A New Method for the Carbon-extension Reactions of Azetidin-2-ones at the 4-Position

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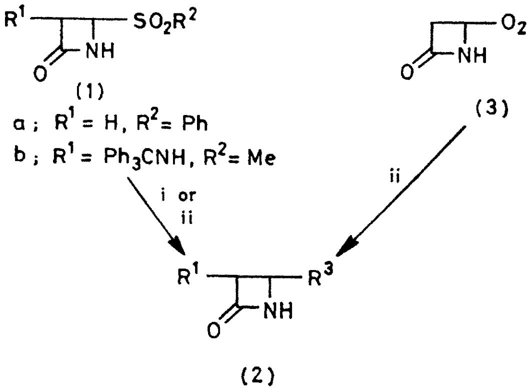
Summary High yields of 4-alkyl-, 4-allyl-, 4-vinyl-, or 4-ethynyl-azetidin-2-ones are obtained by treating 4-sulphonylazetidin-2-ones with either lithium organocuprates or Grignard reagents, but yields from 4-acetoxyazetidin-2-one with Grignard reagents are low

MUCH attention has been focused on carbon–carbon bond formation at the 4-position of azetidin-2-ones since the structures of thienamycin,[1] olivanic acid,[2] and PS-5[3] (containing a 1-carbapenem skeleton) have been elucidated There have been a few reports[4] on carbon-extension reactions at the 4-position of azetidinones, however, there are limitations on the functionalities the extending unit may contain We report here highly efficient and versatile methods for the introduction of a carbon–carbon bond at the position adjacent to the nitrogen atom in β-lactams

Treatment of 4-phenylsulphonylazetidin-2-one (**1a**) with di-n-butyl-copper-lithium in tetrahydrofuran (THF) at

—78 °C for 10 min and then 0 °C for 1·5 h gave 4-n-butylazetidin-2-one (**2a**) in 94% yield; the same product (**2a**) was also obtained from the reaction of 4-acetoxyazetidin-2-one (**3**) with di-n-butyl-copper-lithium in 89% yield. In contrast with the lithium organocuprate, Grignard reagents showed considerable differences in the reactions with (**1a**) and (**3**). Thus 4-ethylazetidin-2-one (**2b**) was obtained in 74·2% yield by the treatment of (**1a**) with ethylmagnesium bromide in THF at —78 °C for 10 min, 0 °C for 30 min, and finally at room temperature for 30 min, whereas the same reaction starting from (**3**) gave (**2b**) in only 12·4% yield. Analogously, 4-vinyl, 4-allyl- and 4-ethynyl-azetidin-2-one derivatives were synthesized by treatment with the corresponding Grignard reagents or organocuprates (Table). When the starting azetidin-2-one has a substituent at the 3-position, such as the tritylamino-β-lactam (**1b**), both *trans*-(**2g**) (52·2% yield) and *cis*-(**2g**) (22·3%) were obtained on treatment with phenylethynylmagnesium bromide in THF at —30 °C for 30 min and at room temperature for 1 h.†

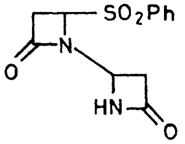


(**2a**); R^1 = H, R^3 = Bu^n
(**2b**); R^1 = H, R^3 = Et
(**2c**); R^1 = H, R^3 = $CH{=}CH_2$
(**2d**); R^1 = H, R^3 = $CH_2CH{=}CH_2$
(**2e**); R^1 = H, R^3 = $C{\equiv}COEt$
(**2f**); R^1 = H, R^3 = $C{\equiv}CSPh$
(**2g**); R^1 = Ph_3CNH, R^3 = $C{\equiv}CPh$

Reagents: i, R^3MgX; ii, $LiCu(R^3)_2$

TABLE. Reactions of 4-phenylsulphonyl- and 4-acetoxyazetidin-2-one with organometallic reagents.

Product	Reagent	Yield from (**1a**) (%)	Yield from (**3**) (%)
(**2a**)	$LiCu(Bu^n)_2$	94·0	89·0
(**2b**)	EtMgBr	74·2	12·4
(**2c**)	$H_2C{=}CHMgBr$	65·5	3·5
(**2d**)	$LiCu(CH_2CH{=}CH_2)_2$	100·0	—
(**2d**)	$H_2C{=}CHCH_2MgCl$	54·9	—
(**2e**)	$EtOC{\equiv}CMgBr$	95·4	—
(**2f**)	$PhSC{\equiv}CMgBr$	68·9	—



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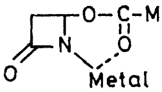

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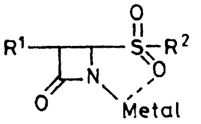

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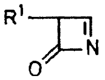

(7)

One exceptional reaction was observed; the reaction of (**1a**) with the Grignard reagent of t-butyl acetate ($BrMgCH_2CO_2Bu^t$)[5] furnished the bisazetidinone (**4**) in 51·7% yield without the desired product. The reactions described here strongly suggest a 1,4-addition of the organometallic reagents to the intermediate azetinone (**7**), derived from 5-membered (**6**) or 6-membered (**5**) co-ordination compounds.

(*Received*, 6*th May* 1980; *Com*. 467.)

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† In the case of 3-(substituted)alkyl-4-phenylsulphonylazetidin-2-one, only the *trans*-isomer was obtained by treatment with a Grignard reagent or a modified Grignard reagent with a catalytic amount of CuBr. Moreover, the above reaction should be carried out using 4-arylsulphonylazetidin-2-ones instead of the 4-alkylsulphonyl derivatives, otherwise low yields are obtained: these results will be reported elsewhere.

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