## Diastereo- and Enantioselective Synthesis of *syn-2*,3-Disubstituted 1,4-Diketones *via* Oxidative Coupling of Metalated Hydrazones

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**Abstract:** An efficient diastereo- and enantioselective synthesis of *syn*-2,3-disubstituted 1,4-diketones **4** is described. Key step of the procedure is the oxidative coupling of the metalated SAMP/RAMP-hydrazones **2** with iodine, followed by oxidative cleavage of the dimerized bishydrazones **3** with ozone and subsequent separation of the minor *meso*-isomer by chromatography. The *d*,*l*-isomers of the title 1,4-diketones **4** are obtained in good overall yields (20 - 64%) and high diastereo- and enantiomeric excesses ( $de \ge 98\%$ ,  $ee = 80 - \ge 95\%$ ).

1,4-Diketones constitute an important class of compounds<sup>1</sup>, for instance as precursors of cyclopentanoids and five-membered heteroaromatics<sup>2</sup>. Although numerous synthetic routes to 1,4-diketones are known<sup>3</sup>, there are only a few asymmetric syntheses of the title compounds published so far<sup>4</sup>, and the direct approach *via* auxiliary controlled oxidative coupling has very recently been reported only for the related 1,4-dicarboxylic acid derivatives<sup>5-7</sup>. The latter reports prompt us to disclose our own early results<sup>8</sup> on the asymmetric synthesis of 1,4-diketones *via* oxidative coupling of metalated SAMP/RAMP-hydrazones with iodine and subsequent removal of the auxiliary by ozonolysis.

As is shown in Scheme 1, symmetrical and unsymmetrical acyclic and cyclic ketones 1 are converted into their corresponding SAMP-hydrazones<sup>9-11</sup>, followed by metalation with *t*-BuOK/*n*-BuLi<sup>12</sup> in ether at -78°C. The resulting azaenolates are trapped with a solution of iodine in THF at the same temperature and, after aqueous work up, the light sensitive bishydrazones 3 are used in the next step without further purification (*d/l.meso* up to 86:14). Oxidative cleavage with ozone and flash chromatography affords the 2,3-disubstituted 1,4-diketones 4. The minor *meso*-isomer is easily separated by further chromatography (MPLC) and the *syn*-configured title diketones 4a-e are isolated in diastereomerically pure form ( $de \ge 98\%$ ), in good to excellent enantiomeric excesses ( $ee = 80 - \ge 95\%$ ) and in good overall yields (20 - 64%). In the case of sterically demanding groups R<sup>1</sup> (e.g.: 4d, R<sup>1</sup>=*t*-Bu) only low overall yields were obtained, even employing KDA as base (see Table 1)<sup>13</sup>.

The (*S*,*S*)-configuration of the 1,4-diketones **4** shown is based on the stereochemical outcome of our previous results<sup>9</sup> employing SAMP-hydrazones, but not yet confirmed. However, as shown in the case of **4d** the (*R*,*R*)-enantiomers are accessible in the same way by using RAMP instead of SAMP as the chiral auxiliary. The diastereomeric excesses of the diketones were determined by <sup>13</sup>C NMR spectroscopy, and the enantiomeric excesses were measured by <sup>1</sup>H NMR shift experiments with Eu(hfc)<sub>3</sub>.

In a futher experiment trifluoromethyl iodide was used instead of iodine as dimerization reagent. Subsequent ozonolysis of the crude product **3a** and purification by flash chromatography gave the 2,3-disubstituted 1,4diketone **4a** with an overall yield of 11%, a *d/l:meso* ratio of 67:33 and an enantiomeric excess of 83%. This example shows that trifluoromethyl iodide can be used as reagent for the oxidative coupling besides the well known reagents like iodine<sup>3i,6,7</sup>, Cu(II)-salts<sup>3p,q,6,7</sup>, Ce(IV)-salts<sup>3j</sup> and TiCl<sub>4</sub><sup>3b,6</sup>. In comparison with iodine, trifluoromethyl iodide leads to similar diastereo- and enantiomeric excesses, but in a much lower yield.



a) SAMP, 60°C, neat. b) **2a-e**: *t*-BuOK, *n*-BuLi, Et<sub>2</sub>O,  $-78^{\circ}$ C; I<sub>2</sub>, THF,  $-78^{\circ}$ C  $\rightarrow$  rt; **2a**: LDA, THF,  $-78^{\circ}$ C; CF<sub>3</sub>I-THF-solution (inverse addition),  $-100^{\circ}$ C  $\rightarrow$  rt. c) 1. O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>,  $-78^{\circ}$ C 2. MPLC (separation of *meso*-diastereomer)

Scheme 1

 Table 1. Asymmetric synthesis of 2,3-disubstituted 1,4-diketones 4

 via oxidative coupling of SAMP-hydrazones 2 with iodine

4	R1	R <sup>2</sup>	overall yield[%]ª	de <sup>b</sup> [%]	ее <sup>с</sup> [%]	$[\alpha]_D^{22}$ (c, CHCl <sub>3</sub> )
a	Et	Me	64	≥98 (42)	81	-57.4 (4.55)
$\mathbf{a}^{d}$	Et	Me	11	≥98 <sup>e</sup> (34)	83e	-59.1 (4.55)
b	-(CH <sub>2</sub> ) <sub>4</sub> -		63	≥98 (35)	f	-81.3 (1.75)
с	Ph	Me	53	≥98 (34)	80	-108.2 (1.26)
dg	t-Bu	Me	20	≥98 (71)	≥95	+17.9 (2.94)
$\mathbf{d}^{g,h}$	t-Bu	Me	20	≥98 (71)	≥95	-17.7 (2.94)
e	<i>i</i> -Pr	Me	59	≥98 (55)	f	-58.5 (1.15)

<sup>a</sup> After chromatography. <sup>b</sup> Determined by <sup>13</sup>C NMR spectroscopy, after separation of the minor *meso*-isomer by MPLC (see experimental part); in parenthesis the *de*-values before MPLC-separation. <sup>c</sup> Determined by <sup>1</sup>H NMR shift experiments with Eu(hfc)<sub>3</sub>. <sup>d</sup> CF<sub>3</sub>I was used as oxidative coupling reagent. <sup>c</sup> The diastereo- and enantiomeric excess was determined by GC-CSP (7 CD-Perme 25 M, 1 bar H<sub>2</sub>). <sup>f</sup> The *ee*-values could not be determined yet. <sup>g</sup> The hydrazone **2** was metalated with KDA and the major *d*/*l*-isomer was separated by precipitation in petroleum ether. <sup>h</sup> RAMP was used as chiral auxiliary

In summary a novel diastereo- and enantioselective synthesis of *syn*-2,3disubstituted 1,4-diketones *via* oxidative coupling of metalated SAMPhydrazones with good overall yields of up to 64% and with high diastereo- and enantiomeric excesses ( $de \ge 98\%$ ,  $ee = 80 - \ge 95\%$ ) has been developed<sup>14</sup>. **Acknowledgements.** This work was supported by Deutsche Forschungsgemeinschaft (Leibniz prize) and the Fonds der Chemischen Industrie. We thank Degussa AG, BASF AG, Bayer AG and Hoechst AG for the donation of chemicals.

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- (13) Synthesis of 2,3-disubstituted 1,4-bishydrazones **3a-e** via oxidative coupling with iodine: SAMP-hydrazones **2** (11 mmol) are added to a suspension of t-BuOK/n-BuLi<sup>12</sup> (11 mmol) in dry Et<sub>2</sub>O (50 mL) at  $-78^{\circ}$ C. After 2h a solution of iodine (10 mmol) in dry THF (10 mL) is added dropwise to the reaction mixture via cannula. After warming to room temperature overnight the reaction mixture is worked up (aqu. NH<sub>4</sub>Cl-solution/Et<sub>2</sub>O/NaSO<sub>4</sub>). The crude products could be used in the next step without further purification.

Synthesis of 1,4-bishydrazone **3a** via oxidative coupling with trifluoromethyl iodide: SAMP-Hydrazone **2a** (1 mmol) is added to a solution of LDA (1.1 mmol) in dry THF (5 mL) at 0°C. After 4h the reaction mixture is cooled to  $-78^{\circ}$ C and added dropwise to a  $-78^{\circ}$ C cold solution of trifluoromethyl iodide (1.12 mmol) in dry THF (5 mL) via cannula. After warming to room temperature the reaction mixture is worked up (aqu. NH<sub>4</sub>Cl-solution/Et<sub>2</sub>O/Na<sub>2</sub>SO<sub>4</sub>). The crude product can be used in the next step without further purification.

Synthesis of 2,3-disubstituted 1,4-diketones **4a-e**: Ozonolysis of hydrazones **3** (5 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at  $-78^{\circ}$ C was controlled by TLC. Subsequently the reaction mixture is warmed to room temperature under an argon stream. The crude products **4** are concentrated *in vacuo* and purified by flash chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O/pentane 1:1). The pure *d*/*l*-isomers of **4** are obtained after MPLC chromatography (Lichroprep® 50cm, 40mm, Si 60, corn size 15-25µm, ether/petroleum ether 1:1, 15ml/min).

(S,S)-4,5-Dimethyloctane-3,6-dione-bis-SAMP-hydrazone **3a**:

yellow oil. IR (CHCl<sub>3</sub>) 1625 cm<sup>-1</sup> (C=N). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 1.05$  (d, J = 6.9 Hz, 6H, CH<sub>3</sub>CH), 1.10 (t, J = 7.4 Hz, 6H, CH<sub>3</sub>CH<sub>2</sub>), 1.59-1.62 (m, 2H), 1.75-1.85 (m, 4H), 1.90-2.04 (m, 6H), 2.31-2.44 (m, 4H), 2.80-2.82 (m, 2H), 2.99-3.17 (m, 6H), 3.33 (s, 6H, OCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 11.00$  (CH<sub>2</sub>CH<sub>3</sub>), 17.79 (CHCH<sub>3</sub>), 22.20 (CH<sub>2</sub>), 24.87 (CH<sub>2</sub>) 27.39 (CH<sub>2</sub>), 41.01 (CHCH<sub>3</sub>) 54.59 (NCH<sub>2</sub>), 59.11 (OCH<sub>3</sub>), 66.04 (NCH), 76.54 (OCH<sub>2</sub>), 174.93 (C=N). MS, *m/z*: 393.9 (M<sup>+</sup>), 265.0 (M<sup>+</sup>-C<sub>6</sub>H<sub>13</sub>N<sub>2</sub>O). HRMS Calcd. for C<sub>22</sub>H<sub>42</sub>N<sub>4</sub>O<sub>2</sub>: 394.33035, found: 394.33035.

(S,S)-4,5-Dimethyl-3,6-octanedione **4a**: colourless oil. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.70 (CH<sub>2</sub>CH<sub>3</sub>), 14.34 (CH<u>C</u>H<sub>3</sub>), 34.59 (CH<sub>2</sub>), 47.80 (CH), 215.15 (C=O). All other spectroscopic data were in agreement with those reported in the literature<sup>15</sup>.

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