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AN IMPROVED, VERSATILE PREPARATION OF TRANS-N-ACYL-N-ALKYL-1-AMINO-1,3-DIENES[1)]

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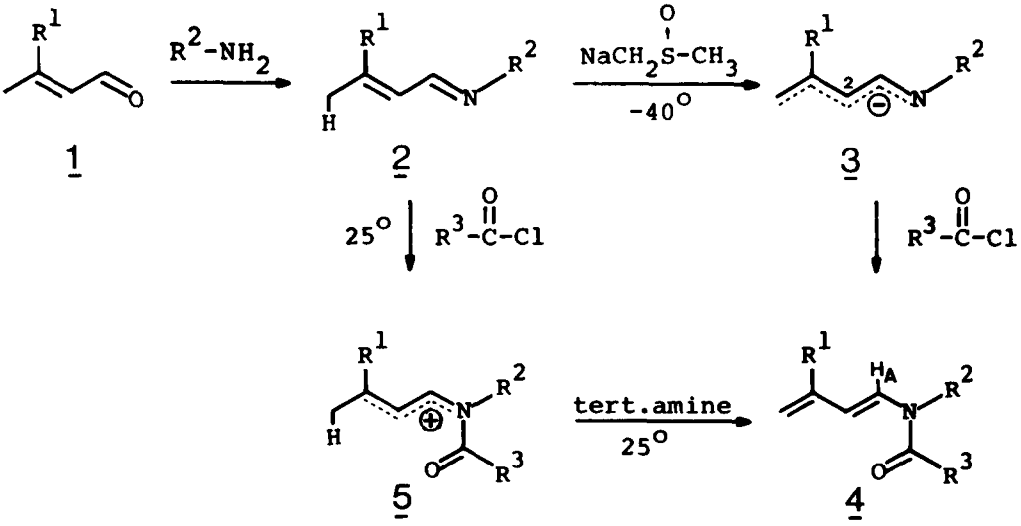
Recent work in this laboratory has shown N-acylamino-1,3-butadienes (4) to be valuable components for intramolecular Diels-Alder reactions. Thus, heating the dienes 4, R^2,R^3 = 3- or 4-alkenyl, readily provides complex hydrogenated indolines and quinolines[2)] as illustrated by the stereocontrolled synthesis of the optically pure alkaloid pumiliotoxin-C[3)]. The previously unknown dienamides 4 [4,5)] were obtained in 40 to 65% overall yield by successive treatment of the conjugated imines 2[8)] with sodium methylsulfinylmethide and an acid chloride at -40°C.



This sequence apparently proceeds by a deprotonation 2 → 3, followed by a selective N-acylation of the nonisolated 1-aza-pentadienyl anions 3[9)]. Practical difficulties are the need for low reaction temperature and strong base; the latter also interferes with imines 2 containing other relatively acidic hydrogens[10)].

We now wish to report a simplified, more general and efficient preparation of the dienes 4. Thus, reaction of the conjugated imines 2 with various acid chlorides in the presence of tert. amines in an inert solvent provided directly the required dienamides 4 in high yields. This modified procedure presumably involves prior acylation of the imine 2 by the acid chloride[11)] to give a delocalized cation 5 which requires only weak bases for deprotonation giving the dienamides 4. Typical reaction conditions, product yields and spectral data are shown in Table 1.

Table 1: Preparation and Properties of the Dienamides 4.

Dienamide	R^1	R^2	R^3	isolated yield	m.p. °C	^{1}H-NMR($CDCl_3$) δH_A, d, J=14Hz	IR.(film) ν_{max}(cm^{-1})	UV.(MeOH) λ_{max}(nm) logε
4a	H	CH_2Ph	Ph	80%[a]	78-80	7.00	1666,1638	256/4.25
4b	H	CH_2Ph	OCH_2Ph	81%[a]	38-39	not visible	1706,1640	254/4.44
4c	H	cyclohexyl	Ph	70%[a] 59%[b]	54-56	6.43	1665sh,1632	250/4.17
4d	H	cyclohexyl	OMe	65%[a,c]	38-40	6.80	1718,1643	257/4.50
4e	H	cyclohexyl	Me	88%[a]	oil	not visible	1670,1635	256/3.97
4f	H	i-C_3H_7	Ph	66%[a]	oil	6.70	1662,1632	254/4.14
4g	H	i-C_3H_7	Me	65%[a]	oil	not visible	1677,1638	259/4.14
4h	H	n-C_6H_{11}	i-C_3H_7	78%[a]	oil	7.04	1677,1637	265/4.45
4i	H	n-C_6H_{11}	OMe	83%[a]	oil	7.15	1730,1654	258/4.43
4j	Me	n-C_3H_7	OMe	49%[b]	oil	7.08	1720,1644	257/4.43
4k	H	6-(2-nonenyl)	i-C_3H_7	95%[d]	oil	not visible	1675,1650 1638	274/3.92
4l	H	6-(2-nonenyl)	Ph	95%[d]	oil	6.50	1665,1630	-
4m	H	Ph	Ph	56%[a]	96-97	7.70	1655sh,1640	278/4.35

a) The imine 2 (10 mmol) was added to a stirred mixture of the acid chloride (10 mmol), diethylaniline (11 mmol) and toluene (20 ml) at +25°C. Stirring of the reaction mixture at +25°C for 15 h, filtration, evaporation of the filtrate and either chromatography or distillation (0.01 Torr) of the residue furnished the pure diene 4.

b) Following procedure a) without isolation of the imine 2 (prepared *in situ*).

c) 5 mmol 2 / 6 mmol MeOCOCl / 7.5 mmol collidine / CH_2Cl_2 / 0°C / 24 h.

d) The imine 2 (3.6 mmol) was added to a stirred mixture of the acid chloride (4 mmol), triethylamine (8 mmol) and CH_2Cl_2 (20 ml) at -78°C. The reaction mixture was warmed up to +5°C over 16 h and chromatographed (SiO_2, toluene/ ethyl acetate).

Thus, bases like triethylamine, pyridine and collidine were successfully used at temperatures below +5°C as exemplified by the preparation of 4d, 4k and 4l. More conveniently, treatment of 2 with an acid chloride and diethylaniline at room temperature in toluene, filtration of the precipitated diethylaniline hydrochloride, followed by distillation of the filtrate furnished the pure dienamides 4 in good to excellent yields[12]. For small scale preparations of 4 a rapid chromatography (5-fold amount of SiO_2) of the crude product appeared to be more suitable. The starting imines 2, in general purified by distillation in vacuo, may be also prepared in situ[8] in toluene (as shown for the preparation of 4c and 4j). Accordingly, a broad series of dienes 4, containing different substituents (R^1, R^2, R^3) are now easily obtained from a crotonaldehyde 1 (R^1), primary amines (R^2) and acid chlorides (R^3). This includes the diene anilide 4m (R^2=Ph), and particularly, the hitherto inaccessible[10] N-acyl-N-benzyl-dienes 4a and 4b which represent doubly protected aminobutadiene equivalents[13]. Both dienes 4a and 4b are crystalline solids which could be stored for 1 year without decomposition[14], 4b at -30° and 4a even at room temperature. Further work illustrating the reactivity of these dienes in intermolecular Diels-Alder additions is to be published[15].

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10) The failure to obtain N-acyl-N-benzyl-1-amino-1,3-butadienes by this route may be attributed to predominant abstraction of a benzylic proton in 2 (R^2= $CH_2C_6H_5$)$^{4a)}$.

11) In contrast, previous attempts to convert 2 to 4 using acid anhydrides/ triethylamine have failed $^{4a)}$.

12) We thank Dr. P. Fünfschilling, Sandoz Ltd, Basel for suggesting to us these particular reaction conditions.

13) For the preparation and use of monoprotected aminobutadiene equivalents see ref. 5.

14) M.p., spectral and chromatographic evidence. This stability compares favorably with that of some diene carbamates, prepared from isocyanates$^{5)}$.

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