1,4-ADDITION OF N,N-DIALKYLPHENYLACETAMIDES TO METHYLENE SUBSTITUTED 1,3-DIHYDRO-3-METHYLENE-2H-INDOL-2-ONES

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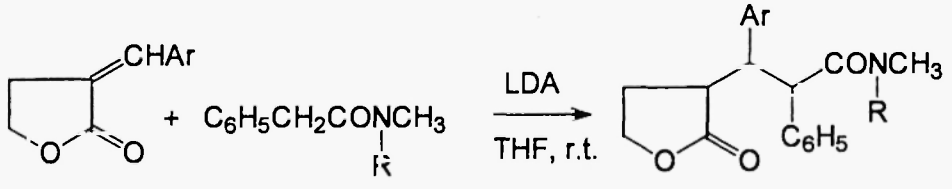
Abstract: Two 3-methylene-2H-indol-2-ones substituted in the methylene group by either a phenyl **6** or two electron withdrawing groups **8** react with the lithium enolates of N,N-disubstituted phenylacetamides and 2H-indol-2-one giving the corresponding products of conjugate 1,4-addition – the 1,3-dihydro-indol-2-ones **7** and **9**.

Introduction

The indolin-2-one ring was found in many alkaloids from plant extracts and other natural sources (1,2). The interesting biological activities of the organic molecules with indolin-2-one moiety as nonsteroidal cardiotonics (3), anestetics (4) and antibacterial agents (5) have drown the attention of many research groups for the study of their synthesis and properties. In context of our interest on the 1,4-addition reaction of some ambident nucleophiles we demonstrated recently that the lithium derivatives of some N,N-disubstituted phenylacetamides **2** add smoothly to 2-arylmethylene-4-butanolides (6). In all cases diastereomeric mixtures of the products **3** were obtained as a result of a typical 1,4-addition reaction with retention of the lacton ring, contrary to some previous reports (7,8):



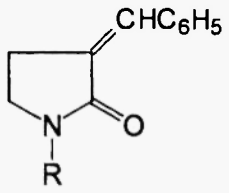
1 **2** **3**

Scheme 1

In connection of our interest on application of the Michael reaction for the preparation of compounds containing heterocyclic ring we decided to extend our investigations on aza-analogues of these lactones – the substituted 3-methylene-2-pyrrolidinones and 3-methylene-indolin-2-one as substrates and the indolin-2-one as CH-agent.

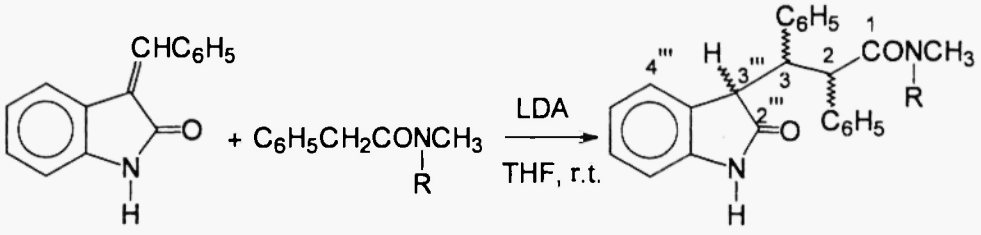
Result and discution

We focused our attention on the behaviour of the 3-phenylmethylene-2-pyrrolidone **4**. Unfortunately, all our attempts to effectuate a conjugate addition of the studied N,N-disubstituted phenylacetamides as well as its cyclic analogue 1,3-dihydroindol-2-one to 3-phenylmethylene-2-pyrrolidone **4** or to its N-acetyl derivative **5** failed.

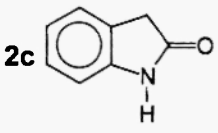


4 R = H
5 R = CH_3CO

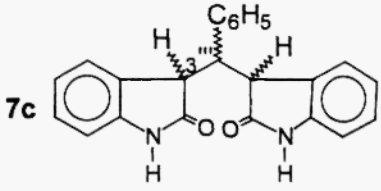
We continue our investigation studying the behaviour of the corresponding 3-benzylidenindol-2-one **6** towards the lithium enolate of N,N-dimethylphenylacetamide **2a**, prepared from the corresponding amide and LDA in THF. At the end of the reaction after purification by column chromatography we obtained the adduct **7a** in 64% yield. Besides the main isomer traces of another one were found in the last 2-3 fractions. The data from the elemental analysis as well as the ^{1}H NMR spectrum of this compound confirm the proposed structure **7a** (2R*3R*3'''R*, for the determination of the configuration see below) as a product of 1,4-addition.



6 **2a** R = CH_3; **b** R = C_6H_5 **7a** R = CH_3; **b** R = C_6H_5



2c



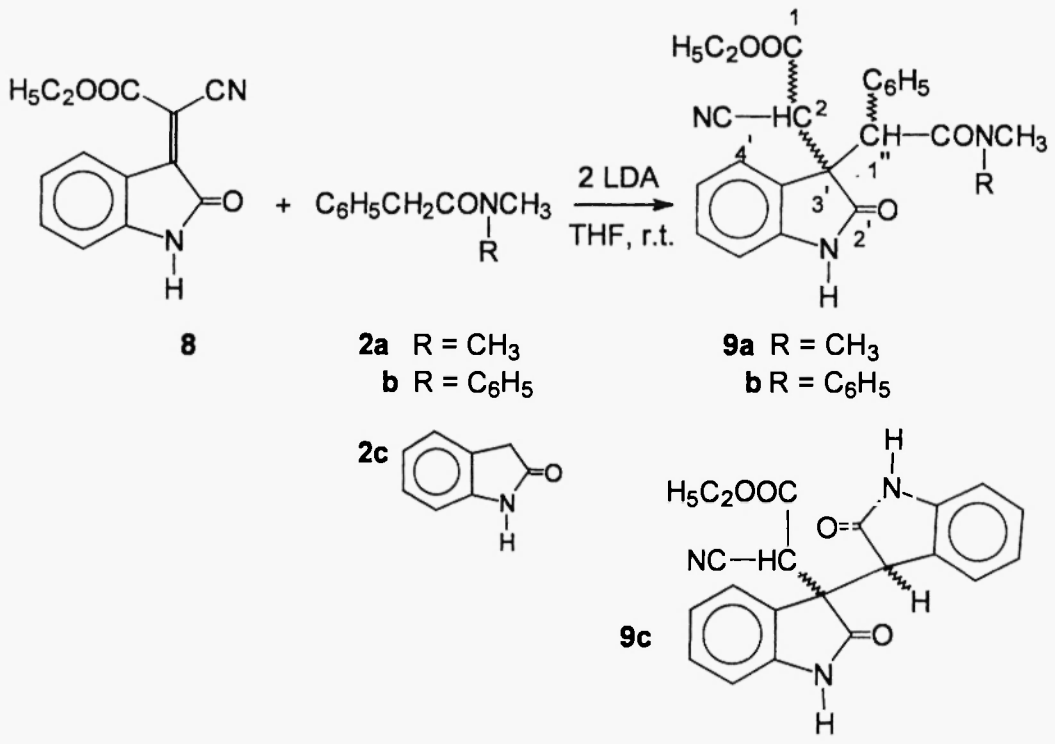
7c

Scheme 2

The interaction of the 3-benzylidenindol-2-one **6** with the N-methyl-N-phenylphenylacetamide **2b** occurs in the same manner. The adduct **7b** (2R*3R*3'''R*, 61% yield) was purified from the starting materials by means of column chromatography and after careful examination of the reaction mixture other diastereoisomers were not found.

The reaction of 1,3-dihydroindol-2-one **2c** with 3-phenylmethylene-2H-indol-2-one (**6**) gave also the expected adduct **7c** (73% yield). The ^{1}H NMR spectrum confirmed that the product is one of the three possible diastereomers. By means of column chromatography we isolated another 9% of the adduct **7c** but as a diastereomeric mixture with the two other isomers.

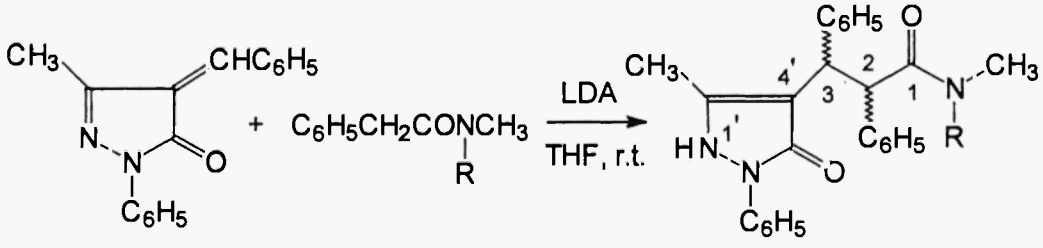
As a next model system for the purpose of our study we choose the ethylester of cyano-(1,2-dihydro-2-oxo-3H-indol-3-ylidene)acetic acid 8. The reaction of the studied lithium enolates 2a-c with this compound proceeds exclusively as 1,4-addition but with inversed regioselectivity.



Scheme 3

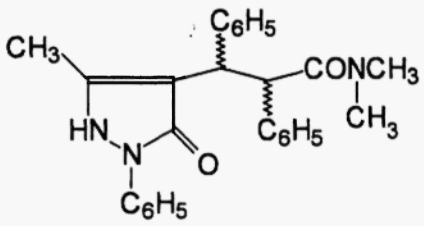
In all cases we obtained the adducts 9a-c as diastereomeric mixtures in different ratios with no preference for specific configurations. By means of column chromatography some of the diastereomers were separated. Detailed analysis of the ^{1}H and ^{13}C NMR spectra of compounds 9a and 9b allowed NMR-spectral characterization of all four possible isomers.

We completed our investigation by studying the behaviour of the 2,4-dihydro-5-methyl-2-phenyl-4-phenylmethylene-3(3H)-pyrazolone 10 toward the lithium derivatives 2a and 2b in the same reaction conditions. The compound 11b obtained after recrystallization represents one of the two possible diastereomers of the product of conjugate addition to the exocyclic double bound as it was expected. This addition was also accompained by a migration of the endocyclic azomethine bond. The ^{1}H NMR spectrum was in accordance with the proposed structure. By means of column chromatography we also isolated a small quantity (about 7 %) of the second diastereomer.

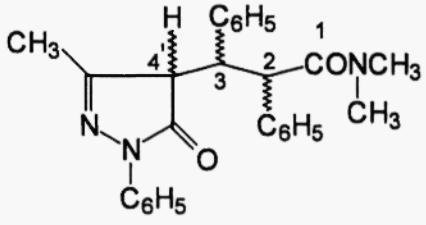


Scheme 4

The reaction of the enolate **2a** proceeds also as conjugate addition. But in this case we obtained a complex mixture of isomers – the two possible diastereoisomers of **11a** as well at least two of four corresponding tautomeric isomers **12**, formed without migration of the endocyclic double bound. By means of column chromatography we obtained small fractions containing pure isomers or mixture of two of them, enabling us to confirm their structure.

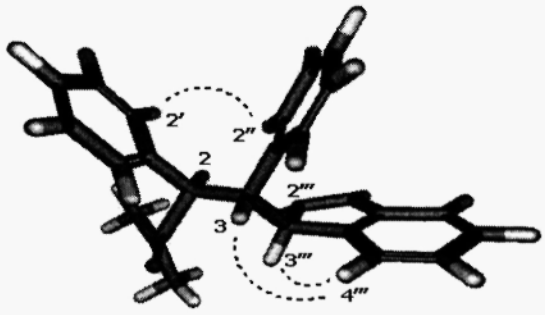


11 a



12

Unambiguous determination of the relative configuration of the chiral carbon atoms in the studied compounds **7** and **9** has been performed by NMR spectroscopy. Both compound couples **9a** and **9b** have been investigated as mixtures. **9a-I** and **9a-II** could not be separated by chromatography. After staying overnight in nmr-tube **9b-III** equilibrates to a diastereoisomeric mixture with **9b-IV** in a 3.5:1 ratio. The configuration of the chiral indol carbon atom is set as R*. Full assignment of the proton and carbon NMR spectra has been made by combined use of 1D and 2D homo- and heteronuclear pulse sequences (COSY, NOESY, HSQC, HSQC-TOCSY, selective DEPT). The relative position of the substituents around the bonds connecting chiral atoms has been determined from the measured values of the vicinal proton-proton and proton-carbon coupling constants using the Karplus relationship and made unambiguous by the observed NOE connectivities between closely spaced protons.



7a
2R*3R*3'''R*

Fig. 1 Predominant conformer for 7a, as deduced from the NMR data ($^3J_{H3\text{-}H3'''}$=4.4 Hz, $^3J_{H2\text{-}H3}$ = 11.4 Hz, $^3J_{H3\text{-}C2'''}$ > 6.0 Hz). Dotted lines indicate close proximity between protons determined from strong NOE signals in the corresponding NOESY-spectra.

From the values of the vicinal proton-proton coupling constants ($^3J_{H2\text{-}H3}$ = 11.4 and $^3J_{H3\text{-}H3'''}$ = 4.4) in compound 7a (see fig. 1, scheme 2) anti-position of protons H2 and H3 and gauche of the protons H3 and H3''

could be deduced. The observed large vicinal proton-carbon coupling ($^3J_{H3\text{-}C2'''} > 6.0$) corresponds to predominant antiperiplanar arrangement of proton H3 and the carbonyl carbon in the indol ring (C2'''). The observed large NOE's between the proton couples H3'''-H4''', H3-H4''' and H2'-H2''' prove the 2R*3R*3'''R*-configuration of this compound. The same configuration for the major isolated isomer of **7b** is deduced by analogy using the proton couplings and NOE-data.

We found compounds **9a-I, 9a-II, 9b-III** and **9b-IV** (see fig.2 scheme 3) most suitable for the configurational assignment. The relevant NMR-parameters are presented in the Table 5. In all four cases the structure of the predominant conformer in solution ($CDCl_3$ and DMSO-d_6) is characterized by close proximity of the proton couples H2-H4' and H2-H1'' giving rise to strong nuclear Overhauser enhancements for these protons. The large values of the vicinal proton-carbon coupling constants H2-C2' and H1''-C3a' corroborate this conclusion. The determination of the configuration of the individual compounds is deduced by interpretation of the large differences in the chemical shifts of protons H4' and of the ethoxy group in the different diastereoisomers due to strong

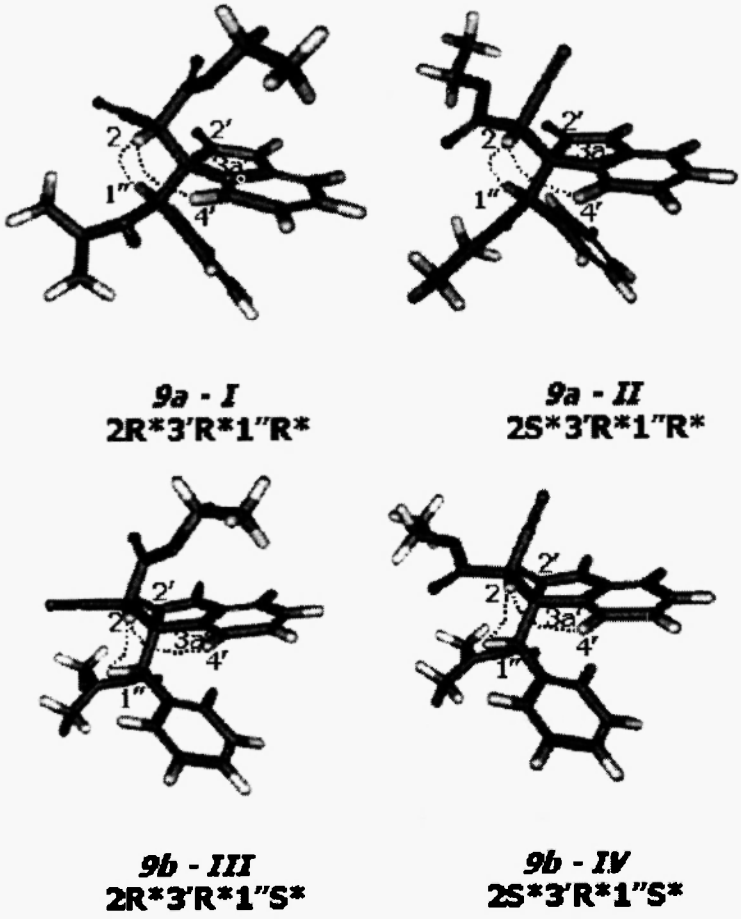


Fig. 2 Predominant conformers for compounds **9a-I, 9a-II, 9b-III** and **9b-IV**, as deduced from the NMR data (Table V). For simplicity the N-phenyl ring in **9b** is represented by a methyl group. Dotted lines indicate close proximity between protons determined from strong NOE signals in the corresponding NOESY-spectra.

ring current effects. In compounds **9b-III** and **9b-IV** large upfield shifts for H4′ are observed (more than 1 ppm). This proton is located above the plane of the phenyl ring that exerts a strong shielding effect, corresponding to 1″S*-configuration. The configuration of C1″ in **9a-I** and **9a-II** is opposite (1″R*), H4′ resonates at lower fields, since it is
located at the periphery of the phenyl ring. The configuration of C2 could be deduced by comparison of the chemical shifts of the methylene and/or methyl protons of the carboxylic group. In the 2R*-compounds the ethoxy group is positioned above the indol ring leading to upfield shifts as compared with more deshielded proton in the compounds with 2S*-configuration.

Conclusion

In summary, the reaction of the methylene substituted 3-methylene-2H-indol-2-ones **6** and **8** with the lithium enolates of N,N-disubstituted phenylacetamides and 2H-indol-2-one proceeds as conjugate 1,4-addition and provides a new approach for the synthesis of the 1,3-dihydro-indol-2-ones **7** and **9** with functionalized lateral chain in position 3 of the indol ring.

Experimental

The NMR spectra were recorded with a Bruker AVANCE DRX-250 spectrometer, ^{1}H NMR at 250.1 MHz in $CDCl_3$ (acetone-d_6 for **7c** and F_3CCOOD for **11b**), TMS as internal standard, ^{13}C NMR at 62.9 MHz, $CDCl_3$ at 77 ppm as internal standard. Samples for the NOESY-spectra have been prepared by blowing nitrogen through the $CDCl_3$ solution. Standard Bruker library pulse sequences for the proton and carbon as well as for the 2D COSY and NOESY spectra have been used. HSQC (9) and selective DEPT (10,11) experiments have been performed with home-written pulse programs. Silica gel 60 (Merck, 0.063-0.2 mm) was used for column chromatography. The starting compounds 3-phenylmethylen-2-pyrrolidinone **4** and its N-acetyl derivative **5** (12), 1,3-dihydro-3-phenylmethylene-2H-indol-2-on **6** (13), ethyl cyano-(1,2-dihydro-2-oxo-3H-indol-3-ylidene)acetate **8** (14) and 2,4-dihydro-5-methyl-2-phenyl-4-phenylmethylene-3(3H)-pyrazolone **10** (15) were prepared according to known procedures. As deprotonating reagent a 2M solution of LDA in tetrahydrofuran/hexan (Merck) was used. The THF was distilled over $LiAlH_4$ before use.

Additon of N,N-disubstituted phenylacetamides to 3-methylene-2-indolones 6 and 8 and 4-methylene-3-pyrazolone 10 - general procedure

To 2.2 ml (4.4 mmol) 2M solution of LDA in 1 ml THF (6.6 mmol for **2c**) at 0°C 2 mmol of the corresponding amide **2a-c** in 3 ml THF were added under argon and the reaction mixture was stirred for 15 min. Then a solution of 2 mmol of the corresponding compound **6**, **8** or **10** in 8-15 ml THF was added. After stirring for 5 hr at room temperature the reaction mixture was quenched with 3 ml 2M HCl. The solvent was evaporated under reduced presure, 20 ml water were added and after cooling the solidified oil was filtered and purified by column chromatography. The yields and the data of the elemental analyses for the major diastereoisomers of **7a-c, 9a-c** and
11a,b are summarized in Table I. For the ^{1}H NMR data of the compounds **7a-c**, **9a-c**, **11a,b** and **12** see Tables II, III, IV and V.

Table-I: Yields and data of the elemental analysis of **7a-c, 9a-c** and **11a,b**

Compound	Yield (%)	Found			Calculated		
		C	H	N	C	H	N
7a	64	77.88	6.51	7.50	78.10	6.29	7.29
7b	61	80.75	6.13	6.18	80.69	5.87	6.27
7c	82	77.72	5.41	7.71	77.95	5.12	7.90
9a	52	68.06	5.72	10.00	68.13	5.72	10.36
9b	61	71.68	5.53	9.20	71.93	5.39	8.99
9c	66	67.21	4.76	11.29	67.19	4.57	11.19
11a	44	75.95	6.67	10.19	76.21	6.40	9.88
11b	41	78.26	6.25	8.28	78.83	6.00	8.62

Table-II: ^{1}H NMR Data of Compounds **7a-c**

Comp.	N-CH_3	H3'''	H3	H2	NH	$H_{arom.}$
7a ($CDCl_3$)	3.00 s 3.27 s	4.09 d J=4.4 Hz	4.24 dd J=4.4 Hz J=11.4 Hz	5.30 d J=11.4 Hz	7.87 s	6.55 m (1H) 6.83-7.12 m (10 H) 7.22-7.28 m (2 H) 7.40 d (1H)
7b ($CDCl_3$)	3.30 s	4.26 d J=4.0 Hz	4.18 dd J=4.0 Hz J=11.5 Hz	4.94 d **J=11.5 Hz**	7.66 s	6.56-7.36 m (19 H)
7c (acetone-d_6)	-	4.55 d J=8.5 Hz, (2H)	3.49 t **J=8.5 Hz**	-	9.32 s (2H)	6.78-6.94 m (8H) 7.10-7.17 m (5H)

Table-III: ^{1}H NMR Data of the Predominant Isomers of the Compounds **9a-c**

Comp.	CH_3	CH_2	N-CH_3	H2	H1''	NH*	H4'
9a -I	1.06 t J=7.1 Hz	4.00 q J=7.1Hz	2.92 s 3.01 s	5.18 s	4.81 s	7.15 s	8.22 d J = 7.3
9a -II	1.31 t J=7.1 Hz	4.23-4.37 m	2.85 s 2.95 s	5.13 s	4.84 s	7.72 s	8.21 d J = 7.4
9a -III	0.88 t J=7.1 Hz	3.80-3.84 m	2.82 s 2.84 s	3.86 s	4.87 s	7.88 s	6.29 d J = 7.5
9b-I	1.06 t J=7.1 Hz	4.00 q J=7.1 Hz	3.26 s	5.24 s	4.60 s	7.04	8.20 J = 7.8
9b- III	0.85 t J=7.1 Hz	3.79 q J=7.1 Hz	3.14 s	3.66 s	4.74 s	8.19 s	6.27 d J = 6.9
9b-IV	1.13 t J =7.1 Hz	4.05-4.15 m	3.22 s	4.83 s	4.62 s	7.74 s	6.69 d J = 7.6
9c	0.87 t J=7.1 Hz	3.90 q J=7.1 Hz	-	5.30 s	4.09 s	10.48 s 10.69 s	

* at ~0.01M/l (concentration dependent)

Table-IV: ^{1}H NMR Data of the Predominant Isomers of the Compounds **11a,b, 12**

Comp.	CH_3C=	N-CH_3	H2	H3	H4′	NH	H arom.
11a	1.89 s	2.63 s 2.95 s	5.52 d J=11.3 Hz	4.39 d J=11.4 Hz	-	2.87 s	6.94-7.91 m (15H)
11b	2.06 s	3.30 s	5.01 d J=7.4 Hz	4.66 d J=7.4 Hz	-	4.10 s	6.84-7.82 m (20H)
12	2.06 s	3.00 s 3.19 s	5.13 d J=11.0 Hz	4.03 dd J=5.2 Hz J=11.0 Hz	4.11 d J=5.2 Hz	-	6.94-7.71 m (15H)

Table-V: NMR data for compounds **9a,b**, relevant for the proof of the configuration

NMR parameter	9a - I	9a - II	9b - III	9b - IV
δ(H-4′)	8.22	8.21	6.27	6.82
δ(CH_2)	3.98	4.29	3.82	4.11
^{3}J(H2-C2′)	6.8	7.1	7.4	4.8
^{3}J(H2 - C3′a)	0.0	0.0	0.0	4.0
^{3}J(H1″ – C3′a)	6.1	5.5	6.0	5.1
^{3}J(H1″ - C2′)	3.0	3.5	0.0	4.1

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