Pergamon

Tetrahedron Letters 42 (2001) 3271–3273

TETRAHEDRON LETTERS

Phenyliodine(III) bis(trifluoroacetate)-mediated oxidation of bisindolylmaleimides to indolo[2,3-*a*]carbazoles

Margaret M. Faul* and Kevin A. Sullivan

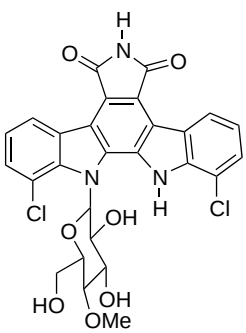
Lilly Research Laboratories, A Division of Eli Lilly and Company, Chemical Process Research and Development Division, Indianapolis, IN 46285, USA

Received 26 February 2001; accepted 8 March 2001

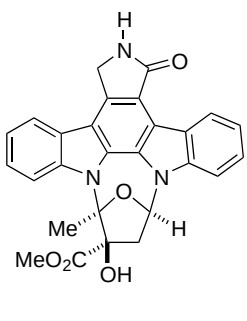
Abstract—A novel protocol for the oxidation of bisindolylmaleimides to the corresponding indolo[2,3-*a*]carbazoles in 15–56% yield with phenyliodine(III) bis(trifluoroacetate) (PIFA) is reported.

Naturally occurring indolo[2,3-*a*]carbazoles, represented by Staurosporine, Rebeccamycin and K252a, possess potent antitumor and protein kinase C inhibitory properties.[1] Their novel structures and significant biological activities have prompted many synthetic efforts towards these natural products and their structural analogs.[2] Even with the apparent simplicity of the indolo[2,3-*a*]carbazole aglycone, numerous diverse approaches to this ring system have been devised.[3] The most direct approach involves oxidation of the corresponding bisindolylmaleimide and numerous methods to perform this reaction have been reported (*hv* with or without I_2 or Pd/C,[4] DDQ with or without *p*-TsOH,[5] $Pd(OAc)_2$,[6] $PdCl_2$, $Pd(O_2CCF_3)_2$,[7] and $CuCl_2$). However these methods are not general and present a number of limitations; (a) reactions with hv/I_2 requires high dilution and long reaction times; (b) reactions with DDQ/*p*-TsOH present problems with removal of DDQ by-products; (c) reactions with Pd are stoichiometric and expensive, and removal of Pd from the insoluble indolo[2,3-*a*]carbazoles present numerous challenges. To address these issues an alternative method for oxidation of bisindolylmaleimides to indolo[2,3-*a*]carbazoles would be desirable.

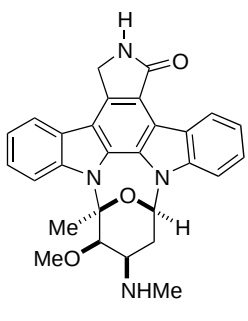
Recently, there has been considerable interest in the use of hypervalent iodine compounds, particularly phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA) as electrophilic oxidants since their reactivities are similar to those of heavy metal reagents, they have low toxicity, are readily available and easy to handle.[8] Domínguez has reported that PIFA is as a novel oxidant in the synthesis of phenanthro[9,10-*d*] fused isoxazoles and pyrimidines.[9] Encouraged by these results we decided to explore the use of PIFA for oxidation of bisindolylmaleimides to indolo[2,3-*a*]carbazoles.



Rebeccamycin



K252a

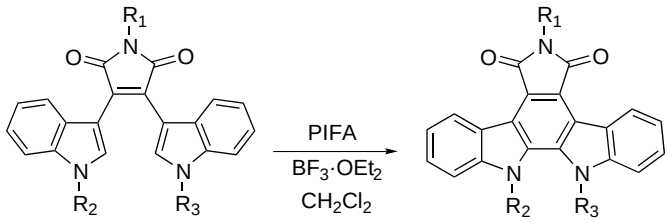


Stauropsporine

* Corresponding author.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00453-1

Table 1. PIFA-mediated formation of indolo[2,3-*a*]carbazoles



1a-e **2a-e** (1)

Entry	Compound	R_1	R_2	R_3	Yield[a] (%)
1	**a**	H	CH_3	H	56
2	**b**	H	CH_3	CH_3	30
3	**c**	H	$(CH_2)_3OBn$	H	37
4	**d**	H	$(CH_2)_3OBn$	CH_3	30
5	**e**	CH_3	H	H	15
6	**f**	H	H	H	0

[a] Yield of analytically pure product.

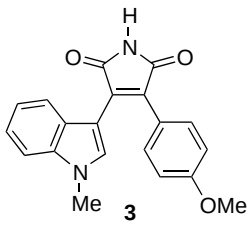
Table 2. Solvent effects on PIFA oxidation of **1c** to **2c**

Entry	Solvent	Yield (%)
1	ACN	20
2	CF_3CH_2OH	Decomp.
3	DMF	Decomp.
4	Et_2O	50
5	Toluene	40
6	THF	Decomp.

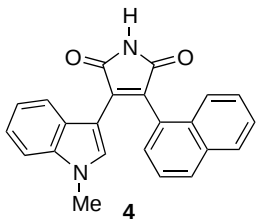
A variety of bisindolylmaleimides were examined (Eq. (1), Table 1).[10] Oxidation of bisindolylmaleimide **1a** has been reported in 70% yield using $Pd(OAc)_2$/HOAc at 110°C.[6] Using PIFA (1.3 equiv.) in CH_2Cl_2 with $BF_3{\cdot}OEt_2$ (1.3 equiv), indolo[2,3-*a*]carbazole **2a** was obtained in 56% yield (entry 1).[11] In contrast to the $Pd(OAc)_2$ conditions, oxidation with PIFA was complete in <1 h at 0°C.[12] Oxidation of **1a** using PIDA afforded <10% **1b**, demonstrating PIFA was the superior oxidant. Oxidation of dimethylsubstituted bisindolylmaleimide **1b**, under the same reaction conditions, gave a 30% yield of **2b** (entry 2).[13] Oxidation of benzyl-protected ethers **1c** and **1d**, afforded **2c** and **2d** in 37% and 30% yield, respectively. PIFA oxidation of the *N*-methyl maleimide **1e** afforded **2e** in only 15% yield (entry 5), while oxidation of **1f**, which would provide direct access to the Staurosporine aglycone **2f**, was unsuccessful (entry 6).

Since reactions of PIFA are favored in poorly nucleophilic polar protic solvents such as CF_3CH_2OH, the effect of solvent on the oxidation of **1c** to **2c** was examined (Table 2). Interestingly Et_2O was found to be the optimal solvent affording a 50% yield of **2c**, while CF_3CH_2OH gave no product. In addition, it appears that it is more favorable to run the reaction as a slurry in toluene, CH_2Cl_2 or Et_2O, since reactions in DMF and THF that solubilize **1c** gave extensive decomposition of starting material. $BF_3{\cdot}OEt_2$ proved to be the optimal Lewis acid for the reaction. Other acids (CSA, HBF_4, TFA) failed to afford any **2c** under identical reaction conditions.

PIFA oxidation of bisindolylmaleimides was unsuccessful when mono-substituted indoles (6-Cl, 6-F) were employed. In addition, maleimides such as **3** and **4** failed to undergo oxidation to the carbazole when treated with PIFA.



3



4

In conclusion, PIFA has been identified as a novel oxidant for conversion of bisindolylmaleimides to the indolo[2,3-*a*]carbazoles. This method should provide an additional approach to access this important class of biologically active compounds.

Acknowledgements

The authors would like to thank Professors Bill Roush and Marvin Miller for helpful discussions during the course of this work.

References

1. (a) Omura, S.; Sasaki, Y.; Iwai, Y.; Takeshima, H. *J. Antibiot*. **1995**, *48*, 535; (b) Gribble, G.; Berthel, S. J. *Stud. Nat. Prod. Chem*. **1993**, *12*, 365.
2. For leading references, see: (a) Bergman, J. *Stud. Nat. Prod. Chem*., *Part A* **1988**, *1*, 3; (b) Link, T.; Raghavan,

S.; Gallant, M.; Danishefsky, S. J.; Chou, T. C.; Ballas, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 2825; (c) Wood, J. L.; Stoltz, B. M.; Goodman, S. N. *J. Am. Chem. Soc.* **1996**, *118*, 10656; (d) Glibert, E. J.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1996**, *188*, 5500.

3. (a) Bergman, J. *Stud. Nat. Prod., Chem. Part A* **1988**, *1*, 3; (b) Gribble, G. W.; Berhtel, S. J. *Stud. Nat. Prod. Chem., Part H* **1993**, *12*, 365.
4. (a) Gallant, M.; Link, J. T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 343; (b) Gallant, M.; Link, J. T.; Danishefsky, S. J. *Tetrahedron. Lett.* **1985**, *26*, 4015; (c) Link, J. T.; Gallant, M.; Danishefsky, S. J.; Huber, S. *J. Am. Chem. Soc.* **1993**, *115*, 3782; (d) Link, J. T.; Gallant, M.; Danishefsky, S. J.; Huber, S. *Tetrahedron. Lett.* **1994**, *35*, 5555.
5. (a) Joyce, R. P.; Gainor, J. A.; Weinreb, S. M. *J. Org. Chem.* **1987**, *52*, 1177; (b) Kleinschroth, J.; Hartenstein, J.; Rudolph, C.; Schaechtele, C. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 55; (c) Ohkubo, M.; Nishimura, T.; Jona, H.; Honma, T.; Morishoma, H. *Tetrahedron.* **1996**, *52*, 8099.
6. Harris, W.; Hill, C. H.; Keech, E.; Malsher, P. *Tetrahedron. Lett.* **1993**, *34*, 8361.
7. Ohkubo, M.; Kawamoto, H.; Ohno, T.; Nakano, M.; Morishima, H. *Tetrahedron* **1997**, *53*, 585.
8. (a) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proc. Int.* **1997**, *29*, 409; (b) Kita, Y.; Arisawa, M.; Gyoten, M.; Nakajima, M.; Hamada, R.; Tohma, H.; Takada, T. *J. Org. Chem.* **1998**, *63*, 6625; (c) Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5857; (d) Kita, Y.; Takada, T.; Ibaraki, M.; Gyoten, M.; Mihara, S.; Fujita, S.; Tohma, H. *J. Org. Chem.* **1996**, *61*, 223.
9. Olivera, R.; SanMartin, R.; Pascual, S.; Herrero, M.; Domínguez, E. *Tetrahedron Lett.* **1999**, *40*, 3479.
10. Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1998**, *63*, 6053.
11. *Typical procedure*: PIFA (740 mg, 1.72 mmol, 1.3 equiv.) was added to a slurry of bisindolylmaleimide **1a** (450 mg, 1.32 mmol) in dry dichloromethane (25 mL) at –40°C under nitrogen. After adding boron trifluoride diethyl etherate (218 μL, 1.72 mmol, 1.3 equiv.) the resulting brown solution was allowed to warm to 0°C. The reaction was quenched with water (5 mL) at 0°C then allowed to warm to room temperature. The solid was isolated by filtration and dried to afford 457 mg crude **2b**. Purification was achieved using silica gel chromatography (1:2 THF:toluene) followed by a reslurry in Et_2O to give 234 mg (56%) **2b** as a yellow solid.
12. No impurities were observed in the reaction mixture and it is assumed that the remaining material was lost to competing dimerization/polymerization pathways
13. Harris (Ref. 6) has reported that oxidation of **1b** using $Pd(OAc)_2$ is unsuccessful. However, we have been able to oxidize **1b** to **2b** in 86% yield using 1.5 equiv. $Pd(OAc)_2$/HOAc at reflux.