ORGANIC LETTERS

2006
Vol. 8, No. 21
4975−4977

A Practical Method for the Synthesis of Indolylaryl- and Bisindolylmaleimides

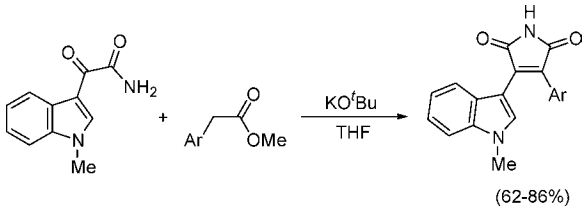
Sudipta Roy, Sujata Roy, and Gordon W. Gribble*

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

ggribble@dartmouth.edu

Received August 28, 2006

ABSTRACT



Indolylaryl and indolylheteroarylmaleimides, including bisindolylmaleimides, are easily prepared by the reaction of *N*-methylindole-3-glyoxylamide with methyl aryl acetates in the presence of potassium *tert*-butoxide in THF.

Indolylarylmaleimides have valuable pharmacological properties.[1,2] For example, indolylarylmaleimide derivatives, particularly bisindolylmaleimides, are reported to be useful in the control and prevention of cancer, central nervous system disorders, Alzheimer's disease, cardiovascular diseases (thromboses, arteriosclerosis, hypertension), dermatological diseases (allergies), inflammation, autoimmune diseases (rheumatoid arthritis), diabetic complications, and viral diseases. Furthermore, bisindolylmaleimide derivatives, such as Ruboxistaurin (LY333531) mesylate (Arxxant), Enzastaurin (LY317615), and Ro 31-7453, are in clinical trials.[3]

Many derivatives of indolylmaleimide have been synthesized and biologically evaluated.[4] The natural bisindolylmaleimide arcyriarubin A is a potent inhibitor of protein kinase C (IC_{50} = 87 nm). Bisindolylmaleimides are also useful intermediates in the synthesis of indolocarbazole alkaloids including arcyriaflavins, staurosporine, rebeccamycin, and other indolocarbazoles that have important biological activities such as anticancer and antiviral activity.[5−7] Indolylmaleimides are also potent plant growth regulators.[8] Recently, bisindolylmaleimides have found potential application as light-emitting diodes.[9] They have also been used

(1) Gribble, G. W.; Berthel, S. J. *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1993; Vol. 12, pp 365−409.

(2) Davis, P. D.; Hill, C. H.; Keech, E.; Lawton, G.; Nixon, J. S.; Sedgwick, A. D.; Wadsworth, J.; Westmacott, D.; Wilkinson, S. E. *FEBS Lett.* **1989**, *259*, 61−63.

(3) Davis, P. D.; Hill, C. H.; Lawton, G. Eur. Patent Appl., 1989, EP 328026. Dannhardt, G.; Peifer, C.; Plutizki, S.; Kramb, J. P. PCT Int. Appl., 2006, WO 2006061212. Van Eis, M.; Von Matt, P.; Wagner, J.; Evenou, J.-P.; Schuler, W. PCT Int. Appl., 2005, WO 2005068455. Asakai, R.; Sodeoka, M.; Katoh, M.; Fujita, M. PCT Int. Appl., 2000, WO 2000047575. Barth, H.; Hartenstein, J.; Rudolph, C.; Schaechtele, C.; Betche, H. J.; Osswald, H.; Reck, R. Eur. Patent Appl., 1990, EP 397060. Dhingra, U. H.; Huryn, D. M.; Keith, D. D. PCT Int. Appl., 1998, WO 9804551. Aiello, L. P.; Jirousek, M. R.; King, G. L.; Vignati, L.; Ways, D. K. PCT Int. Appl., 1997, WO 9740831.

(4) Peifer, C.; Stoiber, T.; Unger, E.; Totzke, F.; Schaechtele, C.; Marme, D.; Brenk, R.; Klebe, G.; Schollmeyer, D.; Dannhardt, G. *J. Med. Chem.* **2006**, *49*, 1271−1281. Lakatosh, S. A.; Luzikov, Y. N.; Preobrazhenskaya, M. N. *Tetrahedron* **2005**, *61*, 8241−8248. Brana, M. F.; Anorbe, L.; Tarrason, G.; Mitjans, F.; Piulats, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2701−2703. Bit, R. A.; Davis, P. D.; Elliott, L. H.; Harris, W.; Hill, C. H.; Keech, E.; Kumar, H.; Lawton, G.; Maw, A.; Nixon, J. S.; Vesey, D. R.; Wadsworth, J.; Wilkinson, S. E. *J. Med. Chem.* **1993**, *36*, 21−29. Davis, P. D.; Hill, C. H.; Lawton, G.; Nixon, J. S.; Wilkinson, S. E.; Hurst, S. A.; Keech, E.; Turner, S. E. *J. Med. Chem.* **1992**, *35*, 177−184.

(5) Knoelker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303−4427.

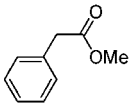
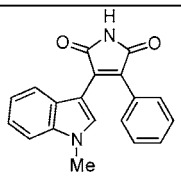
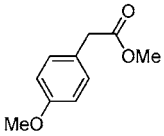
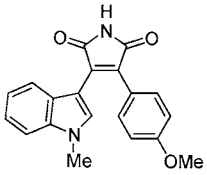
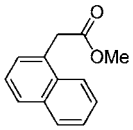
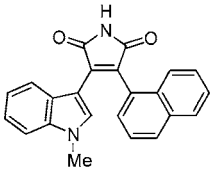
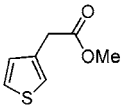
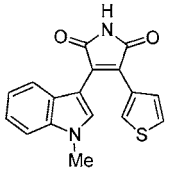
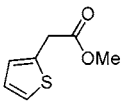
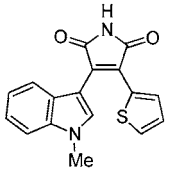
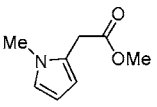
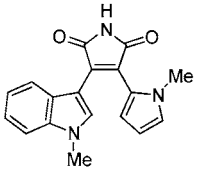
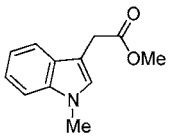
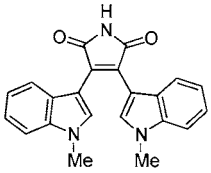
(6) Roy, S.; Eastman, A.; Gribble, G. W. *Tetrahedron* **2006**, *62*, 7838−7845. Roy, S.; Eastman, A.; Gribble, G. W. *Org. Biomol. Chem.* **2006**, *4*, 3228−3234.

(7) Slater, M. J.; Cockerill, G. S.; Littler, E. PCT Int. Appl., 1993, WO 9318765. Sanchez-Martinez, C.; Shih, C.; Zhu, G.; Li, T.; Brooks, H. B.; Patel, B. K. R.; Schultz, R. M.; DeHahn, T. B.; Spencer, C. D.; Watkins, S. A.; Ogg, C. A.; Considine, E.; Dempsey, J. A.; Zhang, F. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3841−3846. Faul, M. M.; Engler, T. A.; Sullivan, K. A.; Grutsch, J. L.; Clayton, M. T.; Martinelli, M. J.; Pawlak, J. M.; LeTourneau, M.; Coffey, D. S.; Pedersen, S. W.; Kolis, S. P.; Furness, K.; Malhotra, S.; Al-Awar, R. S.; Ray, J. E. *J. Org. Chem.* **2004**, *69*, 2967−2975.

(8) Bastiaans, H. M. M.; Donn, G.; Knittel, N.; Martelletti, A.; Rees, R.; Schwall, M.; Whitford, R. PCT Int. Appl., 2005, WO 2005107465.

10.1021/ol0621203 CCC: $33.50
Published on Web 09/21/2006

Table 1. Examples of Indolylarylmaleimide Prepared

entry	methyl arylacetate	product	yield[a] (%)
1	 **4**	 **11**	86
2	 **5**	 **12**	81
3	 **6**	 **13**	65
4	 **7**	 **14**	84
5	 **8**	 **15**	75
6	 **9**	 **16**	75
7	 **10**	 **17**	62

[a] All yields are those obtained after recrystallization.

in sensitization of nanocrystalline TiO_2 films which could be used for the development of photocatalysts immobilized on surfaces.[10] Thus, indolylarylmaleimides are undisputedly a class of biologically active heterocyclic compounds of immense importance and commercial potential.

Only a few methods are available in the literature for the synthesis of indolylmaleimides. The most general method involves the condensation of indole-3-acetamides with aryl glyoxalates or indole-3-glyoxalates with aryl acetamides.[11] Indole-3-acetamides are relatively expensive or can be prepared from pricey indole-3-acetonitriles by basic hydrolysis using hydrogen peroxide and NaOH under phase-transfer conditions.[12] Indole-3-glyoxalates can be prepared either (i) by the treatment of indoles with oxalyl chloride, followed by sodium methoxide, or (ii) by refluxing indole-3-glyoxylic acids in MeOH with a Dowex 50 × 8100 ion-exchange resin. The other method of synthesizing indolylmaleimides involves the reaction of indolyl-3-glyoxylyl chlorides with arylacetic acids and subsequent amination of the resulting maleic anhydrides to afford maleimides.[13] Although the amination reaction to convert maleic anhydrides into maleimides is usually high yielding, only modest yields (~23−43%) were obtained in the coupling reaction to prepare the required indolylaryl maleic anhydrides. Methods that are specific for the synthesis of bisindolylmaleimides are (i) the reaction of indole Grignard reagents with dihalomaleimides,[14] (ii) reaction of indolyl-3-glyoxylyl chlorides with indole-3-acetimidates,[15] and (iii) iodine-promoted oxidative coupling of the indole-3-acetic acid trianion or the methylindole-3-acetate dianion.[16] Although these procedures can be utilized to prepare bisindolylmaleimides, in most cases, the yields are low, the preparation of the starting materials is tedious, or the chromatographic purification of the products is extremely difficult due to the low solubility of maleimides in organic solvents. Thus, there is a great need for a practical and convenient preparation for a broad range of indolylarylma-

(9) Yeh, T.-S.; Chow, T. J.; Tsai, S.-H.; Chiu, C.-W.; Zhao, C.-X. *Chem. Mater.* **2006**, *18*, 832−839. Chiu, C.-W.; Chow, T. J.; Chuen, C.-H.; Lin, H.-M.; Tao, Y.-T. *Chem. Mater.* **2003**, *15*, 4527−4532.

(10) Kaletas, B. K.; Kozhevnikov, V. N.; Zimine, M.; Williams, R. M.; Koenig, B.; De Cola, L. *Eur. J. Org. Chem.* **2005**, 3443−3449. Kaletas, B. K.; Joshi, H. C.; Van der Zwan, G.; Fanti, M.; Zerbetto, F.; Goubitz, K.; De Cola, L.; Koenig, B.; Williams, R. M. *J. Phys. Chem. A* **2005**, *109*, 9443−9455.

(11) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1998**, *63*, 6053−6058. Faul, M. M.; Winneroski, L. L.; Krumrich, C. *Tetrahedron Lett.* **1999**, *40*, 1109−1112.

(12) Girgis, N. S.; Cottam, H. B.; Robins, R. K. *J. Heterocycl. Chem.* **1988**, *25*, 361−366. Faul, M. M.; Winneroski, L. L. PCT Int. Appl., 1998, WO9807693.

(13) Davis, P. D.; Bit, R. A.; Hurst, S. A. *Tetrahedron Lett.* **1990**, *31*, 2353−2356. Davis, P. D.; Bit, R. A. *Tetrahedron Lett.* **1990**, *31*, 5201−5204.

(14) Steglich, W.; Steffan, B.; Kopanski, L.; Eckhardt, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 459−460. Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 552−553.

(15) Bit, R. A.; Crackett, P. H.; Harris, W.; Hill, C. H. *Tetrahedron Lett.* **1993**, *34*, 5623−5626.

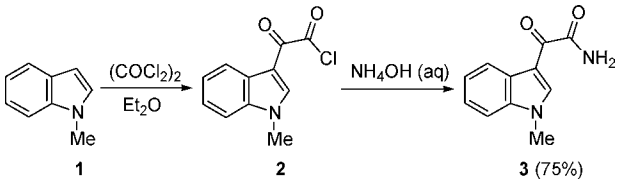
(16) Bergman, J.; Pelcman, B. *Tetrahedron Lett.* **1987**, *28*, 4441−4444.

(17) Representative experimental procedure: To a mixture of *N*-methylindole-3-glyoxylamide (0.21 g, 1 mmol) and methyl phenylacetate (0.4 mL, 2.7 mmol) in THF (8 mL) at 0 °C was slowly added potassium *tert*-butoxide (4 mL, 1 M in THF, 4 mmol). The mixture was stirred for 15 h allowing the mixture to warm slowly to room temperature. It was poured into brine−water (100 mL, 1:1) and extracted with ethyl acetate (3 × 50 mL). The organic phase was washed with brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated, and the residue was recrystallized from ethyl acetate to yield the desired product **11** (0.26 g, 86%) as an orange solid: mp 256−257 °C; IR (thin film) 1756, 1697, 1615, 1592, 1510, 1329, 1243, 743 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.08 (brs, 1H), 8.03 (s, 1H), 7.47 (d, 1H, J = 7.9 Hz), 7.38−7.39 (m, 2H), 7.30−7.35 (m, 3H), 7.11 (t, 1H, J = 7.6 Hz), 6.70 (t, 1H, J = 7.7 Hz), 6.27 (d, 1H, J = 7.9 Hz), 3.90 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 172.5, 172.3, 137.1, 134.8, 132.0, 130.6, 129.6, 128.6, 128.5, 128.1, 124.3, 122.1, 121.3, 120.0, 110.6, 103.1, 33.0; LRMS (EI) *m*/*z* 302 (M^+, 100%), 231, 149, 115; HRMS (EI) calcd for $C_{19}H_{14}N_2O_2$ 302.1055, found 302.1058.

leimides that permits simpler reaction conditions, less complicated steps, easier purification, and higher yields.

We now report a new method for the synthesis of indolylarylmaleimides by the condensation of *N*-methylindole-3-glyoxylamide with the commercially available alkyl aryl acetates. Thus, *N*-methylindole-3-glyoxylamide (**3**) was easily prepared from *N*-methylindole (**1**) by the treatment of oxalyl chloride followed by aqueous ammonium hydroxide (Scheme 1).

Scheme 1

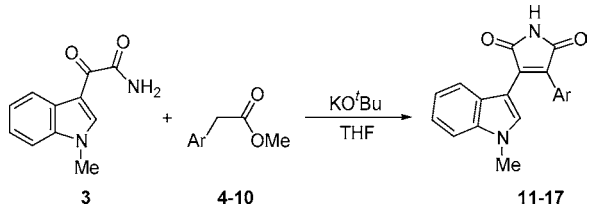


Our initial effort was focused on the synthesis of indolylphenylmaleimide (**11**). After some unrewarding experiments, it was found that the condensation of *N*-methylindole-3-glyoxylamide (**3**) with methyl phenylacetate (**4**) using potassium *tert*-butoxide in THF afforded the desired maleimide **11** in 86% yield after the recrystallization from ethyl acetate (Scheme 2).[17]

Having demonstrated the reaction to be successful for methyl phenylacetate, we evaluated the reaction of other methyl aryl acetates and heteroaryl acetates. The yields of the indolylarylmaleimides are given in Table 1.

All the reactions, except for methyl thiophene-2-acetate (**8**), were performed by addition of a 1 M solution of potassium *tert*-butoxide (4 equiv) in THF to a mixture of *N*-methylindole-3-glyoxylamide and the appropriate methyl aryl acetate (2.7 equiv) in THF at 0 °C followed by slowly

Scheme 2



warming to room temperature. For the synthesis of **15**, 3.3 equiv of methyl thiophene-2-acetate (**8**) was used. Reactions using only 1 equiv of methyl aryl acetates afforded unreacted glyoxylamide **3**, which was difficult to remove due to its high insolubility and which complicated purification.

The results obtained demonstrate that this reaction is successful with a variety of aryl and heteroaryl derivatives. However, the reaction does not work well with the N-unprotected indole-3-glyoxylamide. Work is in progress to optimize the conditions and to explore the scope of this methodology with unprotected indole-3-glyoxylamide.

In conclusion, we have developed a practical and convenient one-pot synthesis of indolylaryl and indolylheteroarylmaleimides. The starting materials are either commercially available or can be easily prepared. The desired compounds are obtained in good yields without difficult chromatographic separation.

Acknowledgment. This investigation was supported in part by the donors of the Petroleum Research Fund (PRF), administered by the American Chemical Society, and Wyeth.

Supporting Information Available: Full experimental procedures and spectral data for **11**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0621203