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DIMETALATED TERTIARY SUCCINAMIDES

ALKYLATION AND ANNELATION REACTIONS

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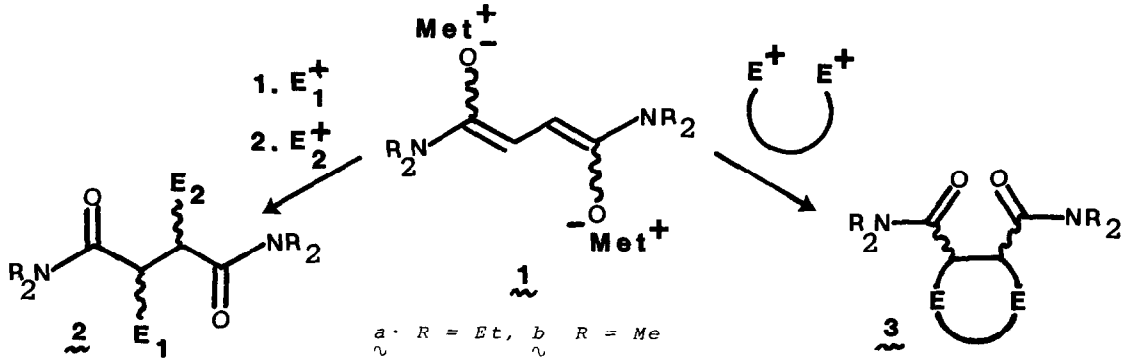
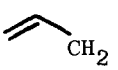
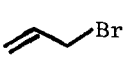
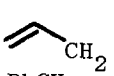
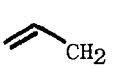
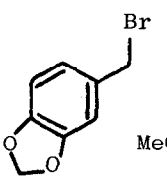
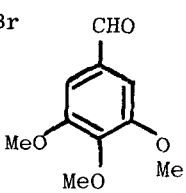
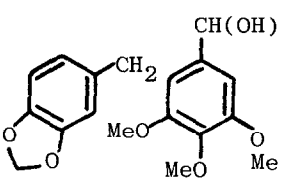
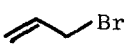
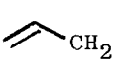
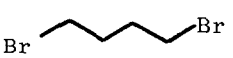
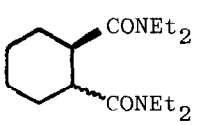
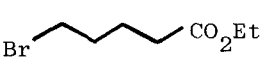
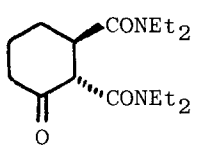
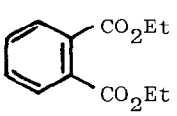
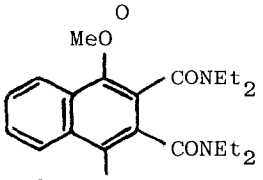
Summary: The reactions of dimetalated succinamides 1 with a variety of electrophiles give 2,3-disubstituted adducts (2) with high diasterioselectivity and annelated products (6-9).

As part of their intensive pioneering studies in multiple anion chemistry, the school of C R Hauser touched briefly upon the metalation of acyclic and cyclic amides and imides [1] In this Letter, we describe the generation of dimetalated succinamides (1)[2] and their use for the stereoselective synthesis of 2,3-disubstituted, additionally functionalized succinamides (2, $E_1 =, \neq E_2$) and for ring annelation processes (3) [3] In the accompanying Letter,[4] we demonstrate the expedience of some of the derived products 2 for the construction of several classes of lignan natural products

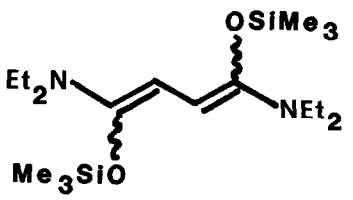


Treatment of N,N-diethyl or -dimethyl succinamide[5] with LDA (2 2 equiv/ THF/-78°C/1h) gives a yellow solution of the dimetalated species 1 which is stable up to 0°C[6] as evidenced by quenching at that temperature with Me_3SiCl to give 4 [7] Treatment of 1 with a variety of electrophiles affords good to excellent yields of 2,3-disubstituted products 2 (Table) Use of two equiv of the same electrophile leads to symmetrically 2,3-disubstituted products

TABLE. Synthesis of 2,3-Disubstituted Succinamides

Entry	Succinamide	Electrophile E_1^+	Electrophile E_2^+	Product[a] (2) E_1	Product[a] (2) E_2	Yield, %[b]	Threo:Erythro[c]
1	N,N-diEt	D_2O	D_2O	D	D	65	>98:<2
2	N,N-diMe	MeI	MeI	Me	Me	78	86:14
3	N,N-diEt	MeI	MeI	Me	Me	91	97:3
4	N,N-diEt	MeI		Me		68	92:8
5	N,N-diMe					83	>98:<2
6	N,N-diMe	$PhCH_2Br$	$PhCH_2Br$	$PhCH_2$	$PhCH_2$	67	92:6
7	N,N-diMe					58	87:13[d]
8	N,N-diMe	MeI	$(PhS)_2$	Me	PhS	58	>98:<2
9	N,N-diMe		$(PhSe)_2$		PhSe	47	75:25
10	N,N-diEt	$PhCO_2Et$	$PhCO_2Et$	PhCO PhCO	H PhCO	30 15	
11	N,N-diEt			**6** 		60	2:1 trans:cis[e]
12	N,N-diEt			**7** 		68	trans only
13	N,N-diEt			 **8**		65[f]	

[a] *All compounds show analytical and spectral (IR, NMR, MS) data in accord with the proposed structures.* [b] *After chromatography (silica gel, EtOAc-hexane, 2:1 eluent).* [c] *Ratios based on isolated, hplc pure substances.* [d] *stereochemistry unknown.* [e] *cis-6 was converted into trans-6 (t-BuOK/t-BuOH/RT/1 h).* [f] *After methylation (NaH/MeI/DMF).*



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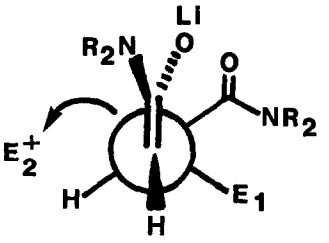

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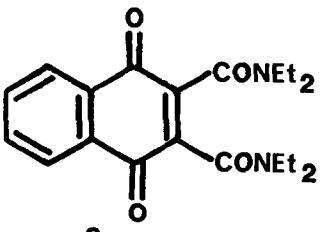

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(entries 1-3,5,6) while sequential addition of 1 equiv of each of two different electrophiles provides succinamides with dissimilar 2,3-disubstitution (entries 4, 7-9) In using different electrophiles, the electrophile which most acidifies the site of substitution must be added last (e g , entries 8,9) The first introduction of a strongly acidifying group (e g PhCO) prevents efficient entry of the second, identical electrophile and, in spite of adding a further equiv of LDA to the monobenzoyl intermediate in situ, a mixture of mono- and dibenzoyl adducts (2 1) is obtained (entry 10) That the major/minor diasteriomers derived from methylation and benzylation (entries 2 and 6) correspond to the threo/erythro configurations respectively was established by their hydrolysis (conc HCl/105^{o}C/6 h) to the known respective 2,3-disubstituted succinic acids, furthermore, the 2,3-dibenzyl succinic acid diasteriomers were cyclized to the corresponding succinic anhydrides [8] Therefore the threo-configuration is tentatively assigned to the major diasteriomer of all products 2 The high threo stereoselectivity may be explained by reference to a model of the monoalkylated, perhaps chelated, enolate (5) [9] Dielectrophiles also undergo smooth condensation with 1 to give cyclohexane derivatives 6 and 7 (entries 11, 12[10]), however, 1,3-dibromobutane failed to give a cyclopentane diamide corresponding to 6 The double Claisen-type condensation of 1a with diethyl phthalate (entry 13) followed by methylation afforded the naphthalene diester 8,[11] on the other hand, Jones oxidation of the reaction mixture furnished the naphthaquinone 9 (66%)

Dimetalated succinamides 1 thus appear to be useful substrates for the preparation of diversely functionalized four-carbon frameworks which show potential for further selective elaboration [12]

Typical Experimental Procedure: To a THF solution of LDA (6 mmol) at -78°C was added dropwise N,N-diethylsuccinamide (684 mg, 3 mmol) in THF (10 mL). After 40 min, the pale yellow solution was quenched with methyl iodide (1 mL, 12 mmol) and the mixture was allowed to attain room temp overnight. Standard work up followed by evaporative distillation gave 606 mg (78%) of product as a colorless liquid, bp 105-108°C/0.05 mm; IR (neat) ν max 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.15-1.45 (18 H, br m), 2.95-3.6 (10 H, br m); MS 254 (M^+).

References and Footnotes

1. Reviews: a) Harris, T.M.; Harris, C.M. Org. React. 1969, 17, 155; b) Kaiser, E.M.; Slocum, D.W. in "Organic Reactive Intermediates," McManus, S.P., ed., Academic Press, N.Y., 1973, p. 337; c) Kaiser, E.M.; Petty, J.D.; Knutson, P.L.A. Synthesis, 1977, 509.

2. Hauser explored only N,C-dianions of succinamides and glutarimides and the N,N,C-trianion of N,N-diphenylsuccinamide (refs. 1b,1c). The first example of a C,C-dianion (norbornene-2,3-dicarboximide) has been recently recorded: Garratt, P.J.; Hollowood, F. J. Org. Chem. 1982, 47, 68.

3. For the generation and reactions of dimetalated diethyl succinate, see a) Long, N.R.; Rathke, M.W. Syn. Commun. 1981, 11, 687; for other vicinal diesters, see b) Bilyard, K.G.; Garratt, P.J. Tetrahedron Lett. 1981, 1755 and refs. therein; Noire, P.D.; Franck, R.W. Tetrahedron Lett. 1982, 1031.

4. Mahalanabis, K.K.; Mumtaz, M.; Snieckus, V. Tetrahedron Lett., following communication in this issue.

5. Prepared from succinic acid under standard conditions. (N,N-diethyl amide: bp 108-110°C/0.15 mm; N,N-dimethyl amide: mp 84-85°C).

6. This contrast with the corresponding dianion of diethyl succinate (ref. 3a).

7. This appears to be a single stereoisomer by hplc and NMR: bp 75-76°C/0.05 mm; NMR ($CDCl_3$) δ 4.35 (2H, s), 2.30 (12 H, s), 0.01 (18 H, s). The same reaction on diethyl succinate yields a mixture of isomers (ref. 3a).

8. 2,3-dimethylsuccinic acid: erythro isomer, mp 202-204°C (lit mp 209°C); threo isomer, mp 123-124°C (lit mp 127°C): Linstead, R.P.; Whalley, M. J. Chem. Soc. 1954, 3722. 2,3-dibenzylsuccinic acid: erythro isomer, mp 204-205°C (lit mp 203°C); cis-anhydride, mp 104-105°C (lit mp 104°C); threo isomer, mp 169.5-170.5°C (lit 172°C); trans-anhydride, mp 122-123°C (lit mp 125°C): Cordier, P.; Gluzel, M.M. Compt. Rend. 1952, 235, 622.

9. For a related model, see Wasmuth, D.; Arigoni, D.; Seebach, D. Helv. Chim. Acta 1982, 65, 344.

10. The first use of ethyl 4-bromobutyrate for annelation (to a dimetalated vicinal diester) is due to Garratt, see ref. 3b.

11. For the use of succinate esters in Claisen condensations, see Jones, G.; Jones, R.K. J.C.S. Perkin I, 1973, 26 and refs. therein. We thank Dr. Gurnos Jones for bringing his studies to our attention.

12. We are grateful to NSERC of Canada for continuing financial support. K.K.M. thanks Jadavpur University, Calcutta for a leave of absence.

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