ORGANIC LETTERS

2003
Vol. 5, No. 11
1999−2001

The First Method for Protection–Deprotection of the Indole 2,3-π Bond

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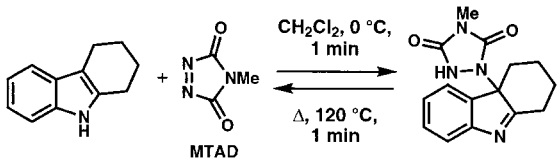
Received April 11, 2003

ABSTRACT



The scope and generality of a new reaction of indoles with MTAD is discussed. In most cases the ene-type reaction proceeds within seconds or minutes at 0 °C to provide the urazole adducts in high yield. This reaction provides the first method for protecting the indole 2,3-double bond since the urazole adducts can be reconverted to the starting indole (retro-ene) simply by heating.

We recently reported a new reaction of indoles with 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) and the application of this method to the first enantioselective synthesis of okaramine N (**2**, Figure 1).[1] Since triazolinediones react similarly to singlet oxygen in ene reactions,[2] we expected that MTAD would react rapidly with an indole. In addition, it appeared reasonable that the resulting *tert*-urazole adducts could be transformed into the starting indole by retro-ene reaction; such a reaction is not possible with the singlet oxygen adduct. This novel strategy was successfully employed to protect the more electron rich indole subunit of **1** from the ensuing further reaction with $^1O_2$. It was expected that the urazole−okaramine conjugate could be converted by thermal retro-ene reaction to okaramine N (**2**). These reactions, in fact, proceeded very well.

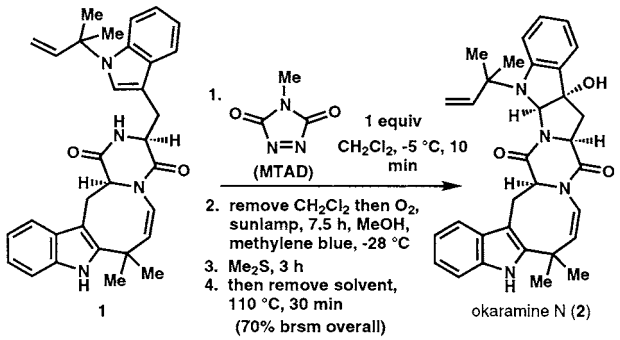


Figure 1. Use of MTAD in the final step of the total synthesis of okaramine N (**2**).

Triazolinediones were first reported in an ene-type reaction by Pirkle and Stickler in 1967. Since then, these species have rarely been employed in synthesis. Recently Adam and coworkers have investigated diastereoselective ene reactions of olefins with MTAD for the synthesis of allylic amines.[3] Experiments with indoles were reported not to yield simple ene adducts.[4]

The efficiency with which MTAD derived urazole−indole adducts can be created and then dismantled by the retro-ene reaction for dihydroindoloazocine systems such as okaramine

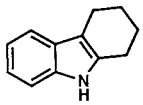
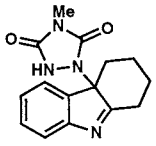
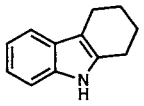
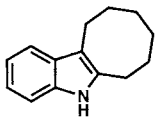
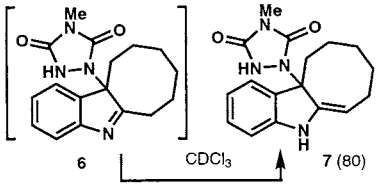
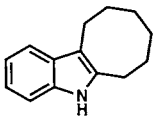
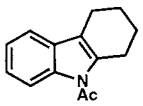
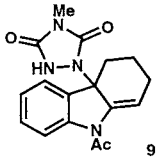
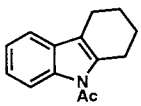
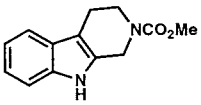
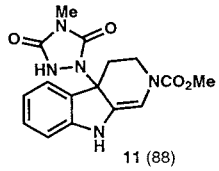
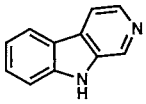
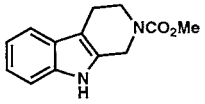
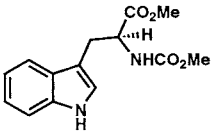
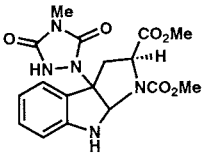
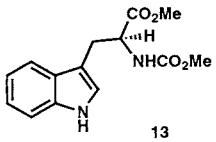
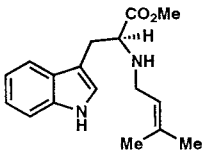
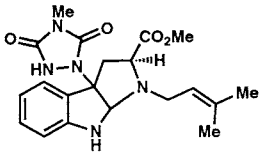
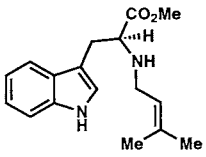
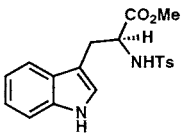
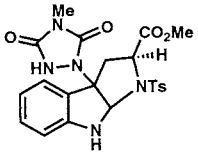
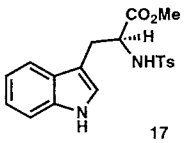
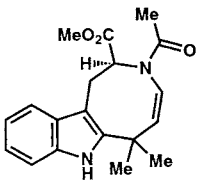
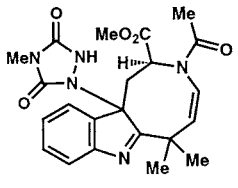
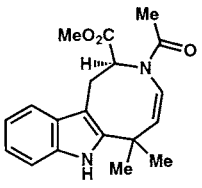
(1) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* Released on the Web April 18, 2003.

(2) (a) Leach, A. G.; Houk, K. N. *Chem. Commun.* **2002**, 1243−1255. (b) Vassilikogiannakis, G.; Elemes, Y.; Orfanopoulos, M. *J. Am. Chem. Soc.* **2000**, *122*, 9540−9541.

(3) (a) Adam, W.; Pastor, A.; Wirth, T. *Org. Lett.* **2000**, *2*, 1295−1297. (b) Adam, W.; Wirth, T.; Pastor, A.; Peters, K. *Eur. J. Org. Chem.* **1998**, *501*, 1−506. (c) Vassilikogiannakis, G.; Stratakis, M.; Orfanopoulos, M. *J. Org. Chem.* **1999**, *64*, 4130−4139.

10.1021/ol034634x CCC: $25.00
Published on Web 05/01/2003

Table 1. Ene Reaction of Indoles with MIAD and Retro-ene Deprotection

substrate	ene product (yield %)	retro-ene product (temp, yield %)
 **3**	 **4** (quant)	 **3** (120 °C, quant)
 **5**	 **6** $\xrightarrow{CDCl_3}$ **7** (80)	 **5** (280 °C, 85)
 **8**	 **9** (84)	 **8** (250 °C, 90)
 **10**	 **11** (88)	 **12** (250 °C, *ca.* 90)  **10** (cat. $MeSO_3H$, 25 °C, 8 h, 68)
 **13**	 **14** (62, 1:1 mixture of diastereomers)	 **13** (280 °C, 90)
 **15**	 **16** (80, 1:1 mixture of diastereomers)	 **15** (250 °C, 65)
 **17**	 **18** (58, 2:1 mixture of diastereomers)	 **17** (240 °C, 74)
 **19**	 **20** (quant)	 **19** (150 °C, quant)

led us to explore the generality and scope of this method with other indoles.

As shown in Table 1, a variety of indoles were found to be amenable to the MTAD protection−deprotection method.[5] The addition of MTAD (1.0−1.2 equiv) takes place at −5 to 0 °C in CH_2Cl_2 and is readily monitored by TLC. The course of the reaction can also be followed visually since the pink color of the MTAD reagent fades as it is consumed. In the case of indole **3** the reaction was instantaneous, while **10** and **13** required 10−30 min in CH_2Cl_2, but reacted

instantly in methanol. The reaction of MTAD with *N*-acetyl indole **8** required 4 h for completion in CH_2Cl_2, but occurred within 10 min in MeOH and 1 min in CF_3CH_2OH. $BF_3 \cdot Et_2O$ accelerated the reaction of MTAD and **8**, but a different ene product resulted from attachment of MTAD to C(2). These results provide clear evidence of protic or Lewis acid catalysis of these ene reactions. Indole **5** reacted rapidly with MTAD to give imine **6**, which isomerized upon standing in $CDCl_3$ to eneamine **7**. Indole **15** reacted with MTAD selectively at the indole site rather than the nearby enophilic double bond. The structure of **4** was confirmed via X-ray crystallography, as depicted in Figure 2.

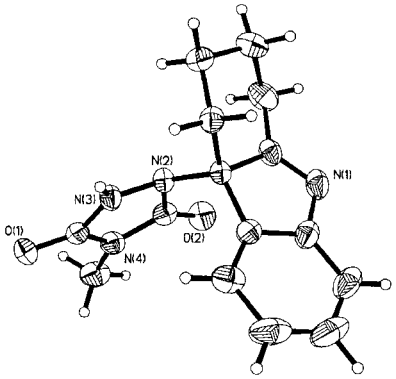


Figure 2. ORTEP representation of the crystalline adduct **4**.

In the cases where the MTAD ene-reaction led to a final imine product (e.g. **1**, **3**, and **19**), the thermal retro-ene process was generally facile at 110−150 °C. Eneamine-type adducts (**7**, **9**, and **11**) and urazole-substituted pyrroloindolines (**14**, **16**, and **18**) were less reactive and required higher temperatures (250−280 °C, in vacuo), but the retro-ene process proceeded smoothly with short contact times in a heated tube flow reactor. Thus, a flask was charged with urazole−indole adduct and connected to a long Pyrex tube (55 × 1 cm, 14/20 joints, which was enclosed in the furnace (20 cm) and connected to an evacuated receiver). Condensation of the pure parent indoles occurred rapidly on the surface of the tube outside of the hot zone in 65−95% yield. With the exception of urazole adduct **11**, this thermolysis procedure simply and routinely furnished the starting parent indoles. It appears that the tertiary carbamate subunit of **11** was eliminated leading to pyrido-indole **12** after the retro-ene reaction and subsequent aromatization. However, eneamine **11** could be converted to the starting indole **10** upon exposure to acid (0.21 equiv of $MeSO_3H$, CH_2Cl_2, 0−23 °C, 30 h, 68% brsm). The high temperatures necessary to excise the urazole residue from **14**, **16**, and **18** are likely a consequence of the difficult ring-chain tautomerization preceding the retro-ene. A variety of acidic, basic, and reducing conditions failed to convert these tryptophan-derived urazole adducts to the parent indoles.

Acceleration of the ene reaction by polar, protic media (e.g. MeOH) indicates that the addition of MTAD to indoles may proceed through a zwitterionic intermediate as depicted in Figure 3. In most cases, if an excess amount of MTAD is added, electrophilic aromatic substitution takes place on the indole aromatic ring. Even carbazole reacts with MTAD slowly to afford a mixture of MTAD adducts. More than one equivalent (1.2) of MTAD is sometimes necessary due to this competing reaction, which accounts for the less than quantitative yield of urazole adduct in most cases.

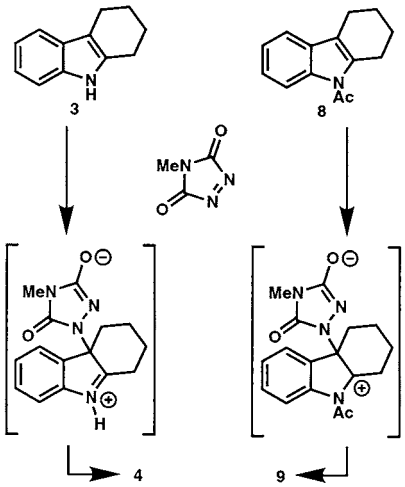


Figure 3. Formation of urazole−indole adducts might proceed via a two-step mechanism.

Differences in reactivity of different indole subunits toward MTAD, as described above, are greater in CH_2Cl_2 than in MeOH. This difference in reactivity was useful since it permitted selective reaction to the *N*-unsubstituted indole in **1** with CH_2Cl_2 as solvent, a key step in the synthesis of okaramine N.[1]

In conclusion, the first general method for protection of the 2,3-π double bond of indoles has been developed. The method is chemoselective for indoles in the presence of double bonds. Electron-rich indoles react faster than electron-deficient ones. The process of protection and deprotection is both rapid and operationally simple.

Acknowledgment. We are grateful to the NIH for a Postdoctoral Fellowship to P.S.B., to the Undergraduate Harvard College Research Program for a summer fellowship to C.A.G, and to Drs. Richard Staples and D.-H. Ryu for expert assistance.

Supporting Information Available: Detailed experimental procedures for all compounds and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034634X

(4) Hall, J. H.; Kaler, L.; Herring, R. *J. Org. Chem.* **1984**, *49*, 2579−2582.

(5) MTAD is commercially available from Aldrich, Inc.