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A ONE STEP SYNTHESIS OF FUNCTIONALIZED LACTAMS AND SPIROLACTAMS FROM UNSATURATED β-KETOAMIDES

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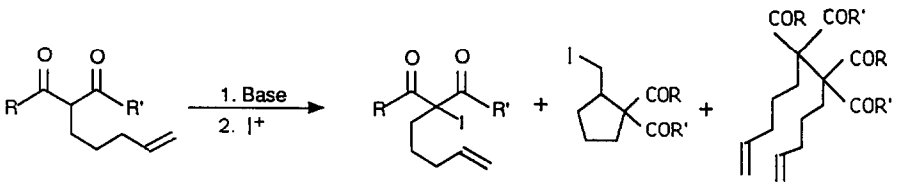
Summary : Treatment of N,N-diallyl and N-alkyl, N-propargyl-β-ketoamides with NaH and then with N-iodosuccinimide led to the formation of iodomethyl- and iodomethylene-β-ketolactams.

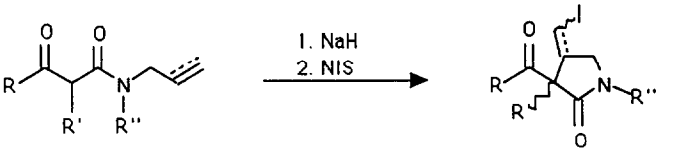
When 2-(pent-4-en-1-yl)-1,3-dicarbonyl compounds 1a and 1b are treated successively by potassium hydride and N-iodosuccinimide α-iododicarbonyl compounds 2a[1] and 2b[2] are obtained in good yields. Recently, it has been pointed out that when the unsaturated malonate 1b is treated by LDA or sodium hydride followed by addition of molecular iodide, the α-iodomalonate derivative 2b was not found, but a mixture of the cyclized compound 3b and of the coupling product 4b was isolated[2].



1
R=R'= alkyl
R=R'= OMe

2a
2b
3b
4b

This result urged us to report our preliminary investigations on a similar reaction involving the cyclization of unsaturated β-ketoamides into lactams and spirolactams. The reaction presented in the table is general and highly selective.

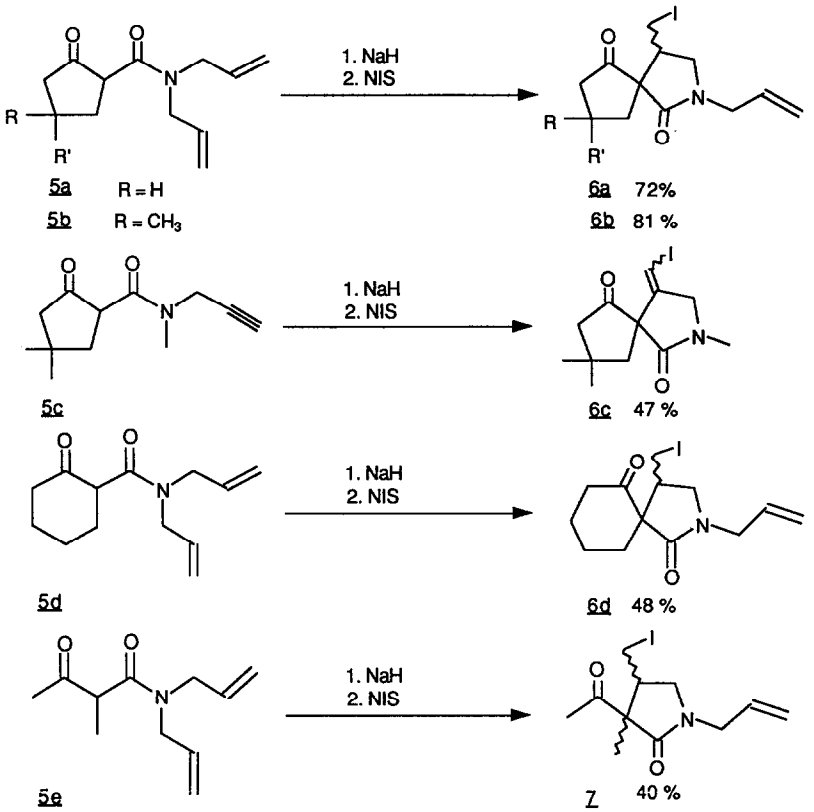


A solution of β-ketoamide[3] (1.45 mmol, 1 eq) in THF (3 ml) was added to a suspension of NaH (1.3 mmol, 0.9 eq) in THF (3 ml) at 20°C. The solution was stirred for one hour and then cooled to -78°C. NIS (1.59 mmol, 1.1eq) dissolved in THF (6 ml) was added and the reaction mixture stirred at -78°C for one hour. After filtration on celite, the solvent was evaporated under reduced pressure and the residue purified by preparative TLC (AcOEt/Hexane).

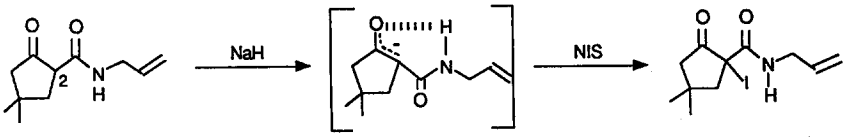
The N,N-diallyl-β-ketoamides 5a and 5b gave the corresponding spirolactams 6a and 6b in good yields. Treatment of N-methyl, N-propargyl-β-ketoamides 5c under the same conditions led to a mixture of Z and E iodomethylene spirolactams 6c, the only observable reaction products. 6a, 6b and 6c are azaspiro|4.4|nonane derivatives. Similarly the azaspsiro|5.4|decane derivative 6d was obtained with high 5-exo selectivity from the cyclohexane derivative 5d. The acyclic β-ketoamide 5e also gave the corresponding lactam 7 in moderate yield. The structures of 6a-6d and 7 were given by their elemental analysis and spectral data[4].

At this stage of our investigations, it is too early to discuss the possible mechanism of the cyclization reactions reported here. Nevertheless, it should be mentionned that attempts to quench radical intermediates with hydroquinone did not change the course of the reaction.

Table : Synthesis of spirolactams 6 and lactam 7



The N-alkyl-β-ketoamide 8 gave the α-iodo-β-ketoamide 9 (isolated in 31% yield). No trace of the spirolactam could be detected in the crude reaction mixture. This result can be interpreted in terms of intramolecular hydrogen bonding between the N-H and the enolate as shown in 8'. Under these conditions, the allylic double bond cannot approach the C-2 carbon and the formation of the α-iodo compound 9 is then favoured over the cyclized product.



8 8' 9 31%

The results reported here establish an efficient one step synthesis of lactam and spirolactams from β-ketoamides. It can certainly be considered as an alternative to the other method already reported for the synthesis of these systems[5].

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References

1. J. Cossy, A. Thellend, unpublished results. 2. D.P. Curran, C.T. Chang, J. Org. Chem., 1989, 54, 3140. 3. a) J. Cossy, D. Belotti, A. Thellend, J.P. Pete, Synthesis, 1988, p. 720. b) J. Cossy, A. Thellend, Synthesis, 1989, p. 753. 4. All the products were fully characterized and their analytical spectroscopic data will be reported in a forthcoming full paper. 5. J. Cossy, C. Leblanc, Tetrahedron Lett., 1989, 30, 4531.

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