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A SYNTHESIS OF SUCCINIMIDES AND GLUTARIMIDES FROM CYCLIC ANHYDRIDES

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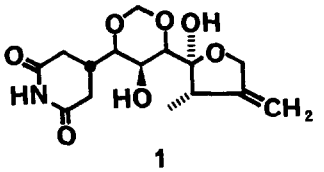
Abstract. The transformation of cyclic anhydrides to their corresponding imides involves a mild three-step sequence: (1) reaction with a primary amine, (2) conversion of the intermediate monoamide to an N-hydroxysuccinimidyl ester using N,N'-disuccinimidyl oxalate (DSO), and (3) cyclization by heating the NHS ester in trichloroethylene in the presence of 4-(dimethylamino)pyridine.

In connection with our interest in the synthesis of protein inhibitors in the cycloheximide family[1] such as sesbanimide[2] (1), we required an efficient procedure for introducing the glutarimide functionality. Published synthetic routes to glutarimides rely on either the dehydration of ammonium glutarates,[3] the dehydration of glutaramic acids,[4] or the pyrolysis of bisglutaramides,[5] but the overall yields for these processes are uniformly low (10-40%). In contrast, the corresponding thermal and chemical dehydrations leading to succinimides proceed in synthetically useful yields.[6] The monoamides 3 of succinic and glutaric acids are readily available from the corresponding anhydrides.[7] As shown in Scheme I, we report that N,N'-disuccinimidyl oxalate (2) converts the monoamides 3 to the intermediate N-hydroxysuccinimidyl esters 4 which cyclize to the desired succinimides[8] and glutarimides[8] in high yields under comparatively mild conditions.



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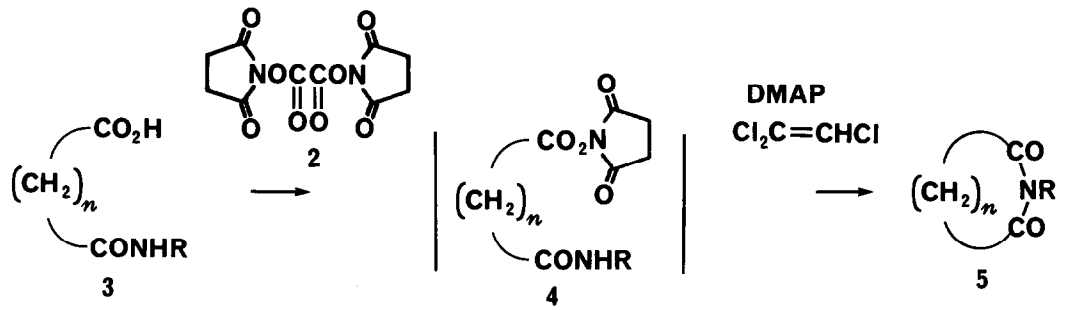
In order to achieve the desired transformation of the monoamides 3 to the imides 5, we converted 3 to the intermediate N-hydroxysuccinimidyl ester 4 using Ogura's reagent, N,N'-disuccinimidyl oxalate[7] (DSO), in acetonitrile containing one equivalent of pyridine as shown in Scheme I. In comparison to the conventional preparation of N-hydroxysuccinimidyl esters from acids using N-hydroxysuccinimide and 1,3-dicyclohexylcarbodiimide,[9] the DSO/pyridine procedure offers the distinct advantage of producing the esters 4 and either gaseous (CO, CO_2) or water-soluble by-products. Heating the intermediate ester 4 in the presence of 4-(dimethylamino)pyridine (DMAP) in trichloroethylene at 87°C (as compared with 200-250°C in the literature procedures) provided the imides 5 in 62-89% yield as shown in Table I.

Scheme I.



The following is a typical experimental procedure. To a suspension of 100 mg (0.534 mmol) of N-n-butylglutaramic acid (3, n=3, R=n-C_4H_9) and 43 µL (0.534 mmol) of anhydrous pyridine in 3 mL of anhydrous acetonitrile under a nitrogen atmosphere was added 152 mg (0.534 mmol) of DSO (2). The suspension was stirred for 2h at 25°C at which time a clear solution of 4 (n=3, R=n-C_4H_9) was obtained. The product was concentrated on a rotary evaporator, diluted with 195 mg (1.60 mmol) of DMAP and 2 mL of trichloroethylene, and refluxed for 5 h (87°C). The solution was diluted with ethyl acetate, washed successively with 2% hydrochloric acid solution and brine, and dried ($MgSO_4$) to afford 70 mg (78%) of 5d: IR(TF) 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3, CH_3), 1.10-1.75 (m, 4, $(CH_2)_2CH_3$), 1.88 (p, J = 6 Hz, 2, $COCH_2CH_2CH_2CO$), 2.60 (t, J = 6 Hz, 4, $COCH_2CH_2CH_2CO$), 3.75 (t, J = 7 Hz, 2, CH_2N).

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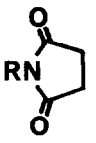
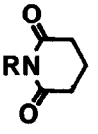
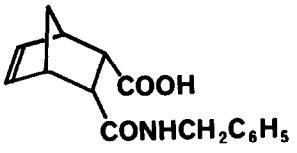
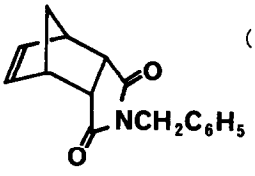
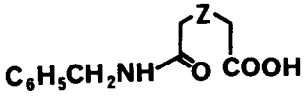
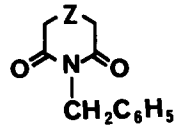
Table I. Synthesis of Succinimides and Glutarimides Using N,N'-Disuccinimidyl Oxalate (2).

Substrate	Conditions[a] (equiv DMAP, reflux time)	Product 5 (Isolated Yield, %)
$RNHCO(CH_2)_2CO_2H$		
3a R = n-C_4H_9	2, 1h	R = n-C_4H_9 (76)[b]
3b R = $CH_2C_6H_5$	2, 1h	R = $CH_2C_6H_5$ (84)[c]
3c R = C_6H_5	2, 1h	R = C_6H_5 (80)[d]
$RNHCO(CH_2)_3CO_2H$		
3d R = n-C_4H_9	3, 5h	R = n-C_4H_9 (78)[b]
3e R = $CH_2C_6H_5$	3, 5h	R = $CH_2C_6H_5$ (83)
3f R = C_6H_5	3, 5h	R = C_6H_5 (77)[e]
3g R = $CH(CH_3)C_6H_5$	5, 24h	R = $CH(CH_3)C_6H_5$ (62)
3h 	2, 1h	(89) 
		
3i Z = $C(CH_3)_2$	3, 5h	Z = $C(CH_3)_2$ (82)
3j Z = O	3, 3h	Z = O (80)

a, the only variations in the general procedure described in the text were the equivalents of DMAP and the reflux time necessary to cyclize the intermediate 4 to the imide 5; b, G. B. Hoey and C. T. Lester, J. Am. Chem. Soc., 73, 4473 (1951); c, E. A. Werner, J. Chem. Soc., 55, 627 (1889); d, A. Laurent and C. Gerhardt, Liebig's Ann. Chem., 68, 27 (1848) and A. Rahman, M. A. Medrano and B. E. Jeanneret, J. Org. Chem., 27, 3315 (1962); e, Bodtker, Diss. Leipzig, 1891 (Beilstein, H21, 383).

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9. All new compounds had satisfactory IR, NMR, and combustion analysis or high resolution exact mass spectral data.

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