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Unexpected Hydrogenation of C–C-Double Bonds with *tert*-Butyl Iodide ¹⁾

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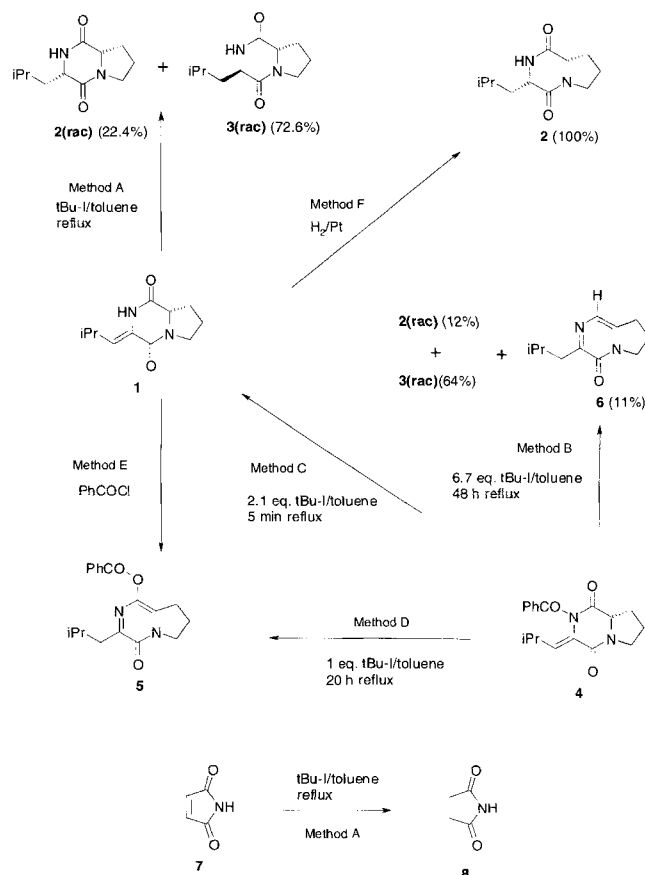
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Abstract. Heating of 3-isobutylidene-2,5-diketopiperazines **1** or **4**, maleinimide or 2,3-dichloro-5,6-dicyano-*p*-benzoquinone with *tert*-butyl iodide in toluene gave rise to hydrogenation of the conjugated C–C-double bond affording 3-isobutyldiketopiperazines **2(rac)** and **3(rac)**, succinimide, or 2,3-dichloro-

5,6-dicyanohydroquinone, respectively. Furthermore, an interesting N–O-migration of a benzoyl group as well as reductive aromatization to pyrazines **5** and **6**, respectively, were observed.

Stereoselective addition reactions (catalytic hydrogenation [1, 2], epoxidation [3], addition of diazomethane [4]) to the C–C-double bond of 3-ylidene-2,5-diketopiperazines, such as **1** or **4**, have been used in the synthesis of interesting α -aminoacid derivatives. Recently the radical addition of an alkyl group by alkylmercury compounds in the presence of NaBH₄ to 3-methylidene-2,5-diketopiperazine was reported generating one new stereogenic centre [5]. We attempted an analogous radical addition to the (*S*)-isobutylidene-2,5-diketopiperazines **1** and **4** using alkyl halides in the presence of tributyltinhydride and AIBN in order to generate two stereogenic centres. Unfortunately no C–C-bond formation could be accomplished. Just unchanged starting material was recovered in most cases. Obviously the higher degree of substitution of the C–C-double bond lowers the reactivity of **1** and **4** as compared with corresponding 3-methylidene-2,5-diketopiperazines. While using *tert*-butyl iodide in the presence of Bu₃SnH/AIBN however a reaction was observed with the isobutylidene-2,5-diketopiperazine **1**. But the product obtained was no alkylation product but a diastereomeric mixture of racemic 3-isobutyl-2,5-diketopiperazines **2(rac)** and **3(rac)**. The same mixture was also obtained in high yield (95%) when the solution of **1** in toluene was refluxed just in the presence of *tert*-butyl iodide (Method A). Obviously, *tert*-butyl iodide served as hydrogenation reagent. The stereoselectivity of this hydrogenation (preferred α -attack affording **3(rac)** as major product, **2(rac)** : **3(rac)** = 10 : 32) is opposite to the known catalytic hydrogenations of 3-alkylidene-2,5-diketopiperazines, where exclusive β -attack was observed [1, 2]. In order to prove the relative configuration of racemic *cis*-compounds **2(rac)** and racemic *trans* **3(rac)** we synthesized optically active *cis*-compound **2** by catalytic hydrogenation (Method F) of the isobutylidene-2,5-diketopiperazines **1** in this stereochemically unambiguous way. The *cis*-product **2(rac)** and the optically active **2** (obtained

by Method F) showed identical NMR spectra while those of the *trans*-compound **3(rac)** and **2** were different. (*S,S*)-Isobutyl-2,5-diketopiperazine **2** is a known natural product



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(for ex-amples see reference [6]). **2** (e.g. reference [7, 8]) and its enantiomer (e.g. reference [9]) and enantiomerically pure *trans*-compounds **3** (e.g. reference [10]) have been repeatedly synthesized by cyclization of di or tripeptides of proline and leucine or starting from ergot-alkaloids.

Further investigations revealed that the *N*-benzoyl-3-isobutylidene-2,5-diketopiperazine **4** could also be hydrogenated to the isobutyldiketopiperazines **2** (12%) and **3** (64%) with *tert*-butyl iodide (Method B). But in addition the isobutyl-2,4-diazinone **6** was obtained in 11% yield. Reactions of lower excess or equimolar quantities of the benzoyl-3-isobutylidene-2,5-diketopiperazine **4** and *tert*-butyl iodide gave rise to the debenzoylated product **1** (Method C) or the rearranged 5-benzoyloxy-pyrazine-2-one **5** (Method D), respectively also depending on the duration of reflux (5 min or 20 h, respectively). *tert*-Butyl iodide could further be used (Method A) to hydrogenate maleinimide or 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) but left maleic anhydride, butenolide and stilbene unchanged. Under the same conditions complex mixtures were obtained with cinnamic aldehyde, diphenylcyclopropanone while acrylamide afforded 3-iodopropanamide. Finally pyrrolidinocyclohexene gave just the corresponding iminium salt after heating with *tert*-butyl iodide in toluene.

The unusual function of *tert*-butyl iodide as hydrogenating reagent is probably caused by its known thermal elimination [11] giving isobutene and HI. The hydrogen iodide formed acts as hydrogen donor generating iodine as by-product which was found in the reaction mixture. HI has been used as hydrogenating reagent for 1,2-diacylalkenes [12] and 3,6-bisylidene-2,5-diketopiperazine [13] before. But just one out of the two C–C-double bond was hydrogenated in the latter case. As proposed in these known cases the hydrogenation itself is probably a multi-step process, i. e. primary addition of hydrogen iodide to the C–C-double bond (formation of **9** and **10**) and reductive C–I bond cleavage at the α -iodocarbonyl moiety by iodide ion generating iodine and an enolate which is finally protonated. These models can also explain why normal α,β -unsaturated carbonyl compounds lacking a second carbonyl group or an enamine moiety and thus do not give α -iodo-carbonyl intermediates or mere enamines were not hydrogenated with *tert*-butyl iodide.



The observed debenzoylation of **4** in the presence of *tert*-butyl iodide is presumably also caused by eliminated hydrogen iodide affording **1** and benzoyl iodide. After longer reaction times these two products react with each other by *O*-benzoylation and proton shift thus affording the 5-benzoyloxy-pyrazine-2-one **5**. Further evidence for this mechanism was found by the successful attempt to transform the 3-isobutylidene-2,5-diketopiperazine **1** to the benzoyloxy-pyrazinone **5** by means of benzoyl chloride (Method E) affording racemic **1** and **4** as by-products. Usually substituents at *N*-heterocycles migrate from the exocyclic *O*-position to the ring

nitrogen atom rather than the other way round. But in the case of the transformation of the *N*-benzoylpiperazindione **4** to the *O*-benzoylpyrazine **5** this unusual migration is driven by aromatization. The phenomenon of racemization in all reactions but method F is due to the high temperature applied. Product **6** formed from **4** in the presence of excess of *tert*-butyl iodide after long reaction times could eventually derive from **5** by HI-hydrogenation of the C=C-double bond and final elimination of benzoic acid.

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Experimental

General. ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively on a BRUKER AC-300 with TMS as internal standard. Mass spectra (HP 5995 A) were measured at 70 eV. Kieselgel, mesh size 0.4–0.6 mm (MERCK), was used for preparative chromatography. Starting materials **1** and **4** were prepared following known procedures [2] from hippuric acid, isobutyraldehyde and L-proline. Maleinimide and DDQ were purchased from ALDRICH.

Hydrogenation of 3-Isobutylidene-2,5-diketopiperazine (1), Maleinimide and 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone with *tert*-Butyl Iodide

Method A: *t*-Bu-I (0.5 mL, 4.2 mmol) was added to a mixture of the 3-isobutylidene-2,5-diketopiperazine **1** (208 mg, 1 mmol), maleinimide (97 mg, 1 mmol) or 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (227 mg, 1 mmol) and dry toluene (10 mL). The mixture was refluxed under argon for 5 h. After evaporation *in vacuo* the remaining material was submitted to flash chromatography on silica gel (acetone/ CHCl_3 = 1:2) or was recrystallized from ethanol/water under argon in case of 2,4-dichloro-5,6-dicyanoquinone.

cis-3-Isobutyl-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione **2**(*rac*)

Colourless crystals (22.4%). *m. p.* 150–152 °C, R_f = 0.29. – ^1H NMR (CDCl_3): δ /ppm = 0.90 (quart., J = 6.6 Hz, 6H, 2 CH_3), 1.71–2.29 (m, 7 H, 3 CH_2 , CHMe_2), 3.55 (m, 2H, NCH_2), 3.94 (dd, J =3.5, J =9.3, 1H, NCH -*i*-Bu), 4.05 (t, J =8.0 Hz, 1H, NCH -5-ring), 6.70 (s, 1H, NH). – ^{13}C NMR (CDCl_3): δ /ppm = 21.7 CH_3 , 23.6 CH_3 , 23.1 $\text{CH}_2\text{CH}_2\text{CH}_2$, 24.9 CHMe_2 , 28.4 CH_2CHN -5-ring, 38.9 CH_2CHMe_2 , 45.8 CH_2N -5-ring, 53.8 CHN -6-ring, 59.3 CH -5-ring, 166.7 CO, 171.0 CO. – IR (KBr): ν/cm^{-1} = 3258 (NH), 1658 (C=O), 1669 (C=O). – MS, m/z (%): 211 ($\text{M}^+ + 1$, 0.8), 210 (M^+ , 0.14), 164 (68), 70 (100). $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_2$ calcd.: C 62.83 H 8.63 N 13.32 (210.3) found: C 62.99 H 8.11 N 13.31.

trans-3-Isobutyl-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione **3**(*rac*)

Colourless crystals (72.6%). *m. p.* 100–102 °C, R_f = 0.24. – ^1H NMR (CDCl_3): δ /ppm = 0.89 (d, J = 7.0 Hz, 6H, 2 CH_3), 1.53–2.33 (m, 7H, 3 CH_2 , CHMe_2), 3.42–3.59 (m, 2H, NCH_2), 3.84–3.93 (m, 1H, NCH -*i*-Bu), 4.01 (dd, J =8.8 Hz, J =2.3 Hz, 1H, NCH -5-ring), 7.84 (s, 1H, NH). – ^{13}C NMR (CDCl_3): δ /ppm = 21.8 CH_3 , 23.4 CH_3 , 22.6 $\text{CH}_2\text{CH}_2\text{CH}_2$,

24.7 CHMe_2 , 29.3 $\text{CH}_2\text{CHN5-ring}$, 42.9 CH_2CHMe_2 , 45.9 $\text{CH}_2\text{N-5-ring}$, 56.5 CHN-6-ring , 58.4 CH-5-ring , 167.0 CO , 170.3 CO . – IR (KBr): ν/cm^{-1} = 3200 (NH), 1682 (C=O), 1653 (C=O). – MS, m/z (%): 211 ($\text{M}^+ + 1$, 0.5), 210 (M^+ , 0.1), 154 (62), 70 (100).

$\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_2$ calcd.: C 62.83 H 8.63 N 13.32
(210.3) found: C 62.61 H 8.33 N 13.34.

Succinimide (8)

Quantitative yield, *m. p.* 123–125 °C (ref. *m. p.* 123–125 °C [14])

2,3-Dichloro-4,5-dicyanohydroquinone

Yield 92%, *m. p.* 260–262 °C (ethanol/water) (ref. *m. p.* 265 °C [15])

Reaction of 4-Benzoyl-3-isobutylidene-2,5-diketopiperazine 4 with *tert*-Butyl Iodide

Method B: *t*-Butyl iodide (0.8 mL, 6.7 mmol) was added to a mixture of the *N*-benzoyl-3-isobutylidenediketopiperazine **4** (312 mg, 1 mmol) and dry toluene (10 mL). The mixture was refluxed under argon for 2d. After evaporation *in vacuo* the remaining material was dissolved in acetone (5 ml) and stirred with saturated aqueous KF at room temperature for 2 days. The mixture was extracted with CHCl_3 (3 × 20 mL). After drying with Na_2SO_4 the solvent was evaporated *in vacuo* and the remainder was finally submitted to flash chromatography on silica gel (acetone/ CHCl_3 1:2) affording **2** (12%), **3** (64.3%) and **6** (11%)

1-Benzoyloxy-3-isobutyl-7,8-dihydro-6H-pyrrolo[1,2-*a*]pyrazine-4-one (6)

Colourless solid, $R_f = 0.35$. – $^1\text{H NMR}$ (CDCl_3): δ/ppm = 0.89 (d, $J = 6.6$ Hz, 6H, 2CH_3), 2.15 (m, 3H, $\text{CH}_2\text{CH}_2\text{CH}_2$, CHMe_2), 2.63 (d, $J = 7.2$ Hz, 2H, CH_2CH), 3.02 (t, $J = 7.7$ Hz, 2H, $\text{CH}_2\text{-C=C}$), 4.06 (t, $J = 7.3$ Hz, 2H, NCH_2), 7.22 (s, 1H, =CH). – $^{13}\text{C NMR}$ (CDCl_3): δ/ppm = 21.9 $\text{CH}_2\text{CH}_2\text{CH}_2$, 23.0 2CH_3 , 27.2 CHMe_2 , 29.8 C-CH_2 , 41.9 CH_2CHMe_2 , 49.0 CH_2N , 118.6 HC=C , 140.6 HC=C , 156 C=N , 157 C=O .

Method C: Following method B by using only 2.1 mmol of *t*-butyl iodide and refluxing for just 5 min. afforded isobutylidene-hexahydropyrrolo[1,2-*a*]pyrazine-2,4-dione **1**, yield after flash chromatography ($R_f = 0.39$, R_f of starting material **4** = 0.54) 17.8%, *m. p.* 168–170 °C (ref. *m. p.* 168–170 °C [2]), $[\alpha]_D^{20} = +28.0$ ($c = 1.85$ CHCl_3).

Method D: Following method B by using only 1 mmol of *t*-butyl iodide and refluxing for 20h afforded 1-benzoyloxy-3-isobutyl-7,8-dihydro-6H-pyrrolo[1,2-*a*]pyrazine-4-one **5** in 90% yield after flash chromatography (EtOAc/hexane 9:1, $R_f = 0.46$, by-products **1** $R_f = 0.30$ and **4** $R = 0.54$). Colourless amorphous solid, *m. p.* 90–96 °C. – $^1\text{H NMR}$ (CDCl_3): δ/ppm = 0.88 (d, $J = 6.7$ Hz, 6H, 2CH_3), 2.12–2.23 (m, 3H, $\text{CH}_2\text{CH}_2\text{CH}_2$, CHMe_2), 2.61 (d, $J = 7.2$ Hz, $\text{CH}_2\text{-CH}$), 2.96 (t, $J = 7.7$, 2H, $\text{CH}_2\text{-C=}$), 4.11 (t, $J = 7.4$ Hz, 2H, NCH_2), 7.42 (m, 2H, arom), 7.54–7.59 (m, 1H, arom), 8.10 (m, 2H, arom). – $^{13}\text{C NMR}$ (CDCl_3): δ/ppm = 23.0 2CH_3 , 21.7 $\text{CH}_2\text{CH}_2\text{CH}_2$, 27.2 (CHMe_2), 29.0 $\text{CH}_2\text{C=}$, 41.6 CH_2CHMe_2 , 49.8 CH_2N , 128.9 N=C= , 129.0 CH_{arom} , 130.7 CH_{arom} , 132.1 C_{arom} , 134.4 CH_{arom} , 155.4 C=N , 155.9 CO , 164.9 CO . – MS, m/z (%): 313 ($\text{M}^+ + 1$, 1), 312 (M^+ , 4), 207 (8), 106 (8), 105 (100).

$\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_3$ calcd.: C 69.21 H 6.45 N 8.97
(312.4) found: C 69.33 H 6.45 N 9.00.

Reaction of 3-Isobutylidene-2,5-diketopiperazine 1 with Benzoyl Chloride

Method E: A solution of 3-isobutylidene-2,5-diketopiperazine **1** (208 mg, 1 mmol) and benzoyl chloride (127 μL , 1.1 mmol) in dry toluene (8 mL) was refluxed under argon for 44 h. After evaporation to dryness under vacuum the remaining material was submitted to flash chromatography (EtOAc/hexane = 9:1) affording racemic **1** (31%, $R_f = 0.30$), racemic *N*-benzoyl-3-isobutylidene-2,5-diketopiperazine **4** (19%, $R_f = 0.54$) and the 1-benzoyloxy-3-isobutyl-7,8-dihydro-6H-pyrrolo[1,2-*a*]pyrazine-4-one (**5**) (54%, $R_f = 0.46$).

Method F: A mixture of the 3-isobutylidene-2,5-diketopiperazine **1** (208 mg, 1 mmol), Pd/C (10%, 40 mg/Aldrich) and EtOH was kept under hydrogen at 1 atm at room temperature for 17 h. After filtration through Celite 545 the filtrate was evaporated *in vacuo*. The remainder was submitted to column chromatography (acetone/ $\text{CHCl}_3 = 1:2$) affording 0.21 g (100 %) of the (*S,S*)-isobutyl-2,5-diketopiperazine **2** as colourless crystals. *m. p.* 150–152 °C (AcOEt/hexane) (reference *m. p.* 151–153 [7]), $[\alpha]_D^{20} = -148.2$ ($c = 1.2$, CHCl_3). The $^1\text{H-NMR}$ and the $^{13}\text{C NMR}$ spectra were identical with the spectra of the racemate **2(rac)**.

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