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Alkylation and Annulation of 3-(Phenylsulfonyl)-2-Alkyl-2,3-Dihydroisoindol-1-ones

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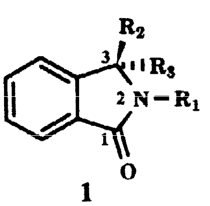
Abstract: The hydroxylactams obtained from reduction of N-substituted phthalimides were phenylthiated and oxidized to give 3-(phenylsulfonyl)-2,3-dihydroisoindol-1-ones. Deprotonation of the sulfones with sodium hydride followed by treatment with electrophiles gave substitution. Sulfones with suitably-disposed α,β-unsaturated ester groups gave cyclic products from intramolecular Michael addition. Desulfurization of the phenylsulfonyl intermediates was effected in quantitative yield using Raney nickel promoted by ultrasound.

The chemistry of dihydroisoindolones (**1**) has been the focus of new synthetic methodology in many research groups.[1] Our interest in dihydroisoindolones as a class of compounds arises from their activity as non-nucleosidic HIV-reverse transcriptase inhibitors,[2] vasodilators[3] and their potential utility as versatile key intermediates to alkaloid classes such as the pyrrolizidinones.[4] New synthetic routes to fused polycyclic dihydroisoindolizidinones such as lennoxamine (**2**),[5] magellanesine (**3**),[6] AKS 186 (**4**)[7] and their analogues are being secured by exploring the reactivity and selective functionalization of substituted phthalimides. This Letter details new synthetic methodology which allows efficient access to new types of fused-ring, polycyclic substituted dihydroisoindolones such as those encountered as core structures in many natural products and synthetic pharmacophores. The demonstration of a rapid, mild and selective method for the reduction of N-substituted phthalimides to the corresponding hydroxylactams with aluminum amalgam[8] prompted an examination of deoxygenation and carbon-carbon bond formation at C-3 (isoindolone numbering).



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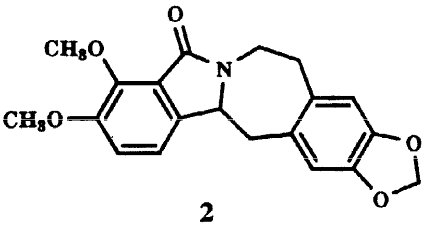

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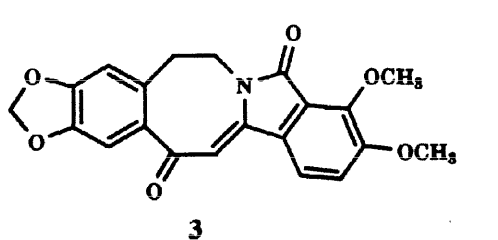

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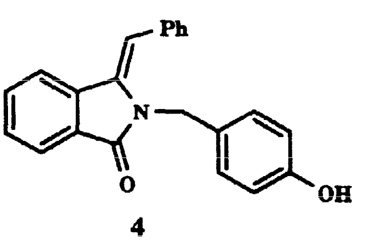

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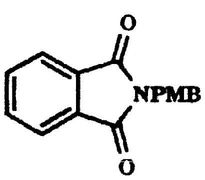
Reduction of N-*p*-methoxybenzyl (PMB) phthalimide (**5**) with aluminum amalgam in tetrahydrofuran (THF)/water (9:1) gave the corresponding N-PMBhydroxylactam (**6**) in 70% unoptimized yield.[8,9] Following a procedure established by Hart in the succinimide series,[4b] hydroxylactam **6** was treated with thiophenol (1.2 eq/rt) in dichloromethane using *p*-toluenesulfonic acid (catalytic) which afforded the phenylthiolactam (**7**) in quantitative conversion after purification by silica gel column chromatography. Oxidation of the phenylthiolactam (**7**) to the corresponding benzylic sulfone (**8**) was then accomplished by means of *m*-chloroperbenzoic acid (2.0 eq) in methylene chloride (0.5 h, rt).[10] Alternatively the conversion of **5** to **7** was effected in 69% yield over the two steps without purification of the intermediate hydroxylactam. Deprotonation of **8** with sodium hydride (from 50% mineral oil disperson) in tetrahydrofuran/dimethylsulfoxide (THF/DMSO, 9:1) or THF/hexamethylphosphoramide (THF/HMPA, 4:1) followed by treatment of the resultant anion with iodomethane or β-phenethyl bromide gave substituted sulfones (**9, 10**) in 55-75% yields. The alkylated benzylic sulfones (**9, 10**) were smoothly desulfonylated to **13** and **14**, respectively, using a Raney nickel/ethanol procedure which utilized high-intensity ultrasound (5 min, 20°C). It should be noted that **14** is the dihydromethoxy analogue of AKS 186 (**4**).[11] Michael addition of the anion generated from **8** with methyl vinyl ketone or methyl acrylate (1.2 eq/rt) gave the adducts **11** and **12**, respectively. Attempts at purifying **11** and **12** by silica gel column chromatography led to decomposition, therefore these intermediates were directly desulfonylated after rapid workup directly prior to the ultrasound protocol. The overall yield of **8** to **15** and **8** to **16** was 51% and 55%, respectively, after isolation and purification by silica gel column chromatography. Unlike their sulfonylated analogues **15** and **16** were stable to chromatography (SiO_2), concentration under reduced vacuum at room temperature and overnight storage in NMR solvent ($CDCl_3$).



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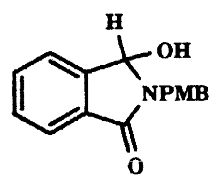

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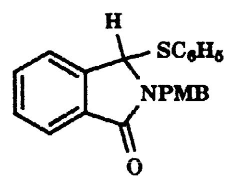

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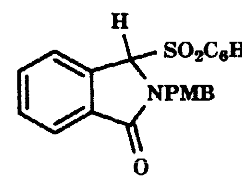

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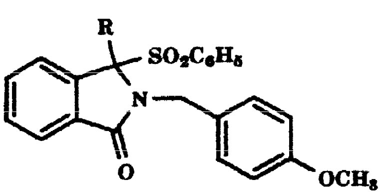
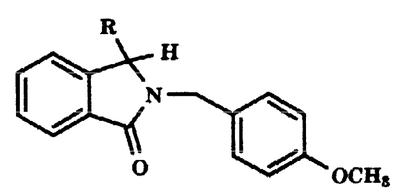
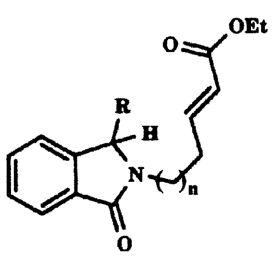


9, R = CH_3
10, R = $CH_2CH_2C_6H_5$
11, R = $CH_2CH_2COCH_3$
12, R = $CH_2CH_2COOCH_3$

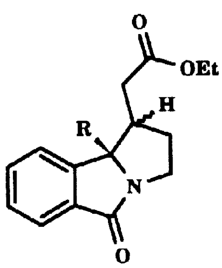


13, R = CH_3
14, R = $CH_2CH_2C_6H_5$
15, R = $CH_2CH_2COCH_3$
16, R = $CH_2CH_2COOCH_3$

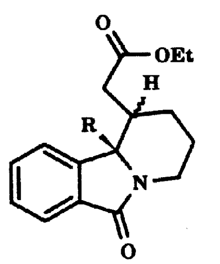
The reactivity of the benzylic α-sulfonyl anions was tested in an intramolecular Michael reaction in order to probe the formation of tricyclic products. Hydroxylactam (**17**), having a suitably disposed α,β-unsaturated ester function, was phenylthiated (thiophenol/*p*-toluenesulfonic acid/CH_2Cl_2) to provide the phenylthioisoindolinoyl pentenoate (**18**) in 66% yield (two steps from the corresponding imide) after silica gel flash chromatography (hexanes/EtOAc, 3:1). Compound **18** was oxidized (MCPBA/CH_2Cl_2/rt) to give the phenylsulfone olefinic ester (**19**) in 70% yield after purification by silica gel flash chromatography (hexanes/EtOAc, 1:1). Ring closure of **19** to the pyrroloisoindolone system (**20**) was effected by treatment of **19** with sodium hydride in DMSO/THF (20 min/rt). Purification of **20** was accomplished by flash-column chromatography on silica gel (hexanes/EtOAc, 1:1) to yield the tricyclic product as an amorphous white solid (91%). Tricyclic sulfone **20** was desulfonylated (Raney nickel/EtOH/ultrasound/5 min) to provide the tricyclic compound **21**[12] in quantitative yield[13] after silica gel chromatography (hexanes/EtOAc, 1:1). The preparation of phenylthiolactam **18a** utilized 4-(*N*-phthaloyl)-1-butyl benzoate (**22**). Imide **22** was reduced [Al(Hg)/THF/H_2O/rt] to the hydroxylactam **23** which was not purified but directly phenylthiated (thiophenol/*p*-toluenesulfonic acid/CH_2Cl_2/rt) to provide phenylthioester **24** (60%) after purification by silica gel column chromatography. Ester **24** was saponified (LiOH/H_2O/CH_3OH/rt/7h) to afford alcohol **25** (92%) after purification by silica gel column chromatography. Alcohol **25** was oxidized (PCC/silica gel/CH_2Cl_2/rt/2 h) to provide aldehyde **26** which was not purified but treated directly with ethoxycarbonylmethyltriphenyl-phosphoniumbromide (NaOH/H_2O/CH_2Cl_2/rt) to give the phenylthio α,β-unsaturated ester (**18a**) in 54% yield (from **25**) after column chromatography. Oxidation of **18a** to the sulfone (**19a**) was effected with portionwise addition of MCPBA (CH_2Cl_2/rt/35 min). Closure of **19a** was accomplished with the same conditions as **19** giving the phenylsulfonylbenzoisoindolizidinone (**20a**, 68%).



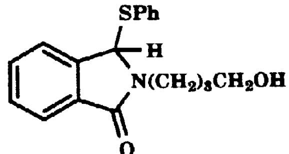
17, R = OH, n = 1
18, R = SPh, n = 1
18a, R = SPh, n = 2
19, R = $PhSO_2$, n = 1
19a, R = $PhSO_2$, n = 2



20, R = $PhSO_2$
21, R = H



20a, R = $PhSO_2$
21a, R = H



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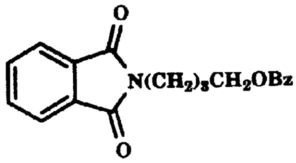

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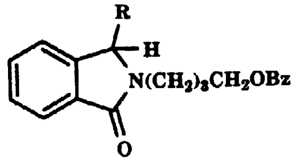
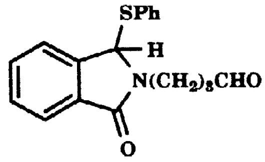


23, R = OH
24, R = SPh



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Desulfonylation of **20a** (Raney nickel/EtOH/ultrasound/5 min) proceeded smoothly and afforded the benzoindolizidinone **21a** (80%) as a (1:1) diastereomeric mixture (detected by 500 MHz NMR).

In summary, 3-(phenylsulfonyl)-2-alkyl-2,3-dihydroisoindol-1-ones are effective carbanion sources for alkylation and Michael addition reactions. The phenylsulfones with suitably disposed α,β-unsaturated groups gave tricyclic compounds in good yields and provides a basis for future natural products synthesis.

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9. All compounds were obtained as chromatographically homogeneous substances and exhibited satisfactory ^{1}H, ^{13}C NMR spectra, IR spectra and/or mass spectral analyses.
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11. Sulfonyl elimination of **10** promoted by quinoline gave the required phenylethylidene function for methoxy AKS-186. These results will be communicated separately.
12. Tricyclic **21** was obtained as a 4:1 mixture of diastereomers as evidenced by ^{1}H NMR (500 MHz).
13. Townsend's desulfurization method was adapted for ultrasound: Devivar, R. V.; Kawashima, E.; Revankar, G. R.; Breitenbach, J.; Kreske, E. D.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1994**, *37*, 2942-2949.