Pergamon

Tetrahedron Letters 40 (1999) 2087–2090

TETRAHEDRON LETTERS

A Facile Scheme for Phthalimide ⇄ Phthalimidine Conversion

Frederick A. Luzzio* and DeAnna Piatt Zacherl[1]

Department of Chemistry, University of Louisville
Louisville, Kentucky 40292

William D. Figg

Medicine Branch, National Cancer Institute
Bethesda, Maryland 20892

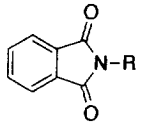
Received 18 December 1998; accepted 8 January 1999

Abstract: Desulfurization of phenylthiolactams using an ultrasound-promoted Raney nickel protocol yields the corresponding *N*-substituted phthalimidines. Benzylic oxidation of the *N*-substituted phthalimidines by treatment with 2, 2'-bipyridinium chlorochromate/*m*-chloroperbenzoic acid (BPCC/MCPBA) affords the original phthalimides. The reduction-desulfurization is applied to the preparation of a deoxythalidomide derivative which is a TNF-α inhibitor.

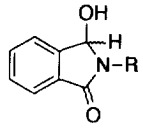
Keywords : oxidation; protecting groups; reduction; sonochemistry.

Phthalimides have served as starting materials and intermediates for the syntheses of many types of alkaloids[2] and pharmacophores.[3] The phthalimide group has also provided the classical means for direct introduction of the masked amino function as well as for *N*-protection of amino acids, amino sugars and simple amino alcohols.[4] This Letter details a straightforward reduction/oxidation sequence which provides facile access to the *N*-substituted phthalimidine (2-alkyl-2,3-dihydroisoindol-1-one) substructure from the corresponding phthalimides. By facilitating the "interconversion" of the phthalimide group to the less reactive phthalimidine core, utilization of the overall process will also augment the serviceability of the phthalimide moiety when used as a protecting agent.

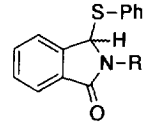
The easily-prepared *N*-substituted phthalimides **1-6** were selectively reduced (Al/Hg/THF/H_2O/rt) to the corresponding hydroxylactams **7-12** using an earlier-described protocol.[5] The *N*-substituted hydroxylactams **7-12** were then directly converted to the corresponding 3-(phenylthio)-2-alkyl-2,3-dihydroisoindol-1-ones **13-18** by means of thiophenol/*p*-toluenesulfonic acid (CH_2Cl_2/rt). Desulfurization of the benzylic phenylthio derivatives **13-18** to the corresponding phthalimidines **19-24** was accomplished by taking advantage of previously-reported heterogeneous sonochemical conditions utilizing commercially-available Raney nickel aqueous suspension with ethanol.[6] During an earlier study we recognized the utility of the 2, 2'-bipyridinium chlorochromate/*m*-chloroperbenzoic acid (BPCC/MCPBA)[7] reagent system as an oxidation system for converting benzylidene acetal groups to hydroxybenzoyl esters and therefore elected to test the response of phthalimidines **19-24**



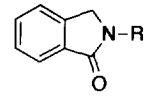
1-6



7-12



13-18

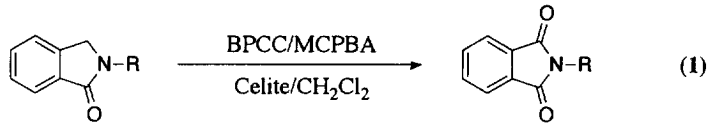


19-24

*E-Mail: FALUZZ01@athena.louisville.edu

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00152-5

to this reagent system (**Eq 1**). Treatment of the *N*-substituted phthalimidines **19-24** with a mixture of 2, 2'-bipyridinium chlorochromate (2 eq.)[8] and *m*-chloroperbenzoic acid (5 eq.) in the presence of Celite using dichloromethane as the solvent afforded the starting phthalimides **1-5** in yields of 45-76%. The



19-24 **1-5** (1)

use of Celite in the oxidation mixture renders the brown reduced chromium tars as a granular suspension thereby facilitating workup and purification. The yields for the conversion of the 2-alkyl-2,3-dihydroisoindol-1-ones **19-24** to phthalimides **1-5** using the BPCC/MCPBA reagent system are listed in **Table 1**. The employment of ultrasound conditions to facilitate the Raney-nickel desulfurization[9] of compounds **13-18** was found to be the best expedient for this process when considering reaction time versus yield. The enhanced mass transfer effect promoted by cavitation-induced turbulent flow is the causative factor of rate increases for the heterogeneous desulfurization. For comparison the ultrasound-promoted conditions for the conversion of compounds **13-18** to **19-24** are listed in **Table 2** along with standard (silent) magnetically-stirred conditions. The general mechanism of the benzylic oxidation promoted by BPCC/MCPBA has been commented on previously;[7] and although many heterogeneous oxochromium(VI)-mediated reactions are enhanced by ultrasound,[10] the BPCC/MCPBA oxidation is completely retarded by sonication. Presumably, the application of high-power ultrasound decomposes the peroxide reactant at a higher rate than the rate of benzylic oxidation of the substrate.

Table 1. BPCC/MCPBA Oxidation of 2-Alkyl-2,3-Dihydroisoindol-1-ones 19-24

Substrate	R	Product	Yield(%)[a,b]
19	$-CH_2CH(CH_3)_2$	**1**	76
20	(-)-$CH(CH_3)Ph$	**2**	70
21	$-CH_2CH_2Ph$	**3**	60
22	$-CH_2Ph$	**4**	55
23	$-CH_2(CH_2)_2CH_2OBz$	**5**	46
24	$-CH_2C_6H_4$-*p*-OCH_3	-	0[c]

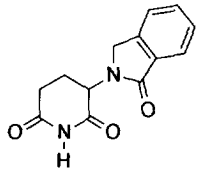
[a]Yields are for isolated purified products. [b]All compounds gave satisfactory ^1H,^{13}C NMR and/or mass spectral data. [c]The isolated product (46%) was 2-(4-methoxybenzoyl)-2,3-dihydroisoindol-1-one resulting from benzylic oxidation of the PMB group.

Table 2. Ultrasound-Promoted Raney Nickel Desulfurization of Compounds 13-18

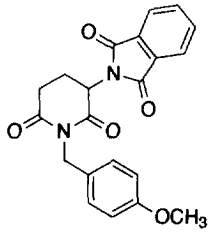
Compound	R	Product[a]/%Yield[b]Silent[c]	%Yield[b,d] Ultrasound[e]
13	$-CH_2CH(CH_3)_2$	**19**/69 (24h)	73 (10min)
14	(-)-$CH(CH_3)Ph$	**20**/85 (4.5h)	85 (10min)
15	$-CH_2CH_2Ph$	**21**/27 (28h)	72 (60min)
16	$-CH_2Ph$	**22**/40 (2.5h)	25 (10min)
17	$-CH_2(CH_2)_2CH_2OBz$	**23**/66 (24h)	37 (20min)
18	$-CH_2C_6H_4$-*p*-OCH_3	**24**/40 (26h)	50 (40min)

[a]Yields are given for isolated purified products. [b]Elapsed reaction times are given in parentheses. [c]Silent reaction refers to agitation with a standard magnetic stirrer. [d]All compounds gave satisfactory ^1H,^{13}C NMR and/or mass spectral data. [e]Generated with a Sonics and Materials VC300 titanium probe (300W/25 KHz) immersed in a jacketed water cooled (20°C) reaction vessel.

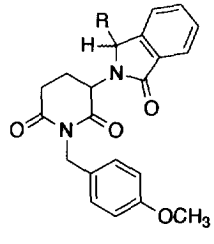
The reduction sequence was applied to the preparation of the deoxythalidomide **25**, an active compound in TNF-α (tumor necrosis factor) screenings.[11] PMB-thalidomide **26**[12] was selectively reduced with aluminum amalgam to provide hydroxylactam **27**. The employment of aluminum amalgam for the reduction of **26** to **27** was an absolute requirement due to the sensitivity of the glutarimide ring to sodium borohydride and similar reductions. Hydroxylactam **27** was directly treated with thiophenol (CH_2Cl_2/*p*-toluenesulfonic acid/rt) to afford phenylthiolactam **28** (88% from **26**) after basic workup. Without further purification phenylthiolactam **28** was directly desulfurized (Ra-Ni/EtOH/24h) to give PMB-deoxythalidomide **29** (98%).[13] PMB-deoxythalidomide **29** was treated with ceric ammonium nitrate (CH_3CN/H_2O, 3:1; rt, 3 h)[14,15] which removed the PMB group and afforded **25** (62%) after silica gel column chromatography. In conclusion, a stepwise deoxygenation sequence[16a] for *N*-substituted phthalimides has been detailed which does not require rigorous purification of intermediates.[16b] The deoxygenated phthalimidine[17] derivatives can then be reconverted to the phthalimides by BPCC/MCPBA, a reagent system which has proven effective in previous oxidations of benzylidene acetals to hydroxybenzoyl esters.



25



26



27, R=OH
28, R=SPh
29, R=H

REFERENCES AND NOTES

1. Results taken in part from the M.S. research of D.P.Z., University of Louisville.
2. See for example: Couture, A.; Deniau, E.; Grandclaudon, P.; Haorau, C. *J. Org. Chem.* **1998**, *63*, 3128-3132. Decroix, B.; Pigeon, P. *Tetrahedron Lett.* **1997**, *38*, 1041-1042. Othman, P.; Pigeon, P. Decroix, B. *Tetrahedron* **1997**, *53*, 2495-2504. Pigeon, P.; Decroix, B. *Tetrahedron Lett.* **1997**, *38*, 2985-2988. Allin, S. M.; Northfield, C.J.; Page, M.I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1997**, *38*, 3627-3630. Kundu, N.G.; Khan, M.W. *Tetrahedron Lett.* **1997**, *38*, 6937-6940. Mamouni, A.; Daich, A. Decroix, B. *Synth. Commun.* **1997**, *27*, 2241-2249. Decroix, B.; Othman, M. *Synth. Commun.* **1996**, *26*, 2803-2809. Pigeon, P.; Decroix, B. *Tetrahedron Lett.* **1996**, *37*, 7707-7710. Fang, F.G.; Feigelson, G.B.; Danishefsky, S.J. *Tetrahedron Lett.* **1989**, *30*, 2743-2746. Fang, F.G.; Danishefsky, S.J. *Tetrahedron Lett.* **1989**,*30*, 2747-2750.
3. Couture, A.; Deniau, E.; Woisel, P.; Grandclaudon, P. *Synthesis* **1997**, 1439-1445. Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **1997**, *53*, 10313-10330. Campbell, J.B.; Dedinas, R.F.; Trumbower-Walsh, S.A. *J. Org. Chem.* **1996**, *61*, 6206-6211.DeClercq, E.; *J. Med Chem.* **1995**, *38*, 2491-2517. Kato, Y.; Takemoto, M.; Achiwa, K. *Chem. Pharm. Bull.* **1993**, *41*, 2003-2006.
4. Green, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis* 2nd Ed.; John Wiley & Sons, Inc: New York, 1991, pp. 309-359. Osby, J.O.; Martin, M.G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 2093-2096. See also Debenham, J.S.; Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Am. Chem.Soc.* **1995**, *117*, 3302-3303 and references therein.
5. Luzzio, F.A.; O'Hara, L.C. *Synth. Commun.* **1990**, *20*, 3223-3234. For other methods of selective imide reductions see: Polniaszek, R.P.; Belmont, S.E. Alvarez, R. *J. Org. Chem.* **1990**, *55*, 215-213. Takacs, J. M.; Weidner, J.J. *J. Org. Chem.* **1994**, *59*, 6480-6483. Ostendorf, M.; Romagnoli, R.; Pereiro, I.; Roos, E.C.; Moolenaar, M.J.; Speckamp, W. N. Heimstra, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1773-1789. Hart, D.J.; Tsai, Y. *J. Org. Chem.* **1982**, *47*, 4403-4409.
6. Luzzio, F.A.; Piatt Zacherl, D. *Tetrahedron Lett.* **1998**, *39*, 2285-2288.
7. Luzzio, F.A.; Bobb, R. A. *Tetrahedron Lett.* **1997**, *38*, 1733-1736.
8. Guziec, F.S., Jr.; Luzzio, F.A. *Synthesis*, **1980**, 691-694.
9. Luche, J.L. *Synthetic Organic Sonochemistry*; Plenum Press: New York, 1998, pp. 241-243.
10. Luzzio, F.A. in *Organic Reactions*; Paquette, L.A., Ed.; John Wiley & Sons, Inc: New York, 1998; Vol 53, pp. 1-221.
11. Kaplan, G.; Sampaio, E.P. **US 5,386,901**, Jan. 31, 1995.
12. Fulmer, Y.; Opliger, C.; Montgomery, J.A. *J. Pharm. Sci.* **1968**, *57*, 757-764.
13. Remarkably the yield of **29** was lower (46%) with ultrasound (20 min/20°C). The ultrasound-promoted desulfurization of **28** was accompanied by loss of the PMB group.
14. Van Aerschot, A.; Jie, L.; Herdewijn, P.; *Tetrahedron Lett.* **1991**, *32*, 1905-1908.
15. We thank Ms. Beth Thomas, University of Louisville, for performing the experiments involving the ceric ammonium nitrate (CAN)-mediated removal of the PMB group of thalidomide intermediate **29**.
16. (a) A similar type of reduction sequence has been reported for amino acid derivatives: Donner, B.G. *Tetrahedron Lett.* **1995**, *36*, 1223-1226. (b) For desulfurization of monothioimides to the corresponding lactams see: Milewska, M.L.; Bytner, T.; Polonski, T. *Synthesis*, **1996**, 1485-1488.
17. A recent communication by Couture (Couture, A.; Deniau, E.; Ionescu, D.; Grandclaudon, P, *Tetrahedron Lett.* **1998**, *39*, 2319-2320) details the generation of benzylic carbanions from phthalimidines and their subsequent reactions with electrophiles.
18. The oxidation of *N*-phenylphthalimidines to the corresponding phthalimides has been reported with Jones reagent: Yamamoto, I.; Tabo, Y.; Gotoh, H.; Minami, T.; Oshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1971**, *25*, 2295-2296.