REDUCTIVE PHOTOCYCLIZATION OF α -METHYLTHIO- AND α -ARYLTHIOENAMIDES

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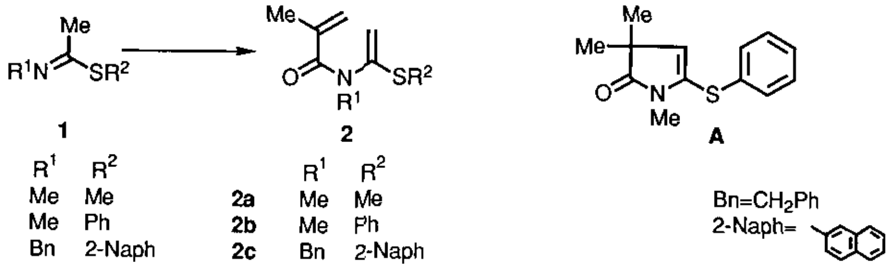
Abstract—Reductive photocyclization of α -methylthio- and α -arylthioenamides (**2a**-**c**) gave six-membered lactams (**3a**-**d**) and five-membered lactams (**4a**,**b**).

Enamide photocyclization[1] has been established as one of the most useful cyclization reactions for constructing six-membered lactams from the readily available enamides. Particularly, reductive photocyclization[2] of enamide in the presence of a hydride reagent has provided a promising and potentially versatile approach to the formation of six-membered lactams possessing a wide variety of functionality. As an extension of our research on reductive photocyclization of enamide, we have investigated the photochemical reaction of the α -methylthio- and α -arylthioenamides (**2a-c**) in the presence of sodium borohydride and found that these enamides undergo reductive photocyclization to give not only six-membered lactams but also five-membered lactams. Phenylthio- and 2-naphthylthioimidates (**1b**,**c**) were readily prepared from the known[3] methylthioimidate (**1a**) by treatment with either thiophenol or 2-naphthalenethiol. Acylation of three thioimidates (**1a-c**) with methacryloyl chloride gave three types of enamides (**2a-c**) in 75-85% yield. Irradiation of the methylthioenamide (**2a**) with a high pressure mercury lamp through a Pyrex filter in the presence of sodium borohydride in acetonitrile-methanol (9:1) gave many products which were carefully separated by column chromatography to give two cyclized products (**3a**)[4] and (**3b**)[5] in 48 and 8% yields respectively.

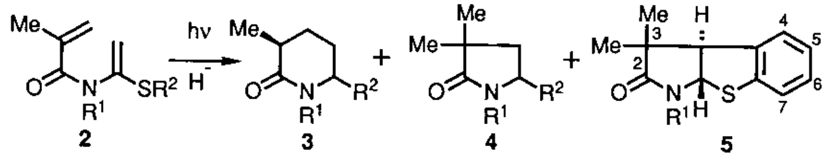
Both lactams (**3a,b**) are the expected six-membered lactams and their stereochemistries were deduced from their spectral data.[4,5] Reductive photocyclization of the phenylthioenamide (**2b**) afforded three products (**3c**),[6] (**4a**),[7] and (**5**)[8] in 6, 20, and 9% yields respectively. The product (**3c**) is an expected six-membered lactam while the product (**4a**) was found to be a five-membered lactam based on the analysis of their spectral data.[7] Analysis of the spectral data[8] of the product (**5**) established its structure as a tricyclic product which would be formed by the double cyclization (Domino cyclization) of the α-phenylthioenamide (**2b**) via an intermediary phenyl vinyl sulfide (**A**)[9] which would be formed in situ by the cyclization of the enamide (**2b**). Very interestingly, reductive photocyclization of the (2-naphthylthio)enamide (**2c**) proceeded smoothly to give two lactams (**3d**)[10] and (**4b**)[11] in 7 and 46% yields respectively, both of which have no naphthylthio group. Desulfurization reaction of the lactams (**3a-c**) and (**4a**) by treatment with tributyltin hydride in the presence of 2,2'-azobisisobutyronitrile gave the known lactams, 1,3-dimethyl-2-piperidinone[12] and 1,3,3-trimethyl-2-pyrrolidinone[13] respectively. Since all these lactams (**3-5**) were not formed under non-photochemical condition (with exclusion of light) or in the absence of sodium borohydride, the above finding provided a new photochemical cyclization of enamide which affords not only six-membered lactam but also five-membered lactam depending upon the substituent at the α-position of the enamide. The newly found reductive photocyclization of the (2-naphthylthio)enamide giving the pyrrolidinone derivatives has been successfully applied to a facile synthesis of 2-azaspiro[4.4]nonane derivative which is a skeleton existing in polyzonimine.[14,15] Reductive photocyclization of the enamide (**6**), prepared from the imidate (**1c**) and cyclopentene-1-carbonyl chloride, gave the spiro compound (**7**)[16] and the six-membered lactam (**8**)[17] in 21 and 13% yields respectively. This new aspect of reductive photocyclization of the α-arylthioenamide would provide a potential method for the construction of the five-membered lactams. Investigation for the reaction mechanism and further application have now been extensively continued.



1 **2** **A**

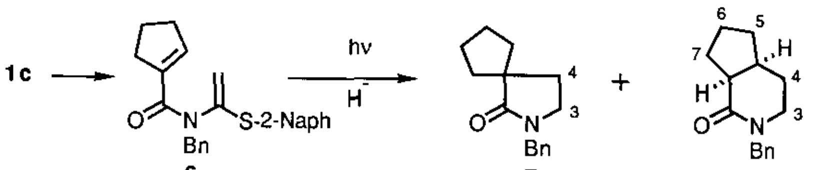
	R^1	R^2
1a	Me	Me
1b	Me	Ph
1c	Bn	2-Naph

	R^1	R^2
2a	Me	Me
2b	Me	Ph
2c	Bn	2-Naph



2 **3** **4** **5**

Entry	**2**	R^1	R^2	**3**	R^1	R^2	(%)	**4**	R^1	R^2	(%)	**5**	R^1	(%)
1	**2a**	Me	Me	**3a**	Me	—SMe	(48)							
				3b	Me	···SMe	(8)							
2	**2b**	Me	Ph	**3c**	Me	SPh	(6)	**4a**	Me	SPh	(20)	**5**	Me	(9)
3	**2c**	Bn	2-Naph	**3d**	Bn	H	(7)	**4b**	Bn	H	(46)			



6 **7** **8**

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3. B. Zeeh and H. Kiefer, Liebigs Ann. Chem., **1975**, 1984.
4. **3a**:colorless oil; ν 1630 cm^{-1}; m/z 173 (M$^+$); δ (500 MHz) 4.38 (ddd, J=4, 3, 1 Hz, 6-Heq), 2.37 (ddq, J=11, 8, 7 Hz, 3-Hax), 1.96 (tdd, J=13, 11, 4 Hz, 4-Hax), 1.24 (d, J=7 Hz, 3-Me).
5. **3b**:colorless oil; ν 1632 cm^{-1}; m/z 173 (M$^+$); δ (500 MHz) 4.38 (t, J=5.5 Hz,

6-Heq), 2.45 (br sextet, J=7 Hz, 3-Heq), 2.17 (dddd, J=14, 9, 7, 3 Hz, 4-Hax), 1.24 (d, J=7 Hz, 3-Me).

6. **3c**:pale yellow oil; ν 1632 cm^{-1}; m/z 235 (M^+); δ (200 MHz) 4.75 (t-like, J=3.5 Hz, 6-Heq), 2.37 (ddq, J=10, 8, 7 Hz, 3-Hax), 1.22 (d, J=7 Hz, 3-Me).
7. **4a**:pale yellow oil; ν 1678 cm^{-1}; m/z 235 (M^+); δ (200 MHz) 4.84 (dd, J=8, 5 Hz, 5-H), 2.37 (dd, J=14, 8 Hz, 4-H), 2.02 (dd, J=14, 5 Hz, 4-H), 1.14, 0.98 (each s, 3-Me× 2).
8. **5**:pale yellow oil; ν 1702 cm^{-1}; m/z 233 (M^+); δ (200 MHz) 4.87 (d, J=12 Hz, 8a-H), 3.38 (br d, J=12 Hz, 3a-H), 2.98 (s, NMe), 1.52, 1.18 (each s, 3-Me × 2). The nuclear Overhauser effect spectroscopy (NOESY) spectrum of **5** showed cross peaks due to the NOE between 3α -methyl and 3a-H and 3β -methyl and 8a-H, indicating the stereochemistry as trans.
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10. M. Mori, Y. Washioka, T. Urayama, K. Yoshiura, K. Chiba, and Y. Ban, J. Org. Chem., 1983, **48**, 4058. **3d**:colorless oil; ν 1622 cm^{-1}; m/z 203 (M^+); δ (200 MHz) 2.52 (br sextet, J=7 Hz, 3-H), 1.33 (d, J=7 Hz, 3-Me).
11. **4b**:colorless oil; ν 1674 cm^{-1}; m/z 203 (M^+); δ (200 MHz) 3.14 (t, J=7 Hz, 5-H_2), 1.84 (t, J=7 Hz, 4-H_2), 1.18 (s, Me× 2).
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13. P. Hullot, Th. Cuvigny, M. Larcheveque, and H. Normant, Can. J. Chem., 1976, **54**, 1098.
14. J. Meinwald, J. Smolanoff, A. T. McPhail, R. W. Miller, T. Eisner, and K. Hicks, Tetrahedron Lett., **1975**, 2367 and cited references.
15. T. Sugahara, Y. Komatsu, and S. Takano, J. Chem. Soc., Chem. Commun., **1984**, 214.
16. **7**:pale yellow oil; ν 1670 cm^{-1}; m/z 229 (M^+); δ (200 MHz) 4.50 (s, $NC\underline{H}_2Ph$), 3.17 (t, J=7 Hz, 3-H_2), 1.89 (t, J=7 Hz, 4-H_2).
17. **8**:pale yellow oil; ν 1620 cm^{-1}; m/z 229 (M^+); δ (200 MHz) 4.74, 4.54 (ABq, J=14 Hz, $NC\underline{H}_2Ph$), 3.20 (t-like, J=7 Hz, 3-H_2), 2.80 (q, J=8 Hz, 7a-H).

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