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Synthesis of a 1,3,4,5-tetrahydrobenzindole β-ketoester

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ABSTRACT

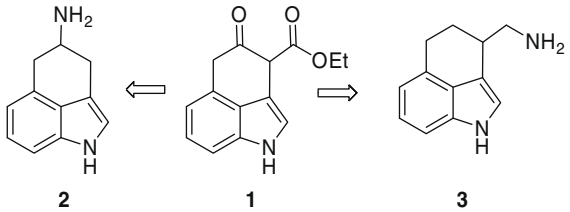
$Pd(OAc)_2$-catalyzed decomposition of ethyl 2-diazo-4-(4-indolyl)-3-oxobutanoate leads to a tricyclic tetrahydrobenzindole compound formed by a formal C–H insertion reaction. This tricyclic indole rearranges to a novel and thermodynamically more stable naphthalene derivative. Treatment of *N*-tosyl-protected ethyl 2-diazo-4-(4-indolyl)-3-oxobutanoate with a base induces facile pyrazole formation.

As part of an ongoing medicinal chemistry project, we became interested in the synthesis of a tricyclic 3,4-substituted indole-building block **1** (Scheme 1) that would allow rapid access to compounds with general structures **2** and **3** from a common intermediate.

Compound **1** has been reported in the literature during a study of an intramolecular C–H insertion reaction of ethyl 2-diazo-4-(4-indolyl)-3-oxobutanoate **18** at the 3-position of the indole core.[1] We started our synthesis toward key intermediate **18** (Scheme 2) with precedence based on literature procedures,[1–3] and we report here our findings from this study.

Benzoyl protection of 4-oxo-4,5,6,7-tetrahydroindole **4** under standard conditions gave Bz-protected compound **5** in 84% yield. Bromination of **5** with $CuBr_2$ gave α-bromo ketone **7** in 81% yield. The bromination reaction had to be monitored carefully to avoid double bromination to the α,α-dibromo ketone. The dibrominated ketone was isolated exclusively if excess copper(II) bromide was added and the reaction time was extended. We decided to remove the Bz-protecting group at this stage to avoid undesired selectivity problems during deprotection later in the synthetic sequence. The benzoyl group was removed with HCl in methanol to give **9** in 90% yield. Introduction of the diazo β-keto ester side chain was achieved by an aldol reaction between **9** and ethyl 2-diazo-acetoacetate.[4] We were unable to isolate alcohols **10** since they underwent spontaneous dehydration to **14** during the aldol reaction. The isolated yield of **14** was very dependent on the reaction temperature and equivalents of diazo ester used. The reaction had to be kept at −20 °C. At room temperature, only a complex product mixture was observed. The isolated yields increased from 15% with 1 equiv to 73% when 5 equiv of the diazoester were used. Compound **14** was, unfortunately, rather unstable and decomposed at room temperature. Due to its instability, it was necessary to expose compound **14** immediately to LiBr in DMF to promote the aromatization reaction to **18**. Diazo compound **18** was found to be stable to the reaction conditions, but the isolated yield of **18** was only 20%. Presumably, the instability of **14** was responsible for the low yield. We screened several different procedures to improve the yield in this aromatization step, but all attempts were unsuccessful. Thus we decided to undertake further studies with the benzoyl-protected compound. When bromide **7** was used in the aldol reaction with ethyl 2-diazoacetoacetate, compound **15** was isolated in 42% yield. The diazo alcohols **11** eliminated water during the aldol reaction and could not be isolated. Diazo bromides **15** also decomposed in solution at room temperature, although to a lesser extent compared to **14**, such that compound **19** was isolated in 54% yield after aromatization. Deprotection of the benzoyl group in **19** was achieved with HCl in ethanol. This successful procedure presents a trade-off between reaction time and decomposition of the diazo compounds **18** and **19**. The diazo functionality is acid sensitive, however, selective deprotection of the Bz-group took place when **19** was treated with 15 equiv of HCl at room temperature. The reaction was very slow, and only a 45% yield of **18** was isolated after three days. Increasing the reaction temperature was incompatible with the diazo functionality, and only unidentifiable decomposition products were observed. The reaction sequence using the benzoyl-protecting group was abandoned due to the modest yields and long reaction times in the final two steps.

We therefore decided to change the initial protecting group. The *N*-tosyl-protecting group was introduced in 95% yield using standard



2 1 3

Scheme 1.

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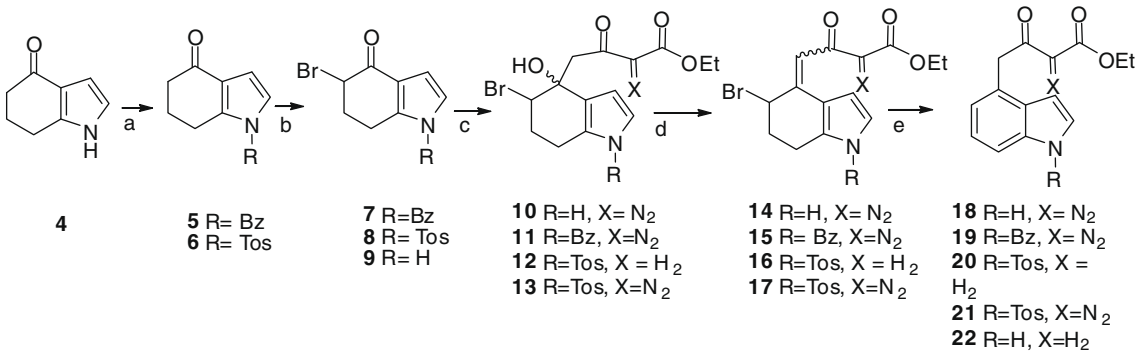


Scheme 2. Reagents and conditions: (a) **5**: BzCl, Et_3N, DMAP, 84%; **6**: NaH, TosCl, 95%; (b) **7**: $CuBr_2$, 77%; **8**: $CuBr_2$, 81%; **9** from **7**: HCl, MeOH, 90%; (c) **10**: ethyl 2-diazoacetoacetate, Et_3N, $TiCl_4$, Ti(O*i*-Pr)$_4$, −20 °C, 73%; **11**: ethyl acetoacetate, NaH, *n*-BuLi, Ti(O*i*-Pr)$_4$, −78 °C, 81%; **12**: ethyl 2-diazoacetoacetate, Et_3N, $TiCl_4$, Ti(O*i*-Pr)$_4$, −20 °C; (d) **14**: cat. TsOH; and (e) LiBr, DMF, 85 °C.

conditions. Exposing *N*-tosyl-protected ketone **6** to the bromination conditions with $CuBr_2$ gave bromo ketone **8** in 81% yield. An aldol reaction between bromo ketone **8** and ethyl 2-diazo-acetoacetate gave alcohols **13**. Once again, the isolated yield of products from the aldol reaction was very dependent on the reaction temperature and equivalents of diazo ester used. At room temperature, only a complex product mixture was obtained. The isolated yields of alcohols **13** increased from 24% with 1 equiv to 58% when 5 equiv of the diazoester was used. We only detected one of the two possible diastereomers of alcohol **13** each time the reaction took place. However, which specific diastereomer that formed seemed to change with reaction conditions, and we were unable to control this transformation. The modest 58% isolated yield of the aldol reaction products turned out to be due to a partial dehydration of diazo alcohols **13** under the reaction conditions to give compounds **17**. The rate of dehydration was much slower compared to alcohols **10** and **11**, such that alcohols **13** could be isolated after silica gel flash chromatography. The overall combined yield for the two transformations was 91%. The *E* and *Z* isomeric alkenes **17** could be isolated and characterized. Both diastereomers of alcohols **13** gave only one isomer of **17** when the dehydration took place during the aldol reaction. However, if either of the diastereomers of alcohols **13** was isolated, they both eliminated water slowly to give what appeared to be the thermodynamically more stable isomer of **17**. The diastereomer formed under the reaction conditions was the least thermodynamically stable of the two isomers as it slowly rearranged to the other isomer upon standing. It was difficult to assign the structure of the two isomers of **17** based on NMR data, thus we performed quantum theory calculations on the two isomers (Fig. 1). The isomer labeled B with *Z*-geometry was predicted to be the thermodynamically more stable isomer by 2.7 kcal/mol. The reaction of **17** with LiBr-promoted aromatization to give diazo compound **21** in 64% yield, independent of the alkene stereochemistry in compound **17**. We attempted an intramolecular C–H insertion reaction on compound **21** to obtain the tosyl-protected analogue of the tricyclic building block **1**. Unfortunately, all attempts failed to give the ring closure at the indole 3-position in compound **21**. It became apparent that it was necessary to remove the tosyl-protecting group before the critical ring closure step, and we therefore focused on procedures for detosylation reactions. Treating compound **21** with a base did not yield the desired diazo compound **18**, but induced facile pyrazole formation. Pyrazole **23** was formed as the major product in all our deprotection experiments independent of the base and reaction temperature. Compound **23** was obtained almost quantitatively within five minutes even when **21** was exposed to a mild base such as TBAF. Formation of pyrazoles is a well known transformation from vinyl diazoacetates,[5] but has not been reported to be a major pathway with keto diazo esters.[6] A plausible reaction mechanism is outlined in Scheme 3.

Abstraction of an α-hydrogen in compound **21** produced an enolate which underwent an intramolecular 1,3-dipolar cycloaddition reaction.[5,7] The resulting five-membered ring rearranged through a 1,3-hydrogen shift led to the completion of the pyrazole ring and the formation of **23**. Detosylation of **21** using reducing reagents was also attempted, but the diazo functionality was incompatible with the reaction conditions and gave compound **20** as the major product. The instability of the diazo functionality in some of the intermediates, and the extremely facile base-induced pyrazole formation forced us to go back and introduce the diazo functional group as late as possible in the synthetic sequence.

The ethyl acetoacetate side chain was introduced using dianion chemistry.[3] The dianion of ethyl acetoacetate was added to a −78 °C solution of bromide **8** and Ti(O*i*-Pr)$_4$ in THF. The reaction was rather sluggish and it was necessary to use 5 equiv of the dianion to achieve an 81% yield of **12**. It was found crucial to keep the reaction temperature low. A complex product mixture was obtained when the reaction was performed at 0 °C. Elimination of water from compound **12** was achieved in high yield with a catalytic amount of *p*-TsOH. The elimination products **16** were obtained as an inseparable mixture of *E* and *Z* isomers. The stereochemistry, however, was lost in the next step with LiBr-promoted aromatization of **16** to

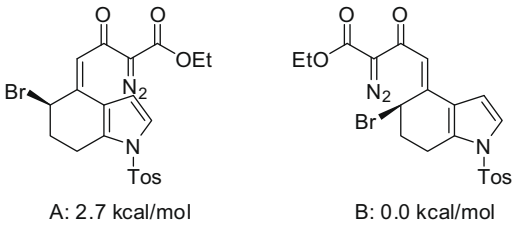
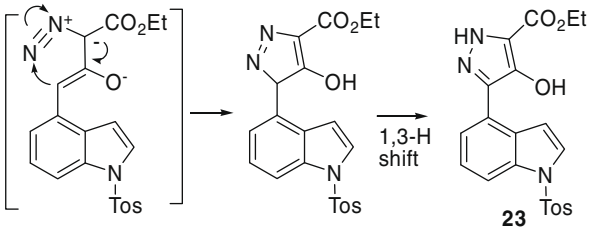
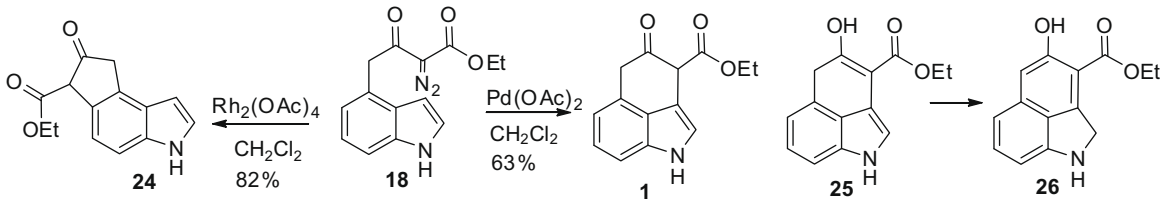


Figure 1. Calculated energies for the *E* and *Z* isomers of **17**.



Scheme 3.



Scheme 4.

produce compound **20** in 80% yield. Deprotection of the tosyl group in **20** was attempted with several different reagents, but the best yield (72%) was obtained with Mg in EtOH. The diazo functionality was installed into compound **22** in 83% yield using a diazo transfer reaction, employing triethylamine and *p*-ABSA.[4]

When diazo compound **18** was exposed to catalytic amounts of $Rh_2(OAc)_4$, formation of the tricyclic indole derivative **24** in 82% yield was observed (Scheme 4). $Rh_2(OAc)_4$ is a kinetically very active catalyst and it has been reported to favor formation of five-membered rings.[8] $Pd(OAc)_2$-catalysis changed the regioselectivity of the C–H insertion reaction where C–H insertion into the indole 3-position took place exclusively. These findings are consistent with literature reports,[1] except that we found dichloromethane to be a better solvent for the Pd-catalyzed reaction. When methanol was used as a solvent, the chemoselectivity was reduced and a competitive O–H insertion reaction into the solvent took place. The tricyclic indole-building block **1** was isolated in 63% yield. Compound **1** was isolated in its enol tautomeric form **25** as judged by ^{1}H NMR analysis. However, **25** rearranged to the thermodynamically more stable naphthalene derivative **26** upon standing for a few hours. The kinetics of this rearrangement could be increased by an addition of a catalytic amount of *p*-TsOH. Quantum theory calculations predict compound **26** to be 15 kcal/mol more thermo-dynamically stable compared to compound **25**, thereby explaining the driving force for this rearrangement. We performed quantum theory calculations to predict the ^{1}H NMR spectra of compounds **25** and **26**. Comparison of the predicted ^{1}H NMR spectra with the experimentally observed ^{1}H NMR data supports our structural assignments (see Supplementary data). Compound **26** and its rearrangement from **25** have not been previously reported, but our findings are consistent with other reports on similar tricyclic indole derivatives.[9]

In summary, we have uncovered a novel rearrangement of a tetrahydroindole core structure to a thermodynamically more stable naphthalene derivative. The experimental observations and structural assignments are supported by quantum chemical calculations. The *N*-tosyl-protected key intermediate indole diazoester in the synthesis toward the tetrahydroindole core was extremely prone to base-catalyzed 1,3-dipolar cycloaddition, giving a novel pyrazole structure.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.032.

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