C_{15}H_{28}N_2O_5$ (316.3): Calcd. C 56.96, H 8.86, N 8.86. Found C 59.92, H 8.85, N 8.30.

Di-(tert-butyl)-1-(1-ethyl-2-oxopentyl)-1,2-hydrazinedicarboxylate **(4b)**:

Yield : 85 %. Viscous liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.92 (t, J = 7.4 Hz, 3H), 1.07(t, J = 7.1 Hz, 3H), 1.46 (s, 18H, $2C(CH_3)_3$), 1.62-2.48 (m, 6H, $CH_2CH_2CH_2$), 4.62 (br, 1H, CHN), 6.48 (br, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 11.33, 13.72, 17.08, 20.82, 28.13, 28.19, 41.92, 67.27, 80.68, 81.71, 155.75, 209.90 ppm. FT-IR (in $CHCl_3$, cm^{-1}): 3269, 2976, 2879, 1745, 1721, 1678, 1520, 1461, 1402, 1370, 1324, 1275, 1256, 1237, 1152, 1092, 1051, 1033, 942, 900, 855. MS (70 eV, 80 °C) *m/z* (%): 344 (M^+) (1), 273 (5), 173 (6), 118 (5), 117 (100), 99 (5), 73 (12), 71 (5), 57 (58). $C_{17}H_{32}N_2O_5$ (344.4): Calcd. C 59.30, H 9.30, N 8.13. Found C 59.60, H 9.43, N 8.17.

Di-(tert-butyl)-1-(-2-oxocyclohexyl)-1,2-hydrazinedicarboxylate **(4c)**:

Yield : 78 %. Viscous liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.43 (s, 18H, $2C(CH_3)_3$), 1.71-2.47 (m, 8H, $CH_2CH_2CH_2CH_2$), 4.83 (dd, J = 9.6 and J = 3.8 Hz, 1H, CHN), 6.47 (br, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.33, 26.73, 28.16, 30.67, 41.40, 64.88, 81.60, 155.26, 160.23, 207.51 ppm. FT-IR (in $CHCl_3$, cm^{-1}): 3340, 2960, 2880, 1752, 1726, 1710, 1643, 1479,1455, 1391, 1245, 1157, 1107, 1048, 1022, 978, 897. MS (70 eV, 60 °C) *m/z* (%): 328 (M^+) (1), 283 (36), 239 (19), 224 (19), 209 (17), 171 (14), 170 (44), 152 (6), 126 (34), 96 (16),87 (5), 82 (9), 70 (25), 69 (6), 58 (87), 57 (100), 55 (13). $C_{16}H_{28}N_2O_5$ (328.4): Calcd. C 58.53; H 8.53, N 8.53. Found C 59.02, H 8.47, N 8.54.

Di-(tert-butyl)-1-(1-methyl-2-oxophenyethyl)-1,2-hydrazinedicarboxylate **(4d)**:

Yield : 65 %. mp: 78°C ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (d, J = 7 Hz, 3H, CH_3), 1.45 (s, 18H, $2C(CH_3)_3$), 3.45 (m, 1H, CHN), 6.8 (br, 1H, NH), 7.4-7.8 (m, 5H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.43, 28.10, 28.17, 59.49, 80.69, 81.64, 128.20, 133.48, 134.93, 155.40, 200.53 ppm. FT- IR (KBr, cm^{-1}): 3330, 3065, 3010, 2990, 2940, 1741, 1726, 1684, 1604, 1496, 1456, 1330, 1244, 1080, 936, 898. MS (70 eV, 80 °C) *m/z* (%): 364 (M^+) (4), 317 (8), 290 (16), 233 (24), 217 (16), 190 (28),145 (4), 119 (20), 105 (32), 91 (8), 77 (16), 57 (100). $C_{19}H_{28}N_2O_5$ (364.4): Calcd. C 62.63, H 7.69, N 7.69. Found C 62.70, H 7.65, N 7.68.

Di-(tert-butyl)-1-(-2-oxo-1,3,-diphenylpropyl)-1,2-hydrazinedicarboxylate **(4e)**:

Yield : 61 %. mp 107°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.47 (s, 18H, $2C(CH_3)_3$), 3.4 (s, 2H, CH_2), 3.65 (br, 1H, CHN), 6.13 (br, 1H, NH), 6.95-7.39 (m, 10H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 28.07, 28.16, 48.82, 53.80, 74.75, 80.90, 81.70, 125.52, 126, 126.57, 129.70, 128.77, 136.72, 152.29, 154.99, 205.01 ppm. FT-IR (KBr, cm^{-1}): 3328, 3091, 3065, 2980, 2820, 1740, 1726, 1670, 1394, 1244, 1159, 1050. MS (70 eV, 80 °C) *m/z* (%): 440 (M^+) (0.2), 321 (20), 221 (8), 166 (100), 147 (9), 121 (7), 104 (4), 91 (8), 77 (5), 57 (100). $C_{25}H_{32}N_2O_5$ (440.5): Calcd. C 68.18, H 7.27, N 6.36. Found C 68.80, H 7.25, N 6.35.

General procedure for amination with $trisN_3$:
In a typical reaction procedure, a cooled (−78 °C) solution of the lithium azaenolate of the hydrazone (formed by the reaction of 1 eq of the hydrazone **2a** (0.128 g) with 1.1 eq of LDA at 0 °C for 4-6 h) was treated with a precooled solution of 1.3 eq of $trisN_3$ (0.401g) in 2ml of THF via cannula. After 2-5 min, the reaction was quenched with aq NH_4Cl solution.An extractive workup, followed by column chromatography (pentane/ether 2:1) affords the aminated product **5a** in 84 % yield (0.343 g).

N-1-{2-[(E)-N,N-Dimethylhydrazino]-1-methylbutyl}-2,4,6-triisopropyl-1-benzenesulfonamide **(5a)**:
Yield : 84 %. Viscous liquid. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.85 (t, J = 6.7 Hz, 3H, CH_3), 1.08 (d, J= 6.5 Hz, 3H), 1.25 (dd, J = .6.9 Hz and 7.0 Hz, 18H, $3C(CH_3)_2$), 1.60 (m, 2H, CH_2), 2.58 (s, 6H, $N(CH_3)_2$), 2.89 (m, 1H, *p*-CH), 3.19 (m, 2H. *o*-CH), 4.32 (m, 1H, CHN), 7.16 (s, Ar-H), 8.42 (br, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 11.88, 18.31, 23.60, 24.80, 27.44, 29.43, 34.13, 36.56, 48.59, 123.60, 136.00, 149.13, 151.66, 170.94 ppm. FT-IR (in $CHCl_3$, cm^{-1}): 3260, 2960, 2870, 2220, 1600, 1460, 1440, 1250, 1120, 900, 740. MS (70 eV, 80 °C) *m/z* (%): 409 (M^+) (20), 394 (2), 365 (8), 323 (8), 302 (8), 217 (8), 187 (16), 175 (20), 142 (60), 119 (16), 91 (20), 72 (10), 59 (100). $C_{22}H_{39}N_3O_2S$ (409.6): Calcd. 64.54, H 9.53, N 10.26. Found C 64.89, H 9.87, N 10.30.

N-1-{2-[(E)-N,N-Dimethylhydrazino]-1-ethylpentyl}-2,4,6-triisopropyl-1-benzenesulfonamide **(5b)**:
Yield : 78 %. Viscous liquid. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.87 (m, 3H, CH_3), 1.22- 1.30 (dd, J = .6.9 Hz and 7.0 Hz, 18H, $3C(CH_3)_2$), 1.64-2.48 (m, 6H, $CH_2CH_2CH_2$), 2.58 (s, 6H, $N(CH_3)_2$), 2.89 (m, 1H, *p*-CH), 3.25 (m, 2H, *o*-CH), 4.36 (m, 1H, CHN), 7.13 (s, 2H, Ar-H), 8.52 (br, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 12.08, 14.53, 20.86, 24.08, 24.20, 25.53, 30.03, 36.24, 48.08, 48.98, 123.53, 136.68, 149.78, 152.78, 171.20 ppm. FT-IR (in $CHCl_3$, cm^{-1}) : 3260, 2960, 2870, 1600, 1450, 1250, 1140, 900, 740. MS (70 eV, 80 °C) *m/z* (%): 437 (M^+) (12), 393 (8), 352 (8), 314 (7), 287 (8), 267 (44), 249 (7), 203 (7), 175 (15), 170 (32), 119 (10), 91 (16), 59 (100). $C_{24}H_{43}N_3O_2S$ (437.6): Calcd. C 65.90, H 9.83, N 9.61. Found C 66.35, H 9.81, N 9.63.

N-1-{2-[(E)-N,N-Dimethylhydrazino]cyclohexyl}-2,4,6-triisopropyl-1-benzenesulfonamide **(5c)**:
Yield : 66 %. Viscous liquid. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.22- 1.30 (dd, J = .6.9 Hz and 7.0 Hz, 18H, $3C(CH_3)_2$), 1.50-1.85 (m, 8H, $CH_2CH_2CH_2CH_2$), 2.53 (s, 6H, $N(CH_3)_2$), 2.89 (m, 1H, *p*-CH), 3.40 (m, 2H, *o*-CH), 4.34 (m, 1H, CHN), 7.14 (s, 2H, Ar-H), 8.4 (br, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.69, 24.80, 25.99, 29.43, 30.98, 34.14, 40.80, 48.46, 123.07, 136.08, 149.30, 151.66, 170.39 ppm. FT-IR (in $CHCl_3$, cm^{-1}) : 3260, 2960, 2870, 1600, 1460, 1440, 1250, 1060, 900, 740. MS (70 eV, 80 °C) *m/z* (%): 421 (M^+) (20), 377 (8), 314 (8), 271 (8), 267 (66), 217 (4), 202 (4), 175 (12), 154 (36), 151 (14), 91 (12), 59 (100). $C_{23}H_{39}N_3O_2S$ (421.6): Calcd. C 65.55, H 9.26, N 9.97. Found C 65.43, H 9.30, N 9.99.

N-1-{2[(E)-N,N-Dimethylhydrazin]-1-methyl-2-phenylethyl}-2,4,6-triisopropyl-1-benzene-sulfonamide **(5d)**:

Yield : 69 %. Viscous liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.19 (d, J = 6.90, 3H, CH_3), 1.22- 1.30 (dd, J = .6.9 Hz and 7.0 Hz, 18H, $3C(CH_3)_2$), 2.53 (s, 6H, $N(CH_3)_2$), 2.89 (m, 1H, *p*-CH), 3.40 (m, 2H, *o*-CH), 4.34 (m, 1H, CHN), 7.14 (m, 7H, Ar-H), 8.4 (s, br, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.00, 23.60, 25.00, 31.43, 34.30, 47.40, 59.73, 126.00, 126.88, 134.47, 141.01, 145.53, 153.85, 157.55, 158.51 ppm. FT-IR (in $CHCl_3$, cm^{-1}) : 3260, 2960, 2870, 1600, 1460, 1440, 1250, 1060, 900, 740. MS (70 eV, 80 °C) *m/z*: 457 (8), 413 (8), 393 (8), 350 (8), 267 (16), 190 (16), 148 (8), 119 (4), 105 (18), 74 (36), 59 (100). $C_{26}H_{39}N_3O_2S$ (457.6): Calcd. C 68.27, H 8.53, N 9.91. Found C 69.53, H 8.16, N 8.87.

N1-{2-[(E)-N,N-Dimethylhydrazino]-1,3-diphenylpropyl}-2,4,6-triisopropyl-1-benzenesulfonamide **(5e)**:

Yield : 65 %. Viscous liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.22-1.30 (dd, J = .6.9 Hz and 7.0 Hz, 18H, $3C(CH_3)_2$), 2.45 (s, 6H, $N(CH_3)_2$), 2.63 (m, 1H, *p*-CH), 3.28 (m, 2H, *o*-CH), 3.67 (m, 2H, CH_2), 4.71 (m, 1H, CHN) 6.45-7.21 (m, Ar-H, 12H), 8.5 (br, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.69, 25.00, 31.43, 34.30, 47.40, 68.12, 126.47, 127.47, 127.45, 128.83, 132.60, 134.23, 138.86, 140.84, 142.00, 154.22, 158.12. 155.51 ppm. FT-IR (in $CHCl_3$, cm^{-1}) : 3260, 2960, 2870, 1600, 1460, 1440, 1250, 1060, 900, 740. MS (70 eV, 80 °C) *m/z* (%): 533 (M^++1) (0.2), 530 (0.4), 475 (1), 429 (4), 384 (2), 309 (4), 293 (11), 266 (12), 206 (16), 178 (88), 161 (20), 131 (80), 91 (100), 45 (48). $C_{32}H_{43}N_3O_2S$ (533.7): Calcd. C 72.05, H 8.06, N 7.87. Found C 72.73, H 8.12, N 7.98.

General procedure for ozonolysis:

In a typical reaction procedure, the compound **5a** (0.409 g, 1 mmol) in dry dichloromethane was subjected to ozonolysis at –30°C. The completion of the reaction was monitored by TLC. The excess of ozone was removed by flushing in argon . The crude product obtained by evaporation of the solvent was purified by column chromatography (pentane/ether 4:1) to afford the tris- protected α- aminoketones **6a** in 63 % yield (0.231 g).

N-1-(1-Methyl-2-oxobutyl)-2,4,6- triisopropyl-1-benzenesulfonamide **(6a)**:

Yield : 63 %. mp: 140°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.85 (t, J = 7.0 Hz, 3H, CH_3), 1.15 (d, J =7.0 Hz, 3H, CH_3), 1.25-1.35 (dd, J = 7.0 and 7.2 Hz, 18H, $3(C(CH_3)_2)$, 1.80 (m, 2H, CH_2), 2.22 (m, 1H, *p*-CH), 2.91 (m, 2H, *o*-CH), 4.21 (m, 1H, CHN), 7.27 (s, 2H, Ar-H), 8.41 (br, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 11.55, 16.41, 23.49, 24.64, 24.72, 26.59, 29.61, 34.21, 42.92, 124.02, 151.39, 209 ppm. FT- IR (KBr, cm^{-1}) : 3220, 2980, 2880, 1720, 1600, 1570, 1470, 1430, 1380, 1360, 1130, 1100, 1090, 990, 890. MS (70 eV, 70 °C) *m/z* (%): 368 (M^++1) (8), 303 (12), 282 (8), 266 (44), 260 (96), 251 (60), 220 (72), 203 (100), 187 (80), 159 (38), 116 (20), 91 (20), 77 (6), 57 (28), 55 (6). $C_{20}H_{33}NO_3S$ (367.5): Calcd. C 65.39, H 8.99, N 3.81. Found C 65.34, H 8.95, N 3.89.

N-1-(1Ethyl-2-oxopentyl)-2,4,6-triisopropyl-1-benzenesulfonamide **(6b)**:

Yield : 60 %. mp: 145°C . ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.85 (t, J = 7.0 Hz, 3H, CH_3), 1.15 (d, J = 7Hz, 3H, CH_3), 1.25-1.35 (dd, J = 7.0 and 7.2 Hz, 18H, $3(C(CH_3)_2)$, 1.80-2.46 (m, 2H, $CH_2CH_2CH_2$), 2.22 (m, 1H, *p*-CH), 2.91 (m, 2H, *o*-CH), 4.21 (m, 1H, CHN), 7.27(s, 2H, Ar-H), 8.41(br, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 11.55, 16.41, 23.49, 24.64, 24.72, 26.59, 29.61, 34.21, 42.92, 124.02, 151.39, 209 ppm. FT-IR (KBr, cm^{-1}) : 3220, 2980,

2880, 1720, 1600, 1570, 1470, 1430, 1380, 1360, 1130, 1100, 1090, 990, 890. MS (70 eV, 60 °C) *m/z* (%): 396 (M^+ +1) (4), 352 (8), 331 (8), 288 (96), 267 (44), 251 (48), 220 (68), 203 (100), 187 (56), 159 (12), 145 (24), 117 (24), 104 (20), 91 (36), 71 (24), 57 (12), 54 (20). $C_{22}H_{37}NO_3S$ (395.6): Calcd. C 66.83, H 9.36, N 3.54. Found C 66.44, H 9.39, N 3.31.

N-1-(2-Oxocyclohexyl)-2,4,6-triisopropyl-1-benzenesulfonamide **(6c)**:

Yield : 55 %. mp: 160°C . ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.24-1.30 (dd, J = 7.0 and 7.2 Hz, 18H, 3($C(CH_3)_2$), 1.40-2.00 (m, 8H, $CH_2CH_2CH_2CH_2$), 2.60 (m, 1H, *p*-CH), 2.90 (m, 2H, *o*-CH), 4.20 (m, 1H, CHN), 7.21 (s, 2H, Ar-H), 8.4 (br, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.50, 24.65, 25.87, 29.57, 34.21, 45.65, 124.05, 136.15, 149.36, 151.63, 204.01 ppm. FT-IR (KBr, cm^{-1}) : 3240, 2960, 2880, 1740, 1600, 1570, 1460, 1380, 1320, 1250, 1180, 990, 880. MS (70 eV, 80 °C) *m/z* (%): 380 (M^+ +1) (2), 315 (12), 298 (12), 272 (94), 251 (60), 220 (72), 203 (100), 187 (92), 159 (44), 145 (24), 117 (8), 104 (20), 91 (32), 69 (36), 55 (16). $C_{21}H_{33}NO_3S$ (379.5): Calcd. C 66.49, H 8.70, N 3.79. Found C 66.52, H 8.71, N 3.78.

N-1-(1-Methyl-2-oxo-2-phenylethyl)-2,4,6-triisopropyl-1-benzenesulfonamide **(6d)**:

Yield : 48 %. mp : 164°C . ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.16 (d, J = 6.0 Hz, 6H, $C(CH_3)_2$), 1.24-1.28 (dd, J = 3.0 and 3.1 Hz, 12H, 2$C(CH_3)_2$), 1.45 (d, J = 6.5 Hz, 3H, CH_3), 2.90 (m, 1H, *p*-CH), 3.58 (m, 2H, *o*-CH), 5.35 (m, 1H, CHN), 7.18- 7.36 (m, 7H, Ar-H), 8.2 (br, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.94, 23.49, 24.52, 24.70, 29.56, 34.19, 47.52, 125.00, 127.79, 129.37, 132.28, 134.44, 138.20, 153.13, 159.00, 178.41. FT- IR (KBr, cm^{-1}) : 3210, 2980, 2830, 1720, 1600, 1570, 1460, 1380, 1320, 1260, 1170, 900, 850. MS (70 eV, 80 °C) *m/z* (%): 416 (M^+ +1) (8), 372 (4), 351 (4), 308 (100), 266 (52), 251 (32), 220 (36), 203 (72), 187 (40), 159 (20), 116 (10), 104 (76), 91 (20), 77 (12), 50 (4). $C_{24}H_{33}NO_3S$ (415.5): Calcd. C 69.39, H 7.95, N 3.37. Found C 68.52, H 7.99, N 3.42.

N-1-(-2-Oxo-1,3-diphenypropyl)-2,4,6-triisopropyl-1- benzenesulfonamide **(6e)**:

Yield : 49 %. mp : 194 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.15-1.20 (d, J = 7.0 Hz, 6H, $C(CH_3)_2$) , 1.25-1.29 (dd, J = 6.1 and 6.5 Hz, 12H, 2C(CH3)2), 3.00 (m, 2H, CH_2), 3.58 (m, 1H, *p*-CH), 3.69 (m, 2H, *o*-CH) , 4.1 (m, 1H, CHN), 7.18- 7.36 (m, 12H, Ar-H), 8.2 (br, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 23.49, 24.52, 24.70, 29.56, 34.19, 39.73 55.52, 123.91, 126.67, 128.20, 131.54, 132.96, 134.20, 137.66, 138.03, 153.60, 158.74, 190.51. FT-IR (KBr, cm^{-1}) : 3210, 2980, 2830, 1720, 1600, 1570, 1460, 1380, 1320, 1260, 1170, 900, 850. MS (70 eV, 80 °C) *m/z* (%): 492 (M^+ +1) (2), 491 (4), 384 (88), 267 (30), 220 (40), 203 (70), 181 (54), 105 (20), 103 (28), 91 (100), 76 (24), 55 (16). $C_{30}H_{37}NO_3S$ (491.6): Calcd. C 73.31, H 7.53, N 2.85. Found C 73.02, H 7.36, N 2.88.

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