Novel Syntheses of 3-Methylene-azetidin-2-one Derivatives and Related Systems

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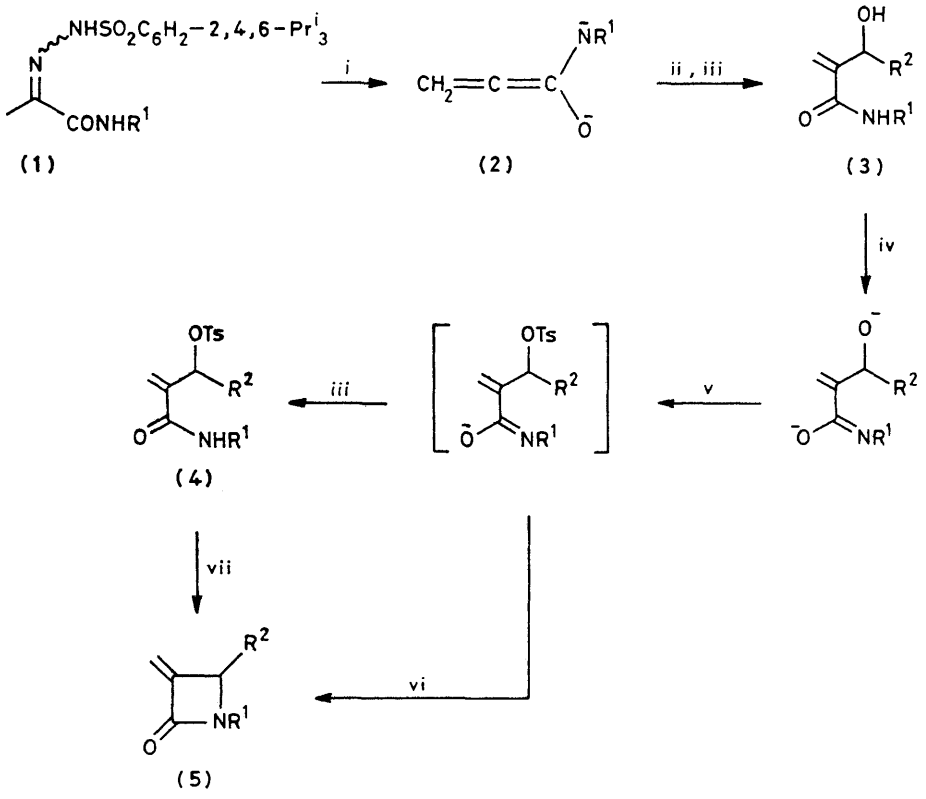
Summary Syntheses of the title compounds *via* 1-lithio-oxy-1-lithio-amino-allene derivatives or lithium phenylethynolate are described.

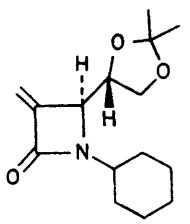
1-LITHIO-OXY-1-LITHIO-AMINO-ALLENE derivatives (**2**) have been conveniently prepared by the reaction of secondary α-keto-amide 2,4,6-tri-isopropylbenzenesulphonylhydrazones (**1**) with an excess of n-butyl-lithium.[1] These dianions were found to react with aldehydes to give the substituted acrylamides (**3**). Herein we report the one-step conversion of such amides (**3**) into 3-methylene-azetidin-2-one derivatives[2] (**5**), (**6**), and (**7**). Such β-lactams are relevant to the synthesis of carbabicyclic antibacterials.

Reaction of the acrylamides (**3**) with 2 equiv. of n-butyl-lithium followed by toluene-4-sulphonyl chloride (TsCl) in tetrahydrofuran (THF) or 1,2-dimethoxyethane (DME) gave the β-lactams (**5**), (**6**), and (**7**) in good yields (Table and Scheme 1). The intermediate toluene-4-sulphonates (**4**) were isolated in some cases after brief reaction; these could be cyclised using sodium hydride. Since α-keto-amides are readily available from isonitriles,[3] α-keto-acyl chlorides,[4] oxamide esters,[5] *etc.*, this synthesis of α-methylene-β-lactams is highly versatile.

Herein, we also report that the β-lactams (**10**) are available from the reaction of an electron-deficient imine with lithium phenylethynolate (**8**) in a novel anionic cyclisa-



SCHEME 1. *Reagents and conditions:* i, Bu^{n}Li (3·2—3·4 equiv.), −78 °C; 25 °C in DME; ii, R^{2}CHO, −78 °C; 25 °C; iii, H_2O; iv, Bu^{n}Li (2 equiv.), THF, −78 °C; v, TsCl (1 equiv.), −78 °C; 25 °C, 10 min; vi, 25 °C, 15 h; vii, NaH, THF, 25 °C.



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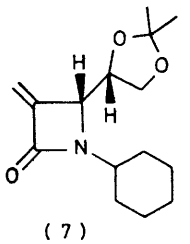

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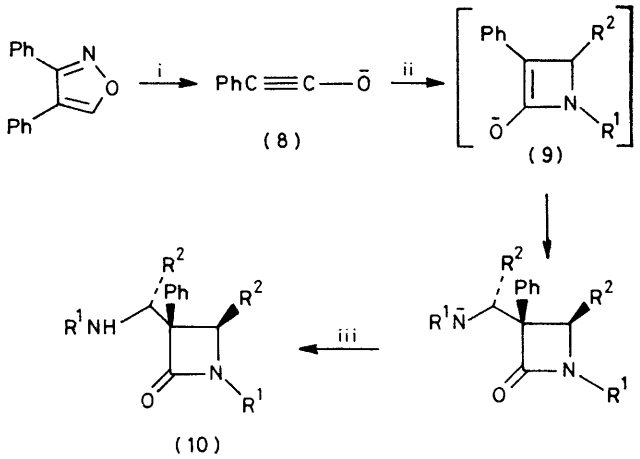
TABLE. Preparation of β-lactams (**5**), (**6**), (**7**), and (**10**).

Product[a]	R^1	R^2	Yield (%)
(**5**)	Cyclohexyl	H	60
(**5**)	"	Me	64
(**5**)	"	Et	68
(**5**)	"	Pr^n	54
(**5**)	"	$n\text{-}C_7H_{15}$	57
(**5**)	$PhCH_2$	Me	51
(**5**)	"	Et	60
(**6**)	—	—	65[b]
(**7**)	—	—	19[b,c]
(**10**)	$C_6H_4\text{-}4\text{-}NO_2$	Ph	66
(**10**)	"	$C_6H_4\text{-}4\text{-}NO_2$	89
(**10**)	"	$C_6H_4\text{-}3\text{-}Me$	58
(**10**)	$C_6H_4\text{-}4\text{-}CO_2Et$	$C_6H_4\text{-}4\text{-}NO_2$	79

[a] All new products were fully characterised by microanalyses and spectral data. [β-Lactams (**5**; $R^1 = PhCH_2$) were not obtained microanalytically pure but exhibited the correct high resolution $M^{+\cdot}$ in the mass spectrometer.] The acrylamides (**3**) were prepared as described elsewhere[1] or by identical routes. R^1,R^2,%: cyclohexyl, Me, 74; cyclohexyl, Pr^n, 83; cyclohexyl, $n\text{-}C_7H_{15}$, 70; $PhCH_2$, Me, 57; $PhCH_2$, Et, 58. [b] β-Lactams (**6**) and (**7**) were prepared using 2,2-dimethyl-(4*R*)-formyl-1,3-dioxolan. Product (**6**) was obtained from the major diastereoisomer of (**3**); (**7**) from the minor. The assignment of stereochemistry is tentative but reasonable since 2,2-dimethyl-(4*R*)-formyl-1,3-dioxolan is *erythro*-selective (ref. 8) with simple carbanions. The intermediate toluene-4-sulphonates (**4**) corresponding to the β-lactams (**6**) and (**7**) exhibited characteristic signals in the n.m.r. spectra, respectively at δ 5·25 (1H, d, *J* 7 Hz) and 5·20 (1H, d, *J* 6 Hz) for the C*H*–OTs protons. [c] β-Lactam prepared by the cyclisation of the isolated toluene-4-sulphonate using sodium hydride; the yield is based on the starting acrylamide.

tion. Using Schöllkopf's procedure,[6] 3,4-diphenylisoxazole[7] was metallated giving the ynolate (**8**). This, as a royal blue solution in THF, reacted with the imines $R^1N{=}CHR^2$ to give the β-lactams (**10**) (Scheme 2, Table). The reaction was highly stereoselective. Tentatively, we assign the stereochemistry based on chelation and steric approach control. The presumed intermediate (**9**) could not be intercepted with an aldehyde.



SCHEME 2. *Reagents and conditions:* i, Bu^nLi, THF, −78 to −60 °C; ii, $R^1N{=}CHR^2$ (1 equiv.), THF, −78 to −50 °C; iii, HOAc (1 equiv.), −50 °C.

Clearly, the anionic reagents (**2**) and (**8**) provide routes to usefully functionalised β-lactam systems.

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