$NaIO_4$-Mediated Decarboxylative Oxidation of γ-Lactam Carboxylic Acids: A Simple Approach towards *N*-Aryl Maleimide Derivatives

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Received 11 September 2009

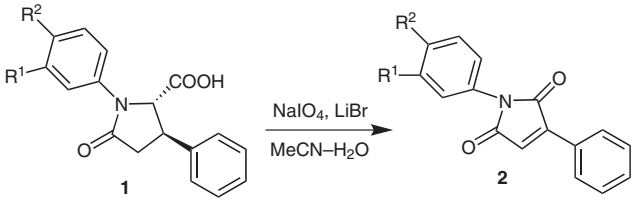
Abstract: A simple methodology has been developed for the synthesis of *N*-aryl maleimides from *N*-aryl γ-lactam-2-carboxylic acids by decaboxylative oxidation and dehydrogenation with the oxidant $NaIO_4$/LiBr in refluxing acetonitrile–water solvent.

Key words: maleimides, decarboxylation, oxidation, γ-lactam 2-carboxylic acids, bromination

Maleimides have been used to design a variety of bioactive materials. They react quickly with cysteine residues and thus can be used as linkers for conjugation of molecules with proteins.[1] They also serve as a synthetic platform in total synthesis, immuno conjugates for cancer therapy, and solid-supported enzyme for synthetic applications.[2] Fused and functionalized maleimides can be used for the synthesis of polycyclic and fused pyridazine derivatives.[3] The reactivity of maleimides is largely based on their Michael accepting ability and dienophilic nature.[4] Zacchino et al. reported that *N*-phenyl- and *N*-phenylalkylmaleimides possess strong antifungal activities when tested in agar dilution assays against a panel of 11 strains of clinically important fungi including *Candida spp*.[5] Despite this, there are few reports in the literature for the synthesis of N-substituted maleimides, the majority of methods reported being based on the reaction of the corresponding maleic anhydride with an amine or ammonium acetate.[6]

Recently, we reported that decarboxylative oxidation of g-lactam carboxylic acids by CAN/$NaBrO_3$ in acetonitrile–water provides succinimide derivatives.[7] A variety of oxidants including lead(IV), cobalt(III), silver(II), manganese(III), thallium(III),[8] and mercury(II)[9] salts, Tungstate (Na_2WO_4/H_2O_2),[10] chromic acid, nonmetallic oxidants, such as nitrosonium or nitronium salts[11] and pyridine *N*-oxide,[12] have also been reported for the decarboxylation of carboxylic acids. Herein, we wish to report a simple methodology for the preparation of *N*-aryl maleimide derivatives from *N*-aryl γ-lactam carboxylic acids by using a transition-metal-free oxidant.

Sudalai et al. have reported that $NaIO_4$/LiBr in the presence of acid oxidizes alkylarenes and benzylic bromides or alcohols to carbonyl derivatives.[13] They have also reported that the same reagent system can also be used for C–H activation at benzylic positions.[14] When we treated the γ-lactam-carboxylic acids[15] (**1a**–**f**) with $NaIO_4$/LiBr in acetonitrile–water (8:2; v/v) at 90 °C they furnished exclusively the 1,3-diaryl maleimide derivatives (**2a**–**f**) in high yields (Scheme 1, Table 1).



Scheme 1

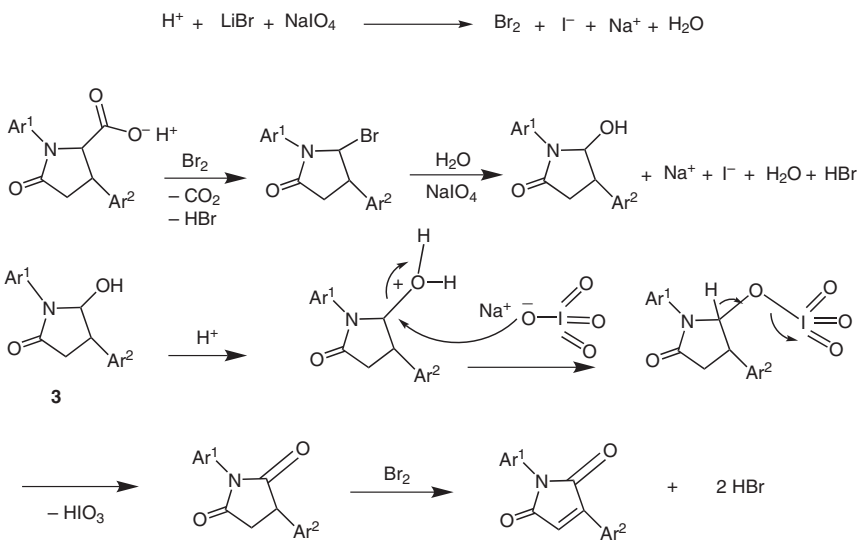
Table 1 Synthesis of *N*-Aryl Maleimides **2** from γ-Lactam-2-carboxylic Acids **1**[a]

Entry	Substrate *N*-aryl-γ-lactam-2- carboxylic acid	Product *N*-aryl-maleimides	Yield (%)
1a	R^1 = H, R^2 = Cl	**2a**	87
1b	R^1 = H, R^2 = F	**2b**	76
1c	R^1 = H, R^2 = Br	**2c**	70
1d	R^1 = R^2 = F	**2d**	81
1e	R^1 = Cl, R^2 = F	**2e**	76
1f	R^1 = H, R^2 = OMe	**2f**	52

[a] Reagents and conditions: All the reactions were carried out with catalytic amount of $NaIO_4$, and 3.5 equiv of LiBr in MeCN–H_2O (8:2) at 90 °C for 5–8 h.

In order to gain insight into the mechanism, the reaction was carried out (1) in the absence of $NaIO_4$ in acetonitrile–water, (2) in the absence of LiBr in acetonitrile–water, and (3) with $NaIO_4$/LiBr in anhydrous acetonitrile. In all cases we observed that no reaction occurred. From these observations and following the concept of decarboxylative oxidation[7] and side-chain bromination in the presence of an oxidizing agent as reported[13,14,16] a plausible mechanism for the above reaction is depicted in Scheme 2. We believe that $NaIO_4$ oxidizes LiBr in the presence of acid to liberate molecular bromine that decarboxylates the acid group and brominates the lactam ring. After aqueous solvolysis in the acidic medium at elevated temperature (90 °C) the alcohols produced would be con-

SYNLETT 2009, No. 20, pp 3333–3335
Advanced online publication: 18.11.2009
DOI: 10.1055/s-0029-1218379; Art ID: D25509ST

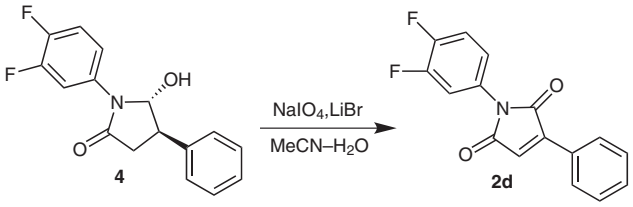


Scheme 2

verted into the maleimide derivatives by reaction with $NaIO_4$/LiBr.

In the above mechanistic path we see that by decarboxylative hydroxylation the γ-lactam carboxylic acids **1** were converted to the 5-hydroxy γ-lactam derivatives **3**, which were then converted into the maleimides **2**.

To prove the generality of the mechanism we performed the reaction on *trans*-5-hydroxy-1,4-diaryl γ-lactam derivative **4** (Scheme 3) and, under the same conditions, we obtained the maleimide derivative, supporting our proposed mechanism as depicted in Scheme 2.



Scheme 3

In conclusion, we have disclosed that $NaIO_4$/LiBr can be used for decarboxylative oxidation of γ-lactam carboxylic acids. This procedure demonstrates that *N*-aryl-maleimide derivatives can be synthesized from γ-lactam carboxylic acids in good yield.

General Procedure

To a flask containing the γ-lactam-2-carboxylic acid **1** (1 mmol) in MeCN (8 mL) and H_2O (2 mL), LiBr (3.5 mmol), and $NaIO_4$ (25 mol%) were added and reaction mixture was heated to 90 °C. The reaction mixture was then refluxed for 6–8 h until completion of reaction (monitored by TLC) and then cooled to r.t. (25–30 °C). The mixture was extracted with CH_2Cl_2, the combined organic layers were washed with a dilute solution of $Na_2S_2O_3$, 5% $NaHCO_3$, and brine then dried over anhyd Na_2SO_4. After filtration, the solution was concentrated under reduced pressure to give the crude product, which was purified by column chromatography [PE (60–80 °C)–EtOAc] to afford the pure product.

1-(4-Chlorophenyl)-3-phenyl-pyrrole-2,5-dione (2a)

Deep brown solid; mp 123–126 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.75 (s, 1 H), 7.34–7.76 (m, 7 H), 7.95–7.98 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 123.95, 127.59 (2 C), 128.35, 129.02 (2 C), 129.14 (2 C), 129.22 (2 C), 129.99, 131.46, 133.47, 143.83, 168.76, 169.07. ESI-HRMS: *m/z* calcd for $C_{16}H_{10}NO_2Cl$ [M + H$^+$]: 284.0490; found: 284.0488.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

Financial support from DST and CSIR (New Delhi) is gratefully acknowledged.

References

(1) Walker, M. A. *J. Org. Chem.* **1986**, *60*, 5352.
(2) (a) Janda, K. D.; Ashley, J. A.; Jones, T. M.; McLeod, D. A.; Schloeder, D. M.; Weinhouse, M. I. *J. Am. Chem. Soc.* **1990**, *112*, 8886. (b) Rusiecki, V. K.; Warne, S. A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 707.
(3) Shigemitsu, Y.; Komiya, K.; Mizuyama, N.; Tominaga, Y. *Dyes Pigm.* **2007**, *72*, 271.
(4) Alizadeh, A.; Movahedi, F.; Esmaili, A. A. *Tetrahedron Lett.* **2006**, *47*, 4469.
(5) Sortino, M.; Filho, V. C.; Corrêa, R.; Zacchino, S. *Bioorg. Med. Chem.* **2008**, *16*, 560.
(6) (a) Metha, N. B.; Phillips, A. P.; Lui, L. F.; Brooks, R. E. *J. Org. Chem.* **1960**, *25*, 1012. (b) Rich, D. H.; Gesellechen, P. D.; Tong, A.; Cheung, A.; Buckner, C. K. *J. Med. Chem.* **1975**, *18*, 1004. (c) Gill, G. B.; James, G. D.; Oates, K. V.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2567. (d) Meyers, A. I.; Lefiar, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243. (e) Miller, S. A.; Chamberlin, A. R. *J. Org. Chem.* **1989**, *54*, 2502. (f) Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy, V. O. *J. Org. Chem.* **1991**, *56*, 5893.

(7) Barman, G.; Roy, M.; Ray, J. K. *Tetrahedron Lett.* **2008**, *49*, 405.
(8) Trahanovsky, W. S.; Cramer, J.; Brixius, D. W. *J. Am. Chem. Soc.* **1974**, *96*, 1077.
(9) Sayre, L. M.; Jensen, F. R. *J. Org. Chem.* **1978**, *43*, 25.
(10) Murahashi, S. I.; Imada, Y.; Ohtake, H. *J. Org. Chem.* **1994**, *59*, 6170.
(11) Doyle, M. P.; Whitefleet, J. L.; DeBruyn, D. J.; Wierenga, W. *J. Am. Chem. Soc.* **1977**, *99*, 494.
(12) Cohen, T.; Song, H.; Fager, J. H. *Tetrahedron Lett.* **1965**, *4*, 237.
(13) Shaikh, T. M. A.; Emmanuvel, L.; Sudalai, A. *J. Org. Chem.* **2006**, *71*, 5043.
(14) Shaikh, T. M.; Sudalai, A. *Tetrahedron Lett.* **2005**, *46*, 5587.
(15) Haldar, P.; Barman, G.; Ray, J. K. *Tetrahedron* **2007**, *63*, 3049.
(16) (a) Barton, D. H. R.; Lachera, B.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 4321. (b) Telvekar, V. N.; Chettiar, S. N. *Tetrahedron Lett.* **2007**, *48*, 4529.