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SHORT STEP SYNTHESES OF INDOLO[2,3-*a*]CARBAZOLES CARRYING AN ALKYL, ALLYL, OR A GLYCOSYL GROUP AT THE 11-POSITION AND A NOVEL 6,7-DIHYDRO-13*H*-CYCLOPENTANO[*mn*]INDOLO[3,2-*c*]-ACRIDINE DERIVATIVE [1]

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Abstract — Novel 1-alkyl-, 1-allyl-, and 1-β-glycosyl-2,2'-biindolyls are prepared. Their Diels-Alder reaction produced 11-alkyl-, 11-allyl-, and 11-β-glycosylindolo[2,3-*a*]carbazoles. Formation of a novel 6,7-dihydro-13*H*-cyclopentano[*mn*]indolo[3,2-*c*]acridine derivative is also reported.

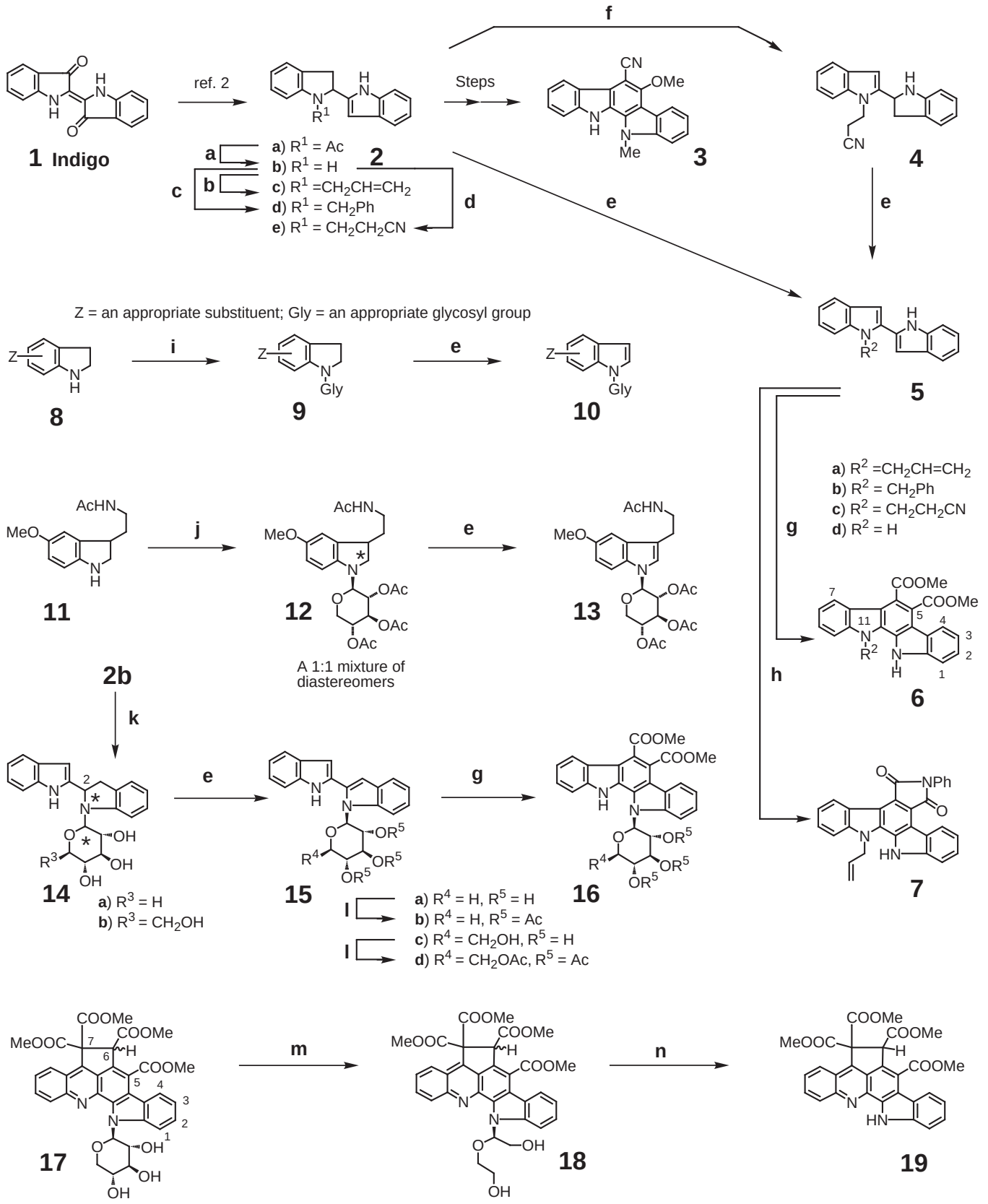
In our ongoing project to develop biologically active compounds, we have created a novel reaction for reducing indigo (**1**) to 1-acetyl-2,3-dihydro-2,2'-biindolyl[2] (**2a**) in 82% yield and demonstrated its versatility as a building block for producing 6-cyano-5-methoxy-12-methylindolo[2,3-*a*]carbazole derivatives[3] (**3**) through 2,3-dihydro-2,2'-biindolyl[4] (**2b**) (Scheme 1). In this communication, we wish to report a short step Diels–Alder approach[5] to indolo[2,3-*a*]carbazoles carrying an alkyl, allyl or a glycosyl group at the 11-position utilizing **2b** as a synthetic intermediate. A novel formation of **17** upon treatment of the adducts, obtained by the reaction of 1-(β-D-xylopyranosyl)-2,2'-biindolyl (**15a**) with dimethyl acetylenedicarboxylate, with refluxing nitrobenzene is described as well.

N-Allylation of **2b** with allyl bromide in the presence of K_2CO_3 afforded **2c** in 90% yield. Subsequent DDQ oxidation in dioxane at room temperature provided 1-allyl-2,2'-biindolyl (**5a**) in 81% yield. Diels-Alder reaction of **5a** either with dimethyl acetylenedicarboxylate or *N*-phenylmaleimide in refluxing nitrobenzene produced **6a** and **7** in 46 and 52% yields, respectively.

The reaction of **2b** with benzyl bromide and K_2CO_3 proceeded in a quantitative yield to give **2d**. After converting **2d** to **5b** in 77% yield by DDQ oxidation, its Diels–Alder reaction with dimethyl acetylenedicarboxylate provided 64% yield of **6b**. Michael addition of **2b** to acrylonitrile gave a complex mixture of products. For this reason, the desired **2e** was obtained at best in only 19% yield under the examined conditions (NaH, KO*t*Bu, or K_2CO_3 in DMF). An alternative trial using 3-bromopropionitrile in the presence of K_2CO_3 provided 56% yield of **4** as major product together with 4% yield of **2e**. DDQ oxidation of **2e** and **4** produced the same product (**5c**) in 69 and 63% yields, respectively. Subsequent Diels–Alder reaction of **5c** with dimethyl acetylenedicarboxylate provided 45% yield of **6c**.

The yields of **6** and **7** are greatly improved comparing with those (below 30% yield) obtained upon reactions of *N*-unsubstituted 2,2'-biindolyl (**5d**).[5a] These results suggest that an introduction of an appropriate substitutient onto the nitrogen atom of 2,2'-biindolyl is a good choice for improving the yield.

Scheme 1



a) NaOMe, MeOH, reflux; **b**) CH_2=$CHCH_2Br$, K_2CO_3, DMF, rt; **c**) $PhCH_2Br$, K_2CO_3, DMF, rt; **d**) CH_2=CHCN, NaH, DMF, 0°C; **e**) DDQ; **f**) $BrCH_2CH_2CN$, DMF, K_2CO_3, 98°C; **g**) dimethyl acetylenedicarboxylate, nitrobenzene, reflux; **h**) *N*-phenylmaleimide, nitrobenzene, reflux; **i**) an appropriate sugar; **j**) i) D-xylose, MeOH, reflux; ii) Ac_2O, pyridine, rt; **k**) D-xylose or D-glucose, MeOH, reflux; **l**) Ac_2O, pyridine, rt; **m**) i) $NaIO_4$, MeOH, H_2O, rt; ii) $NaBH_4$, MeOH, rt; **n**) 0.5N HCl, MeOH, reflux.

We next turned our attention to 11-β-glycosylindolo[2,3-*a*]carbazoles. So, we needed *N*-glycosylated indoles. Preobrazhenskaya and co-workers[6] had reported a suitable glycosylation method to produce **10** without using any protecting group, consisting of heating indolines (**8**) with an appropriate sugar component, followed by DDQ oxidation of the resulting **9**. Combination of their method with the above Diels-Alder approach seemed to be promising to meet our end. We therefore first examined glycosylation method for the synthesis of 1-(β-D-xylopyranosyl)melatonin (**13**). Simple treatment of 2,3-dihydromelatonin[7] (**11**) with D-xylose (3 mol eq) in refluxing MeOH, followed by acetylation with Ac_2O-pyridine, afforded a 1:1 mixture of diastereomers (**12**) in 85% yield. The mixture was oxidized to **13** in 56% yield with DDQ in dioxane at room temperature.

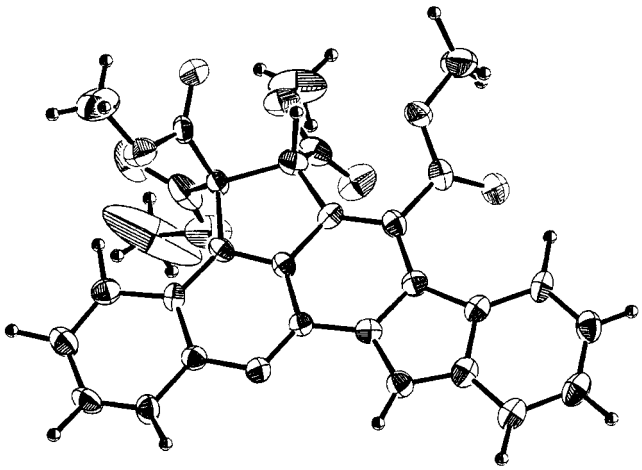
With this successful results, we allowed **2b** to react with D-xylose and D-glucose in refluxing MeOH. The reactions proceeded successfully resulting in the formations of the desired glycosylated products (**14a**) and (**14b**) in 98 and 86% yields, respectively. Although both **14a** and **14b** were inseparable mixtures of diastereoisomers, their oxidation with DDQ in dioxane at room temperature provided **15a** and **15c** as a single stereoisomer in 77 and 69% yields, respectively. These results clearly show that each of **14a** and **14b** is a mixture of stereoisomers at the 2-position. To determine the stereochemistry at the anomeric carbon, **15a** and **15c** were treated with Ac_2O-pyridine to give **15b** and **15d** in 93 and 82% yields, respectively. In the ^{1}H-NMR spectra of these compounds, anomeric protons are readily discernible and their couplimg constants with the adjacent proton are found to be 10 Hz each, proving the presence of β-substituent. ^{1}H-NMR spectrum of **15c** exhibited that it exists as a 1:1 mixture of rotamers.[8]

Diels-Alder reaction of **15a** with dimethyl acetylenedicarboxylate in refluxing nitrobenzene was successful to provide the desired **16a** in 29% yield. Under similar reaction conditions, **15b** and **15c** produced **16b** and **16c** in 33 and 24% yields, respectively.

Introduction of a substituent into the nitrogen atom of 2,2'-biindolyl has improved the solubility to various solvents, even to Et_2O. This enabled us to apply Grieco's[9] 5M $LiClO_4$ conditions to the reaction of **15a** with dimethyl acetylenedicarboxylate. As a result, **16a** was obtained in 30% yield together with nonpolar and polar adducts, each of them being a complex mixture of diastereomeric isomers. Heating of the former adducts in nitrobenzene at reflux for 1 h afforded **16a** in 35% yield. On the other hand, similar reaction of the latter adducts generated two novel products (**17a**) and (**17b**) in 8 and 8% yields, respectively.

Figure 1

ORTEP DRAWING OF **19** (R =0.087)



Treatment of **17a** with methanolic HCl afforded a 1:1 mixture of **17a** and **17b**, proving that these compounds are stereoisomers at the stereogenic center (C-6) of the aglycon, which racemized easily. To

determine the structure of **17a**, deglycosylation was attempted with acids *in vain*. Therefore, **17a** was allowed to react with $NaIO_4$, followed by treatment with $NaBH_4$, to result in **18** as a single product in 83% yield. Acid hydrolysis of **18** proceeded easily to produce beautifully crystallized product (**19**) in 69% yield. The results of its X-Ray single crystallographic analysis are shown in Figure 1, which clearly shows that it has an unexpected 6,7-dihydro-13*H*-cyclopentano[*mn*]indolo[3,2-*c*]acridine skeleton. Studies are in progress on the mechanism of its formation and configurations at the C-6 positions of **17a** and **17b**.

In conclusion, we have succeeded in developing a simple synthetic methodology for producing various indolo[2,3-*a*]carbazoles from indigo. A synthetic route to a novel type of compounds having 6,7-dihydro-13*H*-cyclopentano[*mn*]indolo[3,2-*c*]acridine skeleton is discovered as well.

REFERENCES AND NOTES

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