THIYL RADICAL INDUCED CYCLIZATION OF DIENYLAMIDES FOR LACTAM SYNTHESIS

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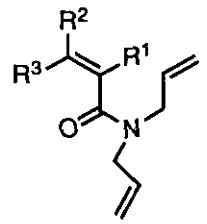
Abstract-- A series of dienylamides have been found to undergo radical cyclization when irradiated in the presence of diphenyl disulfide and thiophenol. The present method provides an attractive entry to the preparation of lactams from easily available dienylamides.

Much attention has been focused on radical initiated cyclization from both synthetic and mechanistic viewpoints in the last decade.[1] Although thiyl radical induced cyclization[2] of dienes has been previously reported on the formation of carbocycles, little has been explored on the preparation of heterocyclic compounds,[3] which are common in most of medicinals and biologically active compounds. In this communication, we describe the first examples of the synthetically useful thiyl radical induced cyclization of the dienylamides which provides easy access to five-, six-, and eight-membered lactams.

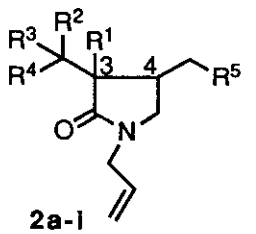
In order to investigate the thiyl radical induced cyclization of dienylamides having two double bonds of different nature such as allyl and acryloyl groups, *N,N*-diallylacrylamide (**1a**)[4] was irradiated in benzene solution (0.01M) with a high-pressure mercury lamp through a Pyrex filter at 5-10°C in the presence of equimolar amount of either diphenyl disulfide (method A), diphenyl disulfide and thiophenol (method B), or thiophenol (method C) to give the cyclized pyrrolidinones in the yields as shown in Table 1. In the method A, two *trans*-3-phenylthiomethylpyrrolidinones (**2a**)[5] and (**2c**)[5] were obtained with 33% recovery of the starting amide (**1a**). Methods B and C gave the almost same results in which *trans*-3-phenylthiomethylpyrrolidinone (**2a**) was obtained as a major product accompanied by the formation of small amount of *cis*- and *trans*-4-phenylthiomethylpyrrolidinones (**2b**).[5]



1a-d

1a: R^1=R^2=R^3=H
1b: R^1=Me, R^2=R^3=H
1c: R^1=R^3=H, R^2=Me
1d: R^1=H, R^2=R^3=Me

Method A, B, or C



2a-l

2a: R^1=R^2=R^3=R^5=H, R^4=SPh
2b: R^1=R^2=R^3=R^4=H, R^5=SPh
2c: R^1=R^2=R^3=H, R^4=R^5=SPh
2d: R^1=Me, R^2=R^3=R^5=H, R^4=SPh
2e: R^1=Me, R^2=R^3=R^4=H, R^5=SPh
2f: R^1=Me, R^2=R^3=H, R^4=R^5=SPh
2g: R^1=R^3=R^4=H, R^2=Me, R^5=SPh
2h: R^1=R^4=H, R^2=R^3=Me, R^5=SPh
2i: R^1=H, R^2=Me, R^3+R^4= =CH_2, R^5=SPh

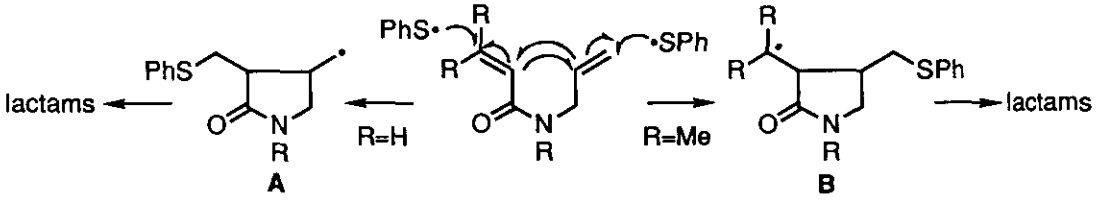
Table 1. Radical Reaction of Dienylamides (**1a-d**)

Substrate	Method[a]	Time(h)	Product(Yield %)[b]		
1a	A	4.5	**2a** (t-31)	**2c** (t-19)	
1a	B	3	**2a** (t-57)	**2b** (22, c: t=1:1)	
1a	C	2	**2a** (t-54)	**2b** (12, c: t=2:1)	
1b	A	2	**2d** (49, c: t=1:1)	**2e** (4)	**2f** (24, c: t=1:1)
1b	B	2	**2d** (89, c: t=1:1)	**2e** (2)	
1c	A	7	**2g** (33, c: t=3:2)		
1c	B	7	**2g** (37, c: t=2:1)		
1d	A	2	**2h** (48, c: t=3:2)	**2i** (c-13)	
1d	B	2	**2h** (63, c: t=2:1)	**2i** (c-1)	

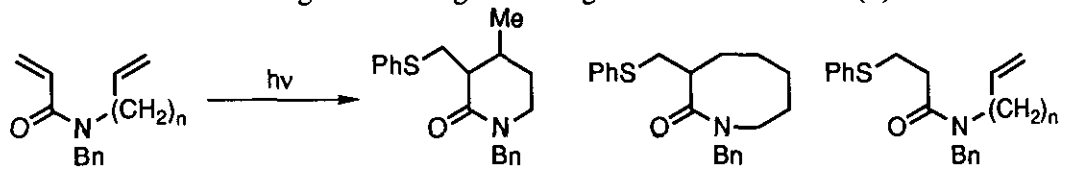
[a] Method A: hv in the presence of $(PhS)_2$; Method B: hv in the presence of $(PhS)_2$ and PhSH; Method C: hv in the presence of PhSH; [b] c: *cis*, t: *trans*

Similarly, the methacrylamide (**1b**) underwent smooth radical cyclization irrespective of the reaction condition A or B to give *cis*- and *trans*-3-phenylthiomethylpyrrolidinones (**2d**)[5] as a major product. Prolonged irradiation of the crotonamide (**1c**) gave *cis*- and *trans*-4-phenylthiomethylpyrrolidinones (**2g**)[5] with 34% recovery of the starting amide (**1c**). The 3-methylcrotonamide (**1d**) underwent smooth cyclization to give *cis*- and *trans*-pyrrolidinones (**2h**)[5] and small amount of the 3-isopropenylpyrrolidinone (**2i**).[5] Thus, thiyl radical was found to bring about smooth 5-*exo*-trig cyclization of dienylamides to give the 3,4-disubstituted pyrrolidinones in moderate yields. However, regioselectivity in the cyclization was depended on the substituent in the acyl group. Acryl- and methacrylamides (**1a, b**) gave mainly 3-phenylthiomethylpyrrolidinones while β-methyl substituted acrylamides (**1c, d**)

gave exclusively the 4-phenylthiomethylpyrrolidinones. Preferential formation of *trans*-3,4-disubstituted pyrrolidinone (**2a**) from the acrylamide (**1a**) is compatible with the case of α-carbamoyl radical cyclization.[6] Main pathway of the cyclization would be proposed as follows. Thiyl radical, formed by the photochemical dissociation of diphenyl disulfide, attacks a double bond of either acryloyl or allyl group depending on the type of double bond to form the cyclized intermediate (**A**) or (**B**) which is then trapped by phenylthio radical or hydrogen radical[7] depending on the presence or absence of thiophenol to give the 3,4-disubstituted lactams.



This newly found radical cyclization was also extended to ω-vinylalkylamides (**1e-h**). The butenylamide (**1e**) gave the 4-methylpiperidinone (**3**)[5] in 87% yield (*cis*:*trans*=6:1) by method B and *cis*-lactam (**3**) in 31% yield by method A. The cyclization of the pentenylamide (**1f**) proceeded in an 8-*endo*-trig manner to give the eight-membered lactam (**4**) and the adduct



(**5a**)[5] in 10-19 and 23-26% yields respectively. The hexenyl- and octenylamides (**1g, h**) underwent no cyclization and gave only adducts (**5b, c**)[5] in 38-63% yield. The phenylthiomethyllactams prepared in this work are attractive precursors for various substituted heterocycles which would be readily prepared by functionalization at phenylthio group.

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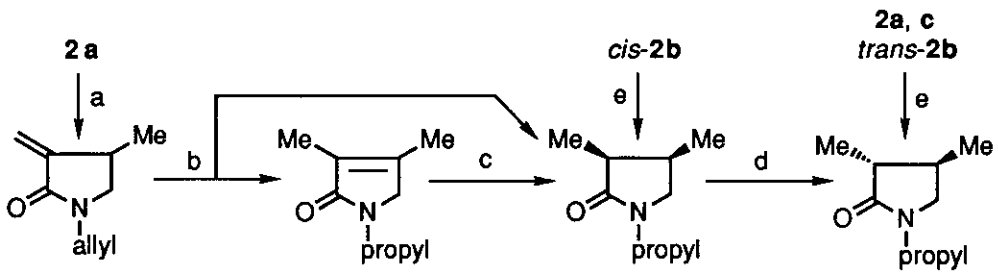
5. Ratios and structures of the stereoisomeric lactams (**2d-f**), (**2i**), and (**3**) and the adducts (**5a-c**) were established by their nmr spectra. In the lactams (**2g, h**), irreversible isomerization[6] of *cis*-lactam to *trans*-isomer by treatment with sodium ethoxide in ethanol established their stereochemistries. Lactams (**2a-c**) were unambiguously converted into the authentic 3,4-dimethyllactams as follows.



a) i) OXONE® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) ii) Δ; b) H_2 (1 atm) - PtO_2; c) H_2 (5 atm) - PtO_2; d) NaOEt, EtOH; e) Raney Ni (W-2)

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