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Synthesis of Functionalized 3,4-Dihydro-2*H*-pyrans by Hetero – *Diels-Alder* Reaction of an Enaminoketone with Enol Ethers

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Summary. The hetero – *Diels-Alder* reaction of 3-(N-acetylbenzylamino)-2-cyano-1-phenyl-2-propen-1-one (**3**) with enol ethers (**4**) leads to diastereoisomeric cycloadducts **5** and **6** in good yields. The structure of the products is discussed in terms of configuration and preferred conformation. Reaction of **5** with sulfuric acid yields 3-benzoyl-1,2-dihydropyridin-2-one (**7**).

Keywords. *Diels-Alder* reaction; α,β-Unsaturated ketone; Enol ethers; 3,4-Dihydro-2*H*-pyran.

Synthese funktionalisierter 3,4-Dihydro-2*H*-pyrane durch Hetero – *Diels-Alder* – Reaktion eines Enaminoketons mit Enolethern

Zusammenfassung. Die Hetero – *Diels-Alder* – Reaktion von 3-(N-Acetylbenzylamino)-2-cyano-1-phenyl-2-propen-1-on (**3**) mit Enolethern (**4**) führt in guten Ausbeuten zu den diastereomeren Cycloaddukten **5** und **6**. Die Strukturen der Produkte werden im Zusammenhang mit ihrer Konfiguration und Vorzugskonformation diskutiert. Die Reaktion von **5** mit Schwefelsäure liefert 3-Benzoyl-1,2-dihydropyridin-2-on (**7**).

Introduction

The hetero – *Diels-Alder* reaction plays an important role in the synthesis of dihydropyran derivatives which are valuable precursors for many natural products such as carbohydrates and alkaloids. There are two synthetic routes leading to hydropyran derivatives *via* [4+2] cycloadditions. The first one is the reaction of electron rich butadienes with electrophilic carbonyl compounds acting as hetero-dienophiles [1, 2]. The second route is the hetero – *Diels-Alder* reaction of 1-oxa-1,3-butadiene with electron rich dienophiles (inverse electron demand) [3]. The incorporation of functional groups in the pyran ring may be conveniently achieved by reaction of substituted dienes and dienophiles. It has been stated that the rate and the yield of these reactions can be substantially increased by introducing electron-withdrawing substituents in position 2 or 3 of the oxabutadiene system [4, 5]. This is due to a lowering of the energy of the LUMO of the diene which then can easier overlap with the HOMO of the dienophile. In addition to the effect of the substituents in the diene, *Lewis* acid catalysts [5] and high pressure [6]

considerably accelerate the *Diels-Alder* reaction and influence its diastereoselectivity [7, 8]. Among these cycloadditions, the reaction of functionalized enaminocarbaldehydes and enaminoketones with enol ethers, leading to 4-amino-3,4-dihydro-2*H*-pyrans, turned out to be an efficient route to 3-amino sugar derivatives [9, 10] that are present in various antibiotics such as gentamycin C or adriamycin. Therefore, the investigation of this synthetic method seems to be of considerable interest.

Results and Discussion

The aim of our studies was to determine the influence of a cyano function at C-3 of 1-oxa-1,3-butadiene on its reactivity in the hetero – *Diels-Alder* reaction with enol ethers. *Tietze et al.* [11] have calculated that a cyano substituent should decrease the energy of the LUMO, thus facilitating the heterodiene reaction [12]. To our knowledge, only *Wyler et al.* [13] have reported the reaction of α,β-unsaturated acyl cyanides with ethyl vinyl ether, leading to 2*H*-pyran-6-carbonitriles. In this paper we describe the reaction of 3-(N-acetylbenzylamino)-2-cyano-1-phenyl-2-propen-1-one (**3**) with various enol ethers leading to 4-amino-3,4-dihydro-2*H*-pyran derivatives.

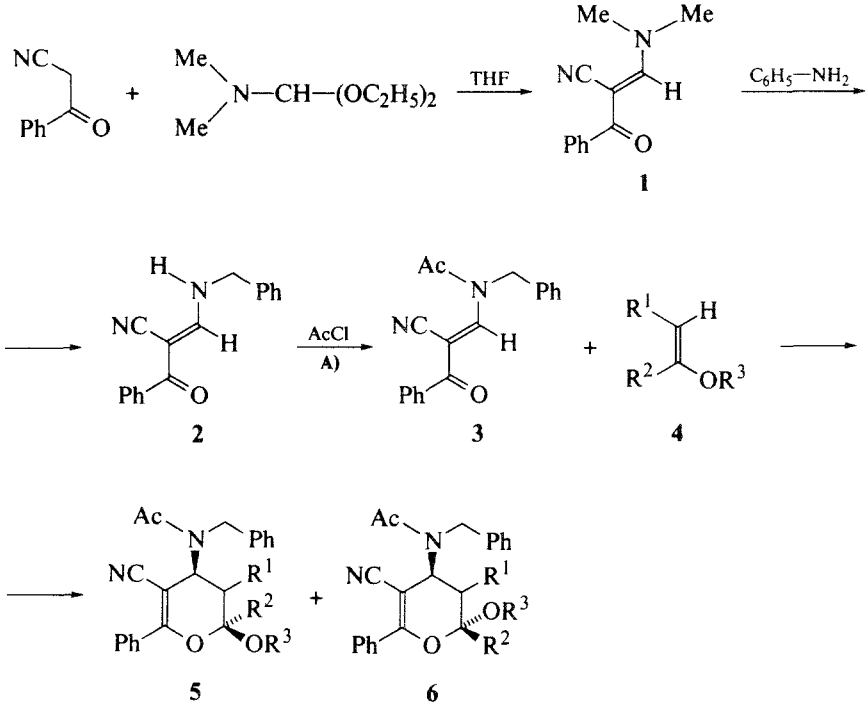
The synthesis of the diene **3** was accomplished in a three step reaction (Scheme 1). Reaction of benzoylacetonitrile with N,N-dimethylformamide diethylacetal in tetrahydrofuran solution affords **1** in 80% yield. However, **1** does not give any cycloadduct with enol ethers. This is due to the electron donating function of the dimethylamino group which raises the LUMO energy of the oxabutadiene system. It has been stated that only N-acylated derivatives of 1-oxa-1,3-butadienes are capable to undergo heterodiene reactions [14]. Therefore, in the next step we carried out the appropriate modification of **1**: the introduction of an acylamino substituent at C-4 of the heterodiene. Reaction of **1** with benzylamine in methylene chloride afforded compound **2** in 92% yield. **2** was in turn transformed into the N-acylo derivative **3** (50%) by reaction with acetyl chloride in the presence of 4-(N,N-dimethylamino)-pyridine and triethylamine. Diene **3** turned out to be the appropriate active reagent for hetero – *Diels-Alder* reactions with enol ethers **4**. The reactions of **3** with **4** were performed in toluene solution at 100–120 °C (48–72 h, Table 1) using a glass pressure bottle. The progress of the reactions was monitored by TLC. The yields of diastereoisomeric products **5** and **6** were moderate to very good. The *cis* diastereoisomes **5** were always the main products. They are formed *via endo*

Table 1. Cycloaddition of enaminoketone **3** with enol ethers **4**

Products	Reaction condition (h/°C[a])	Yield (%)	Ratio of isomers[b]	M.p. (°C)
5a/6a	48/120–130	90	4.0:1.0	117/109
5b/6b	48/120–130	65	3.0:1.0	oil/87
5c/6c	48/120–130	57	5.0:1.0	132/110
5d/6d	72/120–130	61	5.0:1.0	135/176
6e	48/120–130	36		184

[a] Temperature of oil bath; [b] taken from ^{1}H NMR data of crude products

orientation of the reagents in the transition state. The ratio of diastereoisomers in the crude reaction mixture was determined on the basis of ^{1}H NMR spectroscopy. The highest ratio of *endo/exo* selectivity was observed in the reactions of **3** with **4c** and **4d**, leading to a product ratio of **5**:**6** = 5:1. In the case of the reaction of **3** with 1-ethoxycyclohexene (**4e**) only diastereoisomer **6** was isolated (Scheme 1).



4,5,6	R^1	R^2	R^3
a	H	H	C_2H_5
b	H	H	$CH_3(CH_2)_3$
c	H	H	$CH_2CH(CH_3)_2$
d	H	CH_3	CH_3
e	—$(CH_2)_4$—		C_2H_5

A) + Et_3N

Scheme 1

Configuration and conformation of the cycloadducts **5** and **6** have been established by ^{1}H NMR spectroscopy. The conformations of **5** and **6** are governed by the bulky acetylbenzylamino substituent at C-4 which prefers to adopt a *pseudo* equatorial position. In *cis* diastereoisomers **5**, the alkoxy groups at C-2 are oriented equatorially; in *trans* diastereoisomers **6**, they occupy an axial position. The preferred conformations of **5** and **6** (Fig. 1) were deduced from chemical shift values and coupling constants of protons attached to C-2 and C-4.

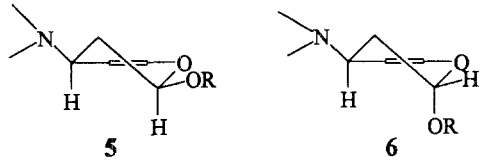


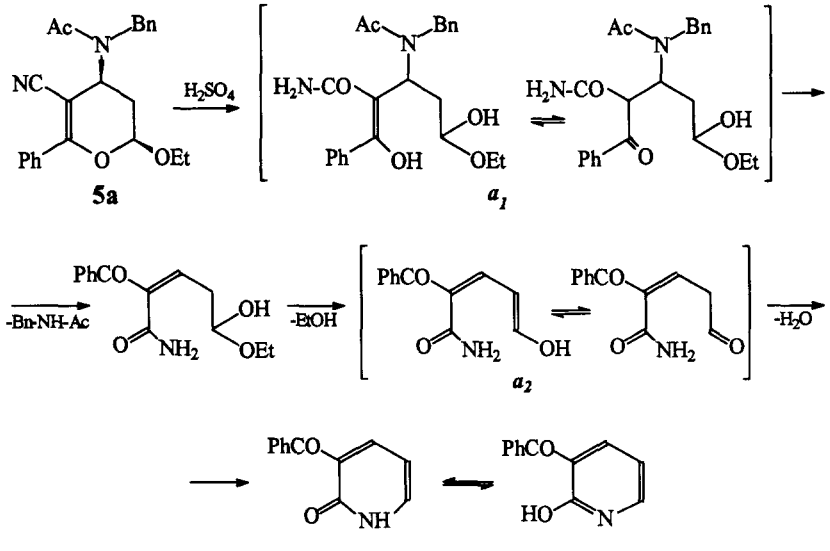
Fig. 1. Preferential conformation of cycloadducts

In cycloadducts **5a**, **5b**, and **5c**, the protons at C-2 resonate as doublets of doublets at $\delta = 5.27$, 5.23, and 5.24 ppm, respectively, with a large and a small coupling constant each (**5a**: $J = 8.6/2.0$ Hz; **5b**: $J = 8.6/2.0$ Hz; **5c**: $J = 6.25/1.8$ Hz) due to coupling with two protons at C-3. Thus, the protons at C-2 in **5** obviously are axial. The protons at C-4 in **5** appear as a doublet of a doublet (**5a**) or as broad signals at $\delta = 5.96$–5.97 ppm (**5b**, **5c**). For *trans* diastereoisomers **6a**–**6c**, the protons attached to C-2 give rise to triplets with small coupling constants ($J = 2.4$–2.6 Hz) at $\delta = 5.27$–5.22 ppm. This suggests that for **6** the conformation with an axial alkoxy group is preferred due to stabilization by the anomeric effect [15]. The protons at C-4 of **6** resonate at $\delta = 5.73$–5.75 ppm and at $\delta = 5.0$–5.1 ppm as ddd (**6a**) and as broad signals (**6b**, **c**). Since reaction of **3** with 1-ethoxycyclohexene **4e** affords only one cycloadduct, we assume that the preferential configuration for this compound is **6e** (*cis* fused rings and the C-8a ethoxy group in an axial position).

To ensure the conformational assignment of the original cycloadducts **5** as *cis*, we have taken into account the fact *cis* isomers of 3,4-2*H*-pyran derivatives undergo transormation to *trans* isomers in the presence of *Lewis* acids. When **5a** was submitted to the action of boron fluoride etherate, a mixture of **5a**/**6a** = 2.6:1 was obtained after 24 h at room temperature (^{1}H NMR analysis). Raising the reaction temperature to 50–70 °C caused decomposition of cycloadduct **5a**.

Experiments with the aim of transforming the cyano function in **5a** into carboxamide by alkaline hydrolysis of **5a** with aqueous sodium hydroxide led to decomposition of the cycloadduct. The only isolated compound from the reaction mixture was identified as acetylbenzylamine.

Acidic hydrolysis of **5a** in concentrated sulfuric acid gave **7** in 75% yield. Analytical data, MS determination of molecular weight ($m/z = 199$), and spectral evidences allowed **7** to be identified as 3-benzoyl-1,2-dihydropyridin-2-one [16]. Formation of **7** can be rationalized as depicted in Scheme 2. In the first step of the reaction, the acidic medium causes the opening of the pyran ring and the hydrolysis of the cyano group to the amide, producing the intermediate $\mathbf{a}_1$. In the next steps, elimination of acetylbezylamine and ethanol furnishes the intermediate $\mathbf{a}_2$ which undergoes intramolecular condensation yielding compound **7**.



Scheme 2

In conclusion, we have shown that the cyano group in enaminone **3** can act as an effective substituent in hetero–*Diels-Alder* reactions leading to functionalized 4-amino-3,4-dihydro-2*H*-pyrans. Further experiments concerning hetero–*Diels-Alder* reactions are in progress.

Experimental

Melting points: Boetius hot stage apparatus (corrected); IR spectra: Bruker IFS 48 (KBr pellets); ^{1}H NMR spectra: Bruker AMX 500 (500 MHz, $CDCl_3$, *TMS* as internal standard); mass spectra: Finnigan MAT 95; microanalyses: Perkin Elmer Analyser 240 (Regional Laboratory of Physicochemical Analyses in Kraków). Enol ethers **4a–d** were commercially available. Ether **4e** (1-ethoxycyclohexene) was prepared according to a known procedure [17]. All solvents were distilled prior to use. Products were isolated by column chromatography on silica gel.

2-Cyano-3-(N,N-dimethylamino)-1-phenyl-2-propen-1-one (**1**)

To a stirred solution of N,N-dimethylforamide diethyl acetal (5.9 g, 40 mmol) in 20 ml of anhydrous *THF*, benzoylacetonitrile (2.9 g, 20 mmol) dissolved in 10 ml of *THF* was added dropwise at room temperature. The stirring was continued for 2 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel using chloroform/methanol (20:1) as eluent. Pale yellow crystals (80%) from *THF*/*n*-hexane, m.p. 117–119 °C.

IR KBr, ν(cm^{-1}): 2184 (CN), 1647 (CO); ^{1}H NMR ($CDCl_3$): $\delta = 3.26$ (s, 3H, CH_3), 3.46 (s, 3H, CH_3), 7.28–7.86 (m, 5H, Ph-H), 7.93 (s, 1H,3-H) ppm; MS (*m/z* (%)): 200 (62) M^+, 199 (100) $[M-H]^+$, 123 (12) $[M-Ph]^+$, 105 (78) $[COPh]^+$, 77 (53) Ph^+; $C_{13}H_{12}N_2O_2$ (200.24); calcd.: C 71.98, H 6.04, N 13.99; found: C 72.26, H 5.61, N 14.02.

3-Benzylamino-2-cyano-1-phenyl-2-propen-1-one (**2**)

To a stirred solution of **1** (4.0 g, 20 mmol) in 15 ml of anhydrous CH_2Cl_2, a solution of benzylamine (2.15 g, 20 mmol) in 10 ml of dichloromethane was added. The stirring was kept for 1.5 h, the solvent was evaporated, and the residue was purified by crystallization from ethanol. Colourless prisms (91.5%), m.p. 140–142 °C.

IR (KBr, ν(cm^{-1}): 3177 (NH), 2926 (CH), 2194 (CN), 1642 (CO); ^{1}H NMR ($CDCl_3$): $\delta = 4.45$ (d, $J = 22$ Hz, 2H, $C\underline{H}_2Ph$), 7.47–8.19 (m, 11H, 3-H, Ph-H), 11.29 (br, 1H, NH) ppm; MS (*m/z* (%)): 262 (94) M^+, 261 (67) $[M-H]^+$, 106 (17) $[NHCH_2Ph]^+$, 105 (13) $[COPh]^+$, 91 (100) $[CH_2Ph]^+$, 77 (13) Ph^+; $C_{17}H_{14}N_2O$ (262.31); calcd.: C 77.84, H 5.38, N 10.68; found: C 77.81, H 5.38, N 10.54.

3-(N-acetylo benzyloamino)-2-cyano-1-phenyl-2-propen-1-one (**3**)

To a solution of **2** (2.6 g, 10 mmol), 4-(N,N-dimethylamino)-pyridine (0.35 g, 0.3 mmol) and anhydrous triethylamine (2.0 g, 20 mmol) in 40 ml of anhydrous *THF*/*t*-butyl methyl ether (1:1), freshly distilled acetyl chloride (1.6 g, 20 mmol) was added at 0 °C. The reaction was carried out in argon atmosphere. The reaction mixture was warmed up to room temperature, then heated for 6 h at 70 °C, and left overnight at room temperature. After addition of *t*-butyl methyl ether (20 ml), the precipitated ammonium salt of pyridine was filtered off, washed with ether (10 ml), and the combined organic layers were evaporated in vacuum. The residue was purified by column chromatography on silica gel using chloroform/ethanol (20:1) as eluent. Crystallization from *t*-butyl methyl ether gave colourless prisms, m.p. 89–90 °C, yield 50%.

IR (KBr, ν(cm^{-1})): 2205 (CN), 1716 (CO), 1668 (CO); ^{1}H NMR ($CDCl_3$): $\delta = 2.47$ (s, 3H, $COCH_3$), 5.48 (s, 2H, $C\underline{H}_2Ph$), 7.25–7.87 (m, 10H, Ph-H), 8.72 (s, 1H, 3-H) ppm; MS (*m/z* (%)): 304 (11) M^+, 303

(15) $[M-H]^+$ 262 (80) $[M-CH_2CO]^+$, 261 (94) $[M-COCH_3]^+$, 234 (12) $[M-COCH_3, CN]^+$, 106 (11) $[NHCH_2Ph]^+$, 105 (21) $[COPh]^+$, 91 (100) $[CH_2Ph]^+$; $C_{19}H_{16}N_2O_2$ (304.34); calcd.: C 74.98, H 5.29, N 9.20; found: C 74.96, H 5.15, N 9.24.

Reaction of **3** *with enol ethers* **4**

Synthesis of 4-(Acetylobenzyloamino)-2-alkoxy-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (**5, 6**)

To a solution of **3** (1.5 g, 5 mmol) in anhydrous toluene (5 ml), the appropriate vinyl ethers **4a–e** (50 mmol, 10 equivalents) and some crystals of hydroquinone were added. The mixture was heated at 100–120 °C in a pressure flask for 48–72 h (TLC control). After removal of toluene and excess of ethers, the mixture was separated and purified by column chromatography on silica gel using ethyl acetate/petrol ether (1:1) for **5/6** and chloroform/methanol (20:1) for **6e**. Reaction conditions and ratio of diastereoisomers for crude products are summarized in Table 1.

5a: IR (KBr, $\nu(cm^{-1})$): 2205 (CN), 1664 (CO), 1614 (C=C); ^1H NMR ($CDCl_3$): $\delta = 1.20$ (t, $J = 7.05$ Hz, 3H, OCH_2CH_3), 2.09 (s, 2.7H, $COCH_3$), 2.37 (s, 0.3H, $COCH_3$), 1.95 (ddd, $J_{gem} = 13.5$ Hz, $J_{4\text{-H},3\text{-Hax}} = 10.0$ Hz, 1H, 3-Hax), 2.26 (ddd, $J_{gem} = 13.5$ Hz, $J_{4\text{-H},3\text{-Heq}} = 7.35$ Hz, $J_{2\text{-H},3\text{-Heq}} = 2.0$ Hz, 1H, 3-Heq), 3.68 (dq, $J_{gem} = 9.4$ Hz, $J_{CH_2,CH_3} = 7.05$ Hz, 1H, OCH_2CH_3), 4.01 (dq, $J_{gem} = 9.4$ Hz, $J_{CH_2CH_3} = 7.05$ Hz, 1H, OCH_2CH_3), 4.51 (d, $J_{gem} = 18.3$ Hz, 1H, CH_2Ph), 4.76 (d, $J_{gem} = 18.3$ Hz, 1H, CH_2Ph), 5.27 (dd, $J_{3\text{-Hax},2\text{-H}} = 8.6$ Hz, $J_{3\text{-Heq},2\text{-H}} = 2.0$ Hz, 1H, 2-H), 5.96 (dd → t, $J_{3\text{-Hax},4\text{-H}} = 10.0$ Hz, $J_{3\text{-Heq},4\text{-H}} = 7.35$ Hz, 1H, 4-H), 7.05–7.76 (m, 10H, Ph-H) ppm; MS (*m/z* (%)): 376 (21) M^+, 285 (67) $[M-CH_2Ph]^+$, 243 (100) $[M-CH_2Ph, COCH_2]^+$, 239 (15) $[M-CH_2Ph, C_2H_5OH]^+$, 105 (22) $[NCH_2Ph]^+$, 91 (19) $[CH_2Ph]^+$; $C_{23}H_{24}N_2O_3$ (376.45); calcd.: C 73.38, H 6.43, N 7.44; found: C 72.97, H 6.04, N 7.13.

6a: IR (KBr, $\nu(cm^{-1})$): 2208 (CN), 1636 (CO) 1614 (C=C); ^1H NMR ($CDCl_3$): $\delta = 1.22$ (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 2.16 (s, 2.3 H, $COCH_3$), 2.40 (s, 0.7H, $COCH_3$), 1.90–2.00 (m, 1H, 3-Hax), 2.05 (ddd, $J_{gem} = 13.2$ Hz, $J_{4\text{-H},3\text{-Heq}} = 6.25$ Hz, $J_{2\text{-H},3\text{-Heq}} = 2.4$ Hz, 1H, 3-Heq), 3.63 (dq, $J_{gem} = 9.46$ Hz, $J_{CH_2,CH_3} = 7.1$ Hz, 1H, OCH_2CH_3), 4.01 (dq, $J_{gem} = 9.46$ Hz, $J_{CH_2,CH_3} = 7.1$ Hz, 1H, OCH_2CH_3), 4.15 (br, 0.3H, CH_2Ph), 4.54 (d, $J_{gem} = 18$ Hz, 0.7H, CH_2Ph), 4.79 (d, $J_{gem} = 18$ Hz, 0.7H, CH_2Ph), 5.25 (br, 0.3H, CH_2Ph), 5.05 (dd, $J_{3\text{-Heq},4\text{-H}} = 6.3$ Hz, 0.3H, 4-H), 5.27 (t, $J_{3\text{-H},2\text{-H}} = 2.4$ Hz, 1H, 2-H), 5.75 (br, 0.7H, 4-H), 7.23–7.75 (m, 10H, Ph-H) ppm; MS (*m/z* (%)): 376 (27) M^+; $C_{23}H_{24}N_2O_3$ (376.45); calcd.: C 73.38, H 6.43, N 7.44; found: C 73.61, H 6.24, N 6.84.

5b: IR (film, $\nu(cm^{-1})$): 2194 (CN), 1655 (CO), 1609 (C=C); ^1H NMR ($CDCl_3$): $\delta = 0.89$ (t, $J_{CH_2,CH_3} = 7.35$ Hz, 3H, $O(CH_2)_3CH_3$), 1.33 (sext, $J_{CH_3,CH_2} = 7.4$ Hz, 2H, $O(CH_2)_3CH_3$), 1.53 (quit, $J_{CH_2,CH_2} = 7.35$ Hz, 2H, $O(CH_2)_3CH_3$), 2.09 (s, 2.65H, $COCH_3$), 2.38 (s, 0.35H, $COCH_3$), 1.95 (ddd, $J_{gem} = 13.5$ Hz, $J_{2\text{-H},3\text{-Hax}} = 6.5$ Hz, 1H, 3-Hax), 2.25 (ddd, $J_{gem} = 13.5$ Hz, $J_{4\text{-H},3_{eq}} = 7.0$ Hz, $J_{2\text{-H},3\text{-Heq}} = 2.0$ Hz, 1H, 3-Heq), 3.60 (dt, $J_{gem} = 9.4$ Hz, $J_{CH_2,OCH_2} = 6.7$ Hz, 1H, $O(CH_2)_3CH_3$), 3.95 (dt, $J_{gem} = 9.4$ Hz, $J_{CH_2,OCH_2} = 6.6$ Hz, 1H, $O(CH_2)_3CH_3$), 4.51 (d, $J_{gem} = 18.0$ Hz, 1H, CH_2Ph), 4.76 (d, $J_{gem} = 18.0$ Hz, 1H, CH_2Ph), 5.24 (dd, $J_{3\text{-Hax},2\text{-H}} = 6.25$ Hz, $J_{3\text{-Heq},2\text{-H}} = 1.8$ Hz, 1H, 2-H), 5.97 (br, 1H, 4-H), 7.21–7.76 (m, 10H, Ph-H) ppm; MS (*m/z* (%)): 404 (45) M^+, 313 (87) $[M-CH_2Ph]^+$, 288 (38) $[M-OC_4H_9, COCH_3]^+$, 271 (100) $[M-CH_2Ph, COCH_2]^+$, 261 (27) $[M-C_4H_9OH, COCH_3, CN]^+$, 239 (58) $[M-CH_2Ph, COCH_3, OH]^+$, 215 (17) $[M-NCH_2Ph, COCH_3, CN, CH_3]^+$, 197 (27) $[M-CH_2Ph, COCH_3, OC_4H_9]^+$, 170 (15) $[M-CH_2Ph, COCH_3, C_4H_9OH, CN^+]$, 148 (27) $[CH_3CONCH_2Ph]^+$, 105 (54) $[NCH_2Ph]^+$, 91 (52) $[CH_2Ph]^+$; $C_{25}H_{28}N_2O_3$ (404.51); calcd.: C 74.23, H 6.98, N 6.93; found: C 74.52, H 7.20, N 6.72.

6b: IR (film, $\nu(cm^{-1})$): 2201 (CN), 1655 (CO), 1611 (CO); ^1H NMR ($CDCl_3$): $\delta = 0.89$ (t, $J_{CH_2,CH_3} = 7.4$ Hz, 3H, $O(CH_2)_3CH_3$), 1.35 (sext., $J_{CH_3,CH_2} = 7.4$ Hz, 2H, $O(CH_2)_3CH_3$), 1.56 (quint, $J_{CH_2,CH_2} = 7.4$ Hz, 2H,

$O(CH_2)_3CH_3$), 2.16 (s, 2.4H, $COCH_3$), 2.39 (s, 0.6H, $COCH_3$), 1.90–2.00 (m, 1H, 3-Hax), 2.06 (ddd, J_{gem} = 13.2 Hz, $J_{4\text{-H},3\text{-Heq}}$ = 6.3 Hz, $J_{2\text{-H},3\text{-Heq}}$ = 2.5 Hz, 1H, 3-Heq), 3.55 (dt, J_{gem} = 9.5 Hz, J_{CH_2,OCH_2} = 6.5 Hz, 1H, $O(CH_2)_3CH_3$), 3.83 (dt, J_{gem} = 9.5 Hz, J_{CH_2,OCH_2} = 6.5 Hz, 1H, $O(CH_2)_3CH_3$), 4.1–4.2 (br, 0.2H, CH_2Ph), 4.53 (d, J_{gem} = 18.0 Hz, 0.8H, CH_2Ph), 4.78 (d, J_{gem} = 18.0 Hz, 0.8H, CH_2Ph), 5.2–5.3 (br, 0.2H, CH_2Ph), 5.0–5.1 (br, 0.3H, 4-H), 5.75 (br, 0.7H, 4-H), 5.25 (t, $J_{3\text{-H},2\text{-H}}$ = 2.6 Hz, 1H, 2-H), 7.23–7.75 (m, 10H, Ph-H) ppm; MS (*m/z*: 404 (34) M^+; $C_{25}H_{28}N_2O_3$ (404.51); calcd.: C 74.23, H 6.98, N 6.93; found: C 73.81, H 7.32, N 6.87.

5c: IR (film, $\nu(cm^{-1})$): 2205 (CN), 1655 (CO), 1605 (C=C); ^1H NMR ($CDCl_3$): δ = 0.89 (d, J_{CH,CH_3} = 6.6 Hz, 6H, CH_3), 1.84 (m, $J_{CH_3,CH}$ = 6.6 Hz, 1H, CH), 2.09 (s, 2.6H, $COCH_3$), 2.37 (s, 0.4H, $COCH_3$), 1.94 (m, 1H, 3-Hax), 2.27 (ddd, J_{gem} = 12.3 Hz, $J_{4\text{-H},3\text{-Heq}}$ = 6.5 Hz, 1H, 3-Heq), 3.36 (dd, J_{gem} = 9.2 Hz, J_{CH,OCH_2} = 6.8 Hz, 1H, OCH_2), 3.73 (dd, J_{gem} = 9.2 Hz, J_{CH,OCH_2} = 6.6 Hz, 1H, OCH_2), 4.51 (d, J_{gem} = 18.0 Hz, 1H, CH_2Ph), 4.76 (d, J_{gem} = 18.0 Hz, 1H, CH_2Ph), 5.23 (dd, $J_{3\text{-Hax},2\text{-H}}$ = 8.6 Hz, $J_{3\text{-Heq},2\text{-H}}$ = 2.0 Hz, 1H, 2-H), 5.97 (br, 1H, 4-H), 7.15–7.75 (m, 10H, Ph-H) ppm; MS (*m/z* (%)); 404 (21) M^+, 313 (77) $[M-CH_2Ph]^+$, 288 (15) $[M-C_4H_9O, COCH_3]^+$, 271 (100) $[M-CH_2Ph, COCH_2]^+$, 239 (28) $[M-NCH_2Ph, COCH_3, OH]^+$, 215 (42) $[M-NCH_2Ph, COCH_3, CN, CH_3]^+$, 197 (13) $[M-CH_2Ph, COCH_3, OC_4H_9]^+$, 105 (13) $[NCH_2Ph]^+$, 91 (10) $[CH_2Ph]^+$; $C_{25}H_{28}N_2O_3$ (404.51); calcd.: C 74.23, H 6.98, N 6.93; found: C 73.82, H 7.00, N 6.67.

6c: IR (film, $\nu(cm^{-1})$): 2205 (CN), 1651 (CO), 1622 (C=C); ^1H NMR ($CDCl_3$): δ = 0.89 (d, J_{CH,CH_3} = 6.6 Hz, 6H, CH_3), 1.86 (m, $J_{CH_3,CH}$ = 6.6 Hz, 1H, CH), 2.17 (s, 2.3H, $COCH_3$), 2.39 (s, 0.7H, $COCH_3$), 1.92–2.0 (m, 1H, 3-H_{ax}), 2.03–2.1 (ddd, 1H, 3-H_{eq}), 3.32 (dd, J_{gem} = 8.9 Hz, J_{CH,OCH_2} = 6.7 Hz, 1H, OCH_2), 3.60 (dd, J_{gem} = 8.9 Hz, J_{CH,OCH_2} = 6.9 Hz, 1H, OCH_2), 4.1–4.2 (br, 0.2 H, CH_2Ph) 5.2–5.3 (br, 0.2H, CH_2Ph), 4.54 (d, J_{gem} = 17.85 Hz, 0.8H, CH_2Ph), 4.78 (d, J_{gem} = 17.85 Hz, 0.8H, CH_2Ph), 5.22 (t, 1H, 2-H), 5.07 (br, 0.4H, 4-H), 5.73 (br, 0.6H, 4-H), 7.24–7.75 (m, 10H, Ph-H) ppm; MS (*m/z* (%)): 404 (22) M^+; $C_{25}H_{28}N_2O_3$ (404.51); calcd.: C 74.23, H 6.98, N 6.93; found: C 74.30, H 7.12, N 6.84.

5d: IR (KBr, $\nu(cm^{-1})$): 2205 (CN), 1651 (CO), 1605 (CO); ^1H NMR ($CDCl_3$): δ = 1.58 (s, 2H, 2-CH_3), 1.65 (s, 1H, 2-CH_3), 2.09 (s, 2.8H, $COCH_3$), 2.4 (s, 0.2H, $COCH_3$), 2.05 (d, J_{gem} = 13.5 Hz, $J_{4\text{-H},3\text{-Heq}}$ = 6.7 Hz, 1H, 3-Heq), 2.15 (m, 1H, 3-Hax), 3.28 (s, 3H, OCH_3), 4.55 (d, J_{gem} = 18.0 Hz, 1H, CH_2Ph), 4.77 (d, J_{gem} = 18.0 Hz, 1H, CH_2Ph), 5.8 (br, 1H, 4-H), 7.23–7.75 (m, 10H, Ph-H) ppm; MS (*m/z* (%)): 376 (7) M^+, 285 (27) $[M-CH_2Ph]^+$, 261 (27) $[M-OCH_3, CH_3, CN, COCH_3]^+$, 253 (100) $[M-CH_2Ph, CH_3OH]^+$, 243 (75) $[M-CH_2Ph, COCH_2]^+$, 211 (42) $[M-CH_2Ph, COCH_3, OCH_3]^+$, 196 (53) $[M-CH_2Ph, COCH_3, OCH_3, CH_3]^+$, 148 (12) $[NCOCH_3(CH_2Ph)]^+$, 105 (80) $[NCH_2Ph]^+$, 91 (88) $[CH_2Ph]^+$, 77 (31) Ph^+; $C_{23}H_{24}N_2O_3$ (376.46); calcd.: C 73.38, H 6.43, N 7.44; found: C 73.16, H 6.10, N 7.30.

6d: IR (KBr, $\nu(cm^{-1})$): 2194 (CN), 1659 (CO), 1622 (CO); ^1H NMR ($CDCl_3$): δ = 1.51 (s, 1.8H, 2-CH_3), 1.65 (s, 1.2H, 2-CH_3), 2.09 (s, 2.3H, $COCH_3$), 2.38 (s, 0.7H, $COCH_3$), 1.81 (dd → t, J_{gem} = 13.5 Hz, $J_{4\text{-H},3\text{-Hax}}$ = 12 Hz, 0.4H, 3-Hax), 1.55 (m, 0.6H, 3-Hax), 2.05 (dd, J_{gem} = 13.5 Hz, $J_{4\text{-H},3\text{-Heq}}$ = 6.2 Hz, 1H, 3-Heq), 3.37 (s, 2.1H, OCH_3), 3.41 (s, 0.9H, OCH_3), 4.15 (d, J_{gem} = 17.9 Hz, 0.3H, CH_2Ph), 4.45 (br, 0.7H, CH_2Ph), 4.85 (br, 0.7H, CH_2Ph), 5.2 (d, J_{gem} = 17.9 Hz, 0.3H, CH_2Ph), 5.07 (dd, $J_{3\text{-Hax},4\text{-H}}$ = 11.8 Hz, $J_{3\text{-Heq},4\text{-H}}$ = 6.2 Hz, 0.3H, 4-H), 6.15 (br, 0.7H, 4-H), 7.23–7.77 (m, 10H, Ph-H) ppm; MS (*m/z* (%)): 376 (43) M^+; $C_{23}H_{24}N_2O_3$ (376.45); calcd.: C 73.38, H 6.43, N 7.44; found: C 73.15, H 6.20, N 7.15.

4-(Acetylo-benzylamino)-8a-ethoxy-2-phenyl-4,4a-dihydro-cyklohexa[b]pyran-3-carbonitrile (**6e**)

IR (KBr, $\nu(cm^{-1})$): 2205 (CN), 1651 (CO), 1622 (CO); ^1H NMR ($CDCl_3$): δ = 0.93 (t, J_{OCH_2,CH_3} = 6.9 Hz, 3H, OC_2H_5), 1.97 (s, 3H, $COCH_3$), 1.25–2.4 (m, 9H, 4a,5,6,7,8-H), 3.56 (dq, 1H, OCH_2), 3.61 (dq, 1H, OCH_2), 4.68 (d, J_{gem} = 17.7 Hz, 1H, CH_2Ph), 4.77 (d, J_{gem} = 17.7 Hz, 1H, CH_2Ph), 5.38 (br, 1H, 4-H),

7.25–7.74 (m, 10H, Ph-H) ppm; MS (*m/z* (%)): 430 (10) M^+, 339 (39) $[M-CH_2Ph]^+$, 297 (62) $[M-CH_2Ph, CH_2CO]^+$, 293 (100) $[M-CH_2Ph, C_2H_5OH]^+$, 251 (39) $[M-CH_2Ph, COCH_3, OC_2H_5]^+$, 236 (14) $[M-NCH_2Ph, COCH_3, C_2H_5OH]^+$, 105 (35) $[NCH_2Ph]^+$, 91 (15) $[CH_2Ph]^+$; $C_{27}H_{30}N_2O_3$ (430.55); calcd.: C 75.32, H 7.02, N 6.51; found: C 75.23, H 7.19, N 5.91.

Reaction of compound **5a** *with sulfuric acid: 3-Benzoyl-1,2-dihydro-pyridin-2-one* (7)

5a (0.2 g, 0.5 mmol) was suspended in sulfuric acid (4 ml, 75%) and heated at 180 °C for 3 h. The mixture was poured onto crushed ice (10 g). After extraction with *t*-butyl methyl ether (3 times 15 ml), the combined organic layers were dried ($MgSO_4$). The solvent was evaporated in vacuum and the residue was crystallized from *t*-butyl methyl ether. Colourless prisms (74%), m.p. 162 °C (Ref. [16]: m.p. 149 °C, uncorr.). IR (HCB, Nujol, $\nu(cm^{-1})$: 3200–2500 (broad, OH), 1650 (CO), 1609 (C=C); ^1H NMR ($CDCl_3$): $\delta = 6.39$ (t, 1H), 7.45–7.77 (m, 5H, Ph-H), 7.87 (d, $J = 7.45$ Hz, 2H), 13.17 (br, 1H, OH) ppm; MS (*m/z* (%)): 199 (65) M^+, 172 (17) $[M-HCN]^+$, 122 (53) $[M-Ph]^+$, 105 (100) $[PhCO]^+$, 94 $[M-PhCO]^+$, 77 $[Ph]^+$; $C_{12}H_9NO_2$ (199.21); calcd.: C 72.35, H 4.55, N 7.03; found: C 71.80, H 4.38, N 7.05.

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