Effect of the Structure of 1-Aza-1,3-dienes on 1,2- *versus* 3,4-Selectivity in Cycloaddition Reactions with Homophthalic Anhydride†

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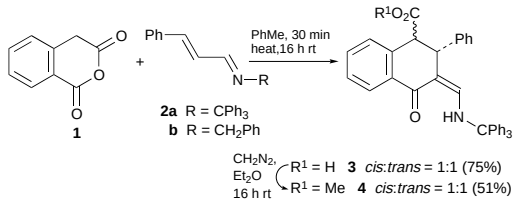
The reaction of homophthalic anhydride **1** with *N*-(cinnamylidene)tritylamine **2a** proceeds as a 3,4-cycloaddition to give 4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acids **3**, with *N*-(cinnamylidene)benzylamine **2b** as a 1,2-cycloaddition with the predominant formation of a 1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid, and with either **2a** or cinnamaldehyde in the presence of Et_3N with the formation of a 2-oxonaphtho[1,2-*b*]pyran-6-carboxylic acid.

Recently we have shown that the reaction of homophthalic anhydride **1** and α,β-unsaturated imines (1-aza-1,3-dienes) proceeds as a cyclocondensation. Thus, **1** and *N*-(cinnamylidene)isopropylamine give rise to isoquinolin-1(2*H*)-one, naphthalen-1(2*H*)-one and pyridin-1(2*H*)-one derivatives as products of competitive 1,2-, 3,4- and 1,4-addition, respectively.[1] *N*-(Cinnamylidene)*tert*-butylamine reacts with **1** to give naphthalen-1(2*H*)-one as a product of 3,4-addition.[1] It is known that the course of the reaction of 1-aza-1,3-dienes with 1,3-dicarbonyl compounds is altered completely when the substituent on nitrogen is changed from benzyl to *tert*-butyl.[2]

Here we disclose the results of a more detailed investigation of the effect of the alkyl substituent at the nitrogen of 1-aza-1,3-dienes on the chemoselectivity of the cycloaddition reactions with homophthalic anhydride **1**. For this purpose the reaction of *N*-(cinnamylidene)tritylamine **2a** and *N*-(cinnamylidene)benzylamine **2b** with **1** is studied.

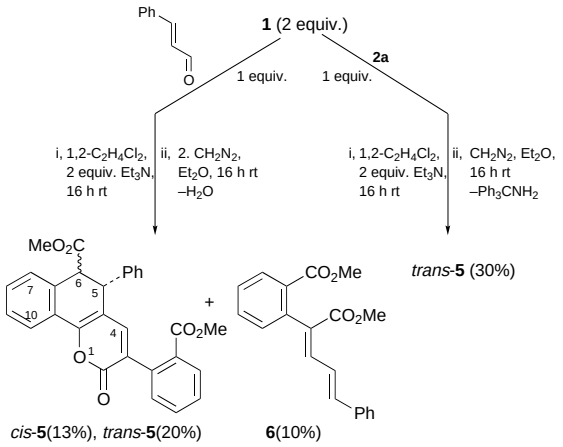
The reaction of **1** and the hitherto unknown **2a** in refluxing toluene proceeds as a 3,4-addition and affords a mixture of *cis*- and *trans*-4-oxo-2-phenyl-3-tritylaminomethylidene-1,2,3,4-tetrahydronaphthalene-1-carboxylic acids **3**, converted by means of diazomethane into the methyl esters **4**. The 1:1 ratio of the diastereoisomers in the crude reaction mixture was established from the ^1H NMR spectrum of the acidic mixture **3**, as well as by column chromatography (CC) of the mixture of esters **4** (Scheme 1).



Scheme 1

The chemoselectivity of the reaction of **1** and **2a** gave us ground to study the influence of Et_3N as a basic catalyst on the reaction course. Using a 2:1:2 ratio of **1**, **2a** and Et_3N at room temperature, *trans*-3-(2-carboxyphenyl)-2-oxo-5-phenyl-5,6-dihydro-2*H*-naphtho[1,2-*b*]pyran-6-carboxylic acid was obtained as the only product and was characterized as the methyl ester *trans*-**5** (Scheme 2).

A mixture of *trans*- and *cis*-3-(2-carboxyphenyl)-2-oxo-5-phenyl-5,6-dihydro-2*H*-naphtho[1,2-*b*]pyran-6-carboxylic acids, characterized as the methyl esters **5** were obtained when **1** reacted with cinnamaldehyde and Et_3N in the same 2:1:2 ratio at room temperature (Scheme 2).



Scheme 2

The reaction of **1** with **2a** or with cinnamaldehyde can be rationalized as proceeding *via* a cycloaddition–elimination sequence. Thus, an initially formed dihydronaphthalenone, acting as a heterodiene, reacts with the 3-en-3-ol form of a second molecule of **1** as a dienophile, accompanied by elimination of tritylamine (in the case of the reaction of **1** and **2a**) or water (when **1** reacts with cinnamaldehyde). 3-Hydroxy-1*H*-2-benzopyran-1-one, as the enol form of **1**, is assumed to be the reactive species in the reaction of **1** with aldehydes.[3] Some amino analogues of the enol form of **1** react with salicylaldehyde, to give 1*H*-2-benzopyran-1-ones, similar in structure to **5**.[4]

The reaction of **1** with freshly distilled **2b**[5] was carried out by a short reflux in THF followed by diazomethane treatment of the reaction mixture (Scheme 3). Thus, methyl *cis*-2-benzyl-1-oxo-3-(2-phenylethenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*cis*-**7**) was obtained as a major product. Unexpectedly, from the reaction mixture the known dihydroisoquinolinone *trans*-**8**[6] was isolated along with the side products **9**[1] and **10**. GC analysis of the crude **2b** done before the vacuum distillation showed the presence ($<10\%$) of an *N*-(benzylidene)benzylamine along with the starting cinnamaldehyde and benzylamine. The quantity of the undesired imine as well as of products of polymerization in the crude **2b** increased during storage.

Thus, the investigation of the chemoselectivity of the reaction of **1** with the 1-azadienes **2a**,**b** shows that **1** reacts with *N*-(cinnamylidene)tritylamine **2a** in a 3,4-addition manner. This result is in agreement with the previously investigated reaction of **1** and *N*-(cinnamylidene)*tert*-butylamine[1] and can be attributed to the presence of the bulky *N*-substituent in the 1-azadiene **2a**. The reaction of **1** with **2b** is shown to be also chemoselective but proceeds as a 1,2-cycloaddition, probably owing to the smaller *N*-benzyl as compared to the *N*-trityl group.

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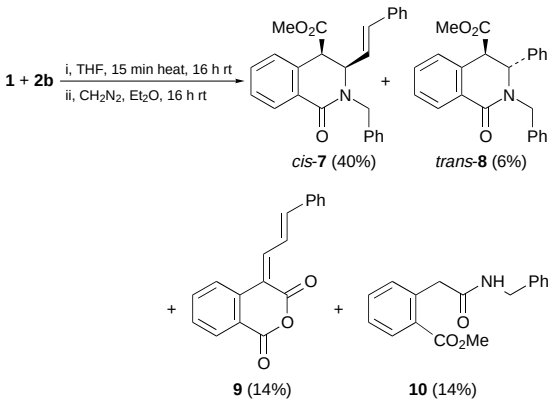
†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1997, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.



Scheme 3

Experimental

TLC: 0.2 mm 'Merck' silica gel $60F_{254}$ on aluminium sheets: solvent system, ether–hexane 1:1 CC: 0.20–0.063 mm 'Merck' silica gel 60 with ethyl acetate–hexane 5:95 and 10:90 as eluents. Mass spectra (MS): JOEL JMS D-300, electron impact (EI), 70 eV. IR spectra: C. Zeiss–Jena Specord IR-71, $CHCl_3$ as solvent if not stated otherwise. ^1H and ^{13}C NMR spectra: Bruker Spectrospin DRX-250 (250 MHz), $CDCl_3$ as solvent. GC analysis: Perkin Elmer Sigma 3B, equipped with FID, at 230 °C. GC–MS (HP-G 1800 A, GCD system): HPMS-5 column; carrier gas helium, MS (EI) 70 eV.

N-(*Cinnamylidene*)*tritylamine* **2a**.—A solution of cinnamaldehyde (1 mmol) and tritylamine (1 mmol) in dry benzene (20 ml) was refluxed for 2 h in a Dean–Stark apparatus. The solution was cooled, and the product was filtered off and recrystallized from benzene to give **2a** (90%), mp 155–156 °C; *m/z* 373 (M^+); ν_{max}/cm^{-1} (Nujol) 1620, 1635; δ_H 6.84 (1 H, d, $J_{3,4}$ 16.0, H-4), 7.19 (1 H, dd, $J_{2,3}$ 8.6, $J_{3,4}$ 16.0, H-3), 7.24–7.50 (20 H, m, arom.), 7.69 (1 H, d, $J_{2,3}$ 8.6, H-2) [Found: C, 89.73; H, 6.10. $C_{28}H_{23}N$ (373.5) requires C, 90.04; H, 6.21%].

Reaction of Homophthalic Anhydride **1** *with* **2a**.—A mixture of **1** (2 mmol) and the imine **2a** (2 mmol) in dry toluene (20 ml) was refluxed for 30 min and left for 16 h at room temperature. The solution was concentrated and the acidic products were filtered off to give in 75% yield a mixture of diastereoisomers **3** in 1:1 ratio of 96% purity, estimated by ^1H NMR integration of the H-3 and H-4 signals for *cis*-**3** and *trans*-**3**; *cis*-**3**: δ_H (the signals of the isomers were identified by selective decoupling) 4.05 (1 H, d, $J_{3,4}$ 5.1, H-3), 4.33 (1 H, d, $J_{3,4}$ 5.0, H-4), 6.46 (1 H, dd, J_{CHNH} 12.4, $J_{—CH=,\ H\text{-}3}$ 0.9, —CH=), 7.0–7.3 (23 H, m, arom.), 8.15 (1 H, m, H-8), 12.07 (1 H, d, *J* 12.5, NH, H-bond); *trans*-**3**; δ_H 4.11 (1 H, d, $J_{3,4}$ 4.1) and 4.22 (1 H, d, $J_{3,4}$ 4.0, H-3 and H-4), 6.61 (1 H, d, J_{CHNH} 12.4, —CH=), 7.0–7.3 (23 H, m, arom.), 8.15 (1 H, m, H-8), 12.15 (1 H, d, J_{CHNH} 12.5, NH, H-bond).

The acidic mixture was dissolved in CH_2Cl_2 and treated with an ethereal solution of diazomethane. The product was purified by CC. Methyl *cis*-4-oxo-2-phenyl-3-tritylaminomethylidene-1,2,3,4-tetrahydronaphthalene-1-carboxylate (*cis*-**4**) (25%), mp 197–199 °C (from ethyl acetate); *m/z* 549 (M^+); ν_{max}/cm^{-1} (Nujol) 1640m, 1740; δ_H 3.51 (3 H, s, CO_2CH_3), 4.05 (1 H, d, $J_{3,4}$ 5.3) and 4.31 (1 H, d, $J_{3,4}$ 5.2, H-3 and H-4), 6.47 (1 H, dd, J_{CHNH} 12.4, $J_{—CH=,\ H\text{-}3}$ 0.9, —CH=), 7.1–7.4 (23 H, m, arom.), 8.08 (1 H, m, H-8), 12.11 (1 H, d, J_{CHNH} 12.4, NH, H-bond). *Methyl* trans-4-*oxo*-2-*phenyl*-3-*tritylaminomethylidene*-1,2,3,4-*tetrahydronaphthalene*-1-*carboxylate* (*trans*-**4**) (26%), mp 224–225 °C (from ethyl acetate); *m/z* and ν_{max} were the same as for *cis*-**4**; δ_H 3.60 (3 H, s, CO_2CH_3), 4.11 (1 H, d, $J_{3,4}$ 4.8) and 4.23 (1 H, d, $J_{3,4}$ 4.8, H-3 and H-4), 6.58 (1 H, d, J_{CHNH} 12.3, NH, H-bond) [Found: C, 82.90; H, 5.91. $C_{38}H_{32}NO_3$ (549.6) requires C, 83.03; H, 5.69%].

*Reaction of Homophthalic Anhydride***1** *with* N-(*Cinnamylidene*)-*tritylamine* **2a** *in the Presence of Triethylamine*.—A mixture of **1** (2 mmol), triethylamine (2 mmol) and the imine **2a** (1 mmol) in dry 1,2-dichloroethane (10 ml) was stirred for 16 h at room temperature. Extraction with 10% aqueous Na_2CO_3 and acidification with conc. HCl afforded an acidic product, which was treated with diazomethane as above. The product was recrystallized to give *methyl* trans-3-(2-*methoxycarbonylphenyl*)-2-*oxo*-5-*phenyl*-5,6-*dihydro*-2H-*naphtho*[1,2-b]*pyran*-6-*carboxylate* (*trans*-**5**) (30%), mp 168–170 °C (from ethanol); *m/z* 466 (M^+); ν_{max}/cm^{-1} 1710, 1720, 1730; δ_H 3.67 (3 H, s) and 3.80 (3 H, s, $2CO_2CH_3$), 4.08 (1 H, d, *J* 4.5) and 4.58 (1 H, d, *J* 4.5, H-5 and H-6), 7.09 (1 H, H-4), 7.15–8.10 (13 H, m, arom.); δ_C 43.8 and 52.2 (C-5 and C-6), 52.3 and 52.7 ($2CH_3O$), 113.6 (C-4a), 123.5, 127.8(2), 128.7(2), 129.1(2), 129.6, 130.2, 130.6, 130.7, (13 C arom.), 141.1 (C-4), 127.4, 128.9, 130.8, 131.5, 135.8, 140.2, (5 C, arom., C-3), 153.4 (C-11), 161.2 (C=O, lactone), 167.6 and 172.3 (2COO) [Found: C, 74.64; H, 4.83; $C_{29}H_{22}O_6$ (466.5) requires C, 74.67; H, 4.75%].

Reaction of Homophthalic Anhydride **1** *with Cinnamaldehyde in the Presence of Triethylamine*.—A mixture of **1** (2 mmol), triethylamine (2 mmol) and cinnamaldehyde (1 mmol) in 1,2-dichloroethane (10 ml) was stirred for 16 h at room temperature. The reaction mixture was worked up as above and the crude product was purified by CC. Methyl *cis*-3-(2-methoxycarbonylphenyl)-2-oxo-5-phenyl-5,6-dihydro-2*H*-naphtho[1,2-*b*]pyran-6-carboxylate (*cis*-**5**) (13%), mp 177–179 °C (from ethanol); *m/z* and ν_{max} were the same as for *trans*-**5**; δ_H 3.54 (3 H, s) and 3.68 (3 H, s, $2CO_2CH_3$), 4.34 (1 H, d, *J* 7.3) and 4.54 (1 H, d, *J* 7.3, H-3 and H-4), 7.14 (1 H, s, H-2), 7.2–8.1 (13 H, m, arom.); δ_C 45.1 and 50.6 (C-5 and C-6), 51.8 and 52.2 ($2CH_3O$), 113.3 (C-2), 123.9, 128.2, 128.4, 128.5, 128.6, 128.7(2), 128.9(2), 130.1, 130.6, 130.7, 132.0, (13 C, arom.), 140.4 (C-2′), 127.8, 128.4, 130.9, 132.2, 135.9, 137.6, (5 C, arom., C-2′), 153.9 (C-1), 161.1 (C=O, lactone), 167.6 and 170.9 (2COO). *Trans*-**5** (20%), mp 168–170 °C (from ethanol). Methyl 2-(methoxycarbonylphenyl)-5-phenylpenta-2,4-dienoate **6** (10%), mp 194–196 °C; *m/z* 322 [M^+, $C_{20}H_{18}O_4$ (322.4)]; ν_{max}/cm^{-1} 1620, 1720; δ_H 3.72 and 3.81 (each 3 H, s, $2CH_3OOC$), 6.58 (1 H, dd, *J* 15.5, 11.4, H-4), 7.49 (1 H, dd, *J* 15.5, H-5), 7.62 (1 H, dd, *J* 11.4, 0.5, H-3), 7.1–7.5 (8 H, m, arom.), 8.10 (1 H, m, H-3′).

Reaction of Homophthalic Anhydride **1** *with* N-(*Cinnamylidene*)-*benzylamine* **2b**.—To a solution of **1** (2 mmol) in THF (10 ml) at 60 °C under argon atmosphere, a solution of imine **2b**[5] (2 mmol; bp 142–143 °C at 0.5 mmHg) in THF (10 ml) was added during 10 min. The mixture was heated for 15 min, left at room temp. for 16 h and then treated with diazomethane and purified by CC. Methyl *cis*-2-benzyl-1-oxo-3-(3-phenylethenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate *cis*-**7** (40%), oil; *m/z* 397 [m^+, $C_{26}H_{23}NO_3$ (397.4)]; ν_{max}/cm^{-1} 1640, 1730; δ_H 3.70 (3 H, s, $COOCH_3$), 4.06 (1 H, d, *J* 15.1) and 5.56 (1 H, d, *J* 15.0, NCH_2), 4.34 (1 H, d, *J* 5.4, H-4), 4.42 (1 H, d, *J* 5.5, 8.5, H-3), 6.09 (1 H, dd, *J* 15.7, 8.5, H-9), 6.41 (1 H, d, *J* 15.7, H-10), 7.2–7.5 (13 H, m, arom.), 8.23 (1 H, m, H-8). Methyl *trans*-2-benzyl-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate *trans*-**8** (6%), mp 125–126 °C (from methanol); *m/z* 371 (M^+); IR and ^1H NMR spectra were in agreement with lit.[6] 4-cinnamylidene-2-benzopyran-1,3(4*H*)-dione **9** (14%), mp 222–224 °C (from chloroform) (lit.,[1] 220–221 °C). Product **9** was also isolated from the organic layer after extraction with 10% aq. Na_2CO_3 of the reaction mixture of another batch. Also isolated was N-*benzyl*-[2-(*methoxycarbonyl*)*phenyl*]*acetamide* **10** (14%), mp 115–118 °C (from ethanol); *m/z* 283 (M^+); ν_{max}/cm^{-1} 1640, 1705; δ_H 3.85 (3 H, s, $COOCH_3$), 3.92 (2 H, s, CH_2CO) 4.40 (2 H, d, *J* 5.8, CH_2N), 6.82 (1 H, br. s, NH), 7.2–7.5 (8 H, m, arom.), 7.95 (1 H, d, *J* 8.0, H-6) [Found: C, 72.22; H, 5.93. $C_{17}H_{17}NO_3$ (283.3) requires C, 72.06; H, 6.05%].

The ratio of *cis*-**7** to *trans*-**8** was estimated by ^1H NMR integration of the signals for $COOCH_3$.

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