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A Multicomponent One-Pot Reaction Integrating a Bis-functional Carbohydrate Derivative

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Abstract: The one-pot reaction of enantiopure nitroenone 2 with an aniline and benzaldehyde resulted in ring anellation forming two new carbon-carbon bonds and gave access to pharmacologically interesting dihydropyridine derivatives and further to the analogous quinolines.

Keywords: Carbohydrates; Condensations, Combinatorial Chemistry; Quinolines.

Combinatorial Chemistry has become an important tool in drug research, not only for the tuning of existing, but also for the discovery of new lead structures. For the required construction of compound libraries[1] the generation of structural diversity is a particular challenge.

So far, carbohydrates have found relatively little attention in combinatorial chemistry. One application was the generation of libraries based on oligosaccharides[2] or structurally related mimetics such as the amide-linked saccharides (saccharide-peptide hybrids).[3] Furthermore, carbohydrates have been employed as templates[4] that are, due to their high degree of functionalization, suitable for combinatorial approaches.[5] In the resulting compounds the typical carbohydrate epitopes are, however, concealed. In some cases, advantage was taken of carbohydrates as chiral auxiliaries.[6] Other authors have used only one functionality of carbohydrate derivatives to include them in small molecule libraries,[7] also with the help of multicomponent reactions.[8]

Multicomponent reactions[9] allow for an efficient construction of compound libraries, if a high number of compounds representing the components are readily available. Frequently, isonitriles[10] have been employed in this context. We present here a novel multicomponent reaction based on a bis-functional carbohydrate building block in conjunction with an aniline and an aldehyde.

Swern oxidation of nitro sugar **1**[11] yielded the alkoxy-nitroenone **2**[12] with electronic properties interesting for further reactions. First experiments demonstrated that amines react rapidly to afford ketene-N,O-acetals such as **3** cleanly and in good yields. With longer reaction times and especially with electron rich anilines, azo derivatives of type **4** were obtained, presumably by electrophilic attack of an intermediate

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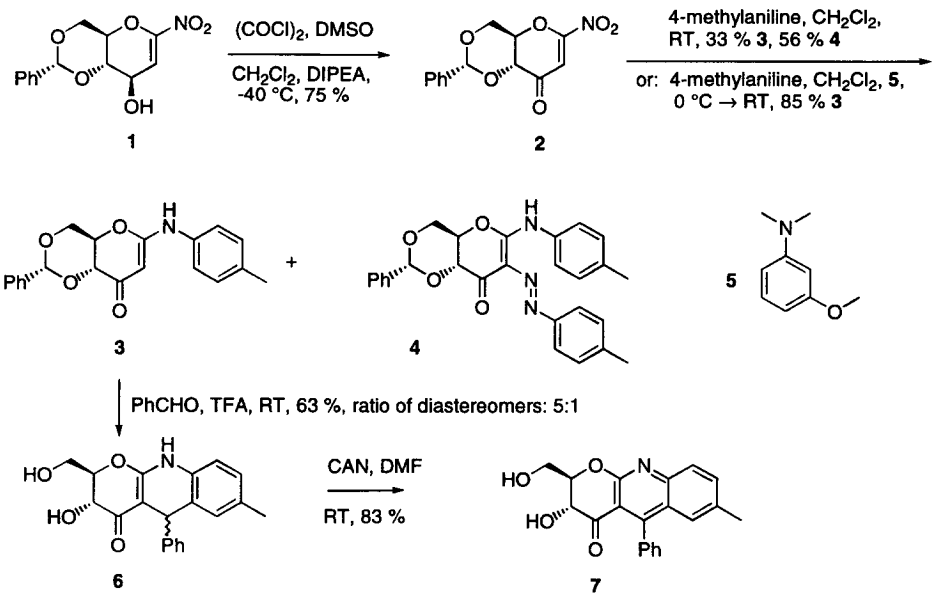
diazonium salt resulting from nitrosation of the aniline by in situ generated nitrosonium derivatives. To avoid these by-products and to be more flexible in the possible range of reaction time and temperature, the diazonium derivatives were trapped with 3-dimethylaminoanisole, which indeed suppressed the formation of alkenyl-azo derivatives (cf. Scheme 1).



Scheme 1

The ketene-N,O-acetals of type **3** reacted with aldehydes in the presence of trifluoroacetic acid forming two new C,C-bonds and leading to sugar-anellated dihydroquinolines of type **6**. Under the reaction conditions used, the benzylidene protective group was cleanly removed. In most cases, a mixture of diastereomers resulted which were not separated. Unsubstituted aniline yielded in more than 90 % one diastereomer, its 5[*S*] configuration was established by X-ray crystallography.[13] According to a comparison of the ^{1}H NMR spectra the 5[*S*] isomers were always prevailing. Oxidation of **6** with ceric ammonium nitrate furnished a single quinoline derivative in good yield demonstrating that the diastereomers **6** were epimeric at the newly formed asymmetric center.

The transformation of **2** to the dihydroquinoline **6** could be accomplished in a one-pot reaction.[14] The reaction was carried out under conditions allowing automated parallel synthesis followed by automated HPLC purification. In the one-pot reaction the yields were lower than in the sequential reaction with intermediate purification. Interestingly, the stereoselectivities improved, however, and in many cases only one diastereomer could be detected (Table 1).

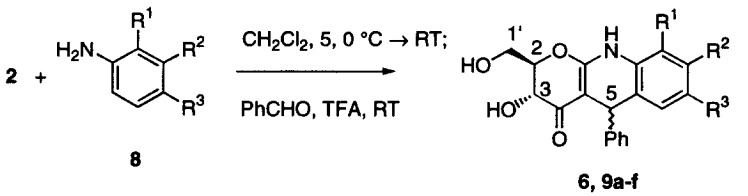


Table 1. One-pot reaction of alkoxy-nitroenone **2** with different anilines.

Product	R^1	R^2	R^3	Solvent	Diastereomer ratio 5[*S*]/5[*R*]	Yield [%]
9a	H	OMe	H	CH_2Cl_2	5[*S*] only	52
9b	H	OPh	H	CH_2Cl_2	5[*S*] only	36
9c	H	OH	H	CH_3CN	5[*S*] only	55
9d	H	OMe	OMe	CH_2Cl_2	5[*S*] only	55
9e	H	phenylene		CH_2Cl_2	3 : 2	40
9f	phenylene		H	CH_2Cl_2	4 : 1	40
6	H	H	Me	CH_2Cl_2	16 :1	14

This novel multicomponent reaction provides an efficient access to a high number of hydroxylated derivatives of the pharmacologically interesting dihydropyridines[15] and quinolines.

Acknowledgement

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12. The structure of **2** has been established by X-ray analysis; results have been deposited at the Cambridge Crystallographic Data Centre (deposition number CCDC 11892112).
13. Deposition number: CCDC 125068.
14. **Typical procedure**: To a solution of **2** (150 mg, 0.541 mmol) in CH_2Cl_2 (1.5 ml) was added **5** (79 µl, 0.54 mmol) followed by 3,4-dimethoxyaniline (166 mg, 1.08 mmol) under argon and at 0 °C. After stirring for 1 h the ice bath was removed, and the dark red suspension was kept at room temperature for 1 h. Then benzaldehyde (55 µl, 0.54 mmol) and trifluoroacetic acid (1.5 ml) were added. After 5 h the dark violet solution was concentrated to a syrup, treated with pyridine (0.5 ml) under argon, and concentrated again. Flash chromatography (toluene: EtOH = 12:1, 50 g, then 12 g SiO_2) gave **9d** (115 mg, 55 %) as a solid: $[\alpha]_D^{20}$ = + 279.0 (*c* = 0.3144 in DMSO); ^{1}H-NMR (250 MHz, [D$_6$]DMSO, 25°C, TMS): δ = 10.20 (s, 1 H; NH), 7.24 - 7.16 (m, 4 H; Ph-H), 7.08 (m$_c$, 1 H; Ph-H), 6.79, 6.61 (2 s, 2 H; MeOPh-H), 5.19 (d, ^3J(O-H,3-H) = 4.3Hz, 1 H; OH), 5.04 (s, 1 H; PhCH), 4.96 (dd, ^3J(O-H,1'a-H) = 4.3Hz, ^3J(O-H,1b'-H) = 6.0Hz, 1 H; OH), 4.09 (ddd, ^3J(2-H,3-H) = 12.1Hz, ^3J(2-H,1'b-H) = 3.5Hz, ^3J(2-H,1'a-H) = 1.5Hz, 1 H; 2-H), 3.99 (dd, ^3J(3-H,O-H) = 4.3Hz, ^3J(3-H,2-H) = 12.1Hz, 1 H; 3-H), 3.87 (ddd, ^3J(1'a-H,1'b-H) = 12Hz, ^3J(1'a-H,2-H) = 1.5Hz, ^3J(1'a-H,O-H) = 4.3Hz, 1 H; 1'a-H), 3.76 (ddd, 1 H; 1'b-H), 3.69 (s, 3 H; OCH_3), 3.63 (s, 3 H; OCH_3); MS(ISP): *m/z*(%): 406(13) [MNa^+], 384(100) [MH^+]; HR-MS(pos. ESI): *m/z* : calc. for $C_{21}H_{22}O_6N$ [MH^+]: 384.1447, found: 384.1445.
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