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A Practical Alternative to Sulfonyl Activation of Aziridines: Ring-Opening of N-Diphenylphosphinoyl Aziridines by Carbon Nucleophiles

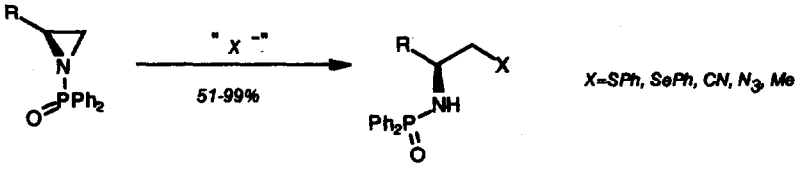
Helen M.I. Osborn and J.B. Sweeney,*
University of Bristol, School of Chemistry, Cantock's Close, Bristol BS8 1TS UK

and

William Howson,
Parke-Davis Neuroscience Research Centre, Addenbrookes Hospital Site, Hills Road, Cambridge CB2 2QB UK

Abstract: *The ring-opening reaction of N-diphenylphosphinoylaziridines by Copper (I)-modified Grignard reagents proceeds in good to excellent yield and with complete regiospecificity.*

The utility of aziridines as β-amino cation equivalents is well-known. We recently reported the first ring-opening reactions of dithiane anions with N-tosyl aziridines[1] and subsequently extended those studies to address the problems of deprotection inherent in tosyl aziridine chemistry. Thus, we described the first preparation of N-phosphinoylated[2] aziridines and described the preliminary results of our investigations into ring-opening reactions of these

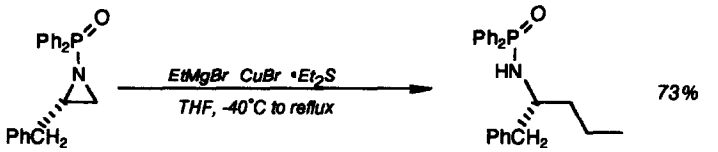


SCHEME 1

heterocycles.[3] Heteroatom-centred nucleophiles effected ring-opening of these aziridines in good yield with regiospecificity (scheme 1), but the reaction of carbon-centred nucleophiles was not as productive. Cyanide ion and dimethylcopper lithium were the only reagents found to be useful for ring-opening reactions of N-phosphinoyl aziridines; other organocopper reagents (both lower and higher order) and organolithium reagents reacted *via* preferential attack at phosphorous to give diarylalkylphosphine oxides in good to excellent yield. Under a variety of conditions, including

simple copper (I) catalysis, Grignard reagents were unreactive. These observations prompted us to eliminate copper catalysis from our studies and given that the use of Lewis acids to enhance the favourability of ring-opening at the expense of phosphoryl transfer was not successful, we anticipated that the reaction was limited to the examples described earlier.[1] Given the ease of deprotection of the N-diphenylphosphinoyl (Dpp) group[2,3] when compared to the difficulties encountered in cleaving sulfonamide bonds, this was a significant limitation to the process. We have very recently discovered that the presence of diethylsulfide empowers copper mediation of the reactions of Grignard reagents with N-Dpp-aziridines and allows ring-opening by carbon nucleophiles to proceed in good yield and with regiospecificity, thus making the method the first realistic alternative to tosyl activation of aziridines.

When ethylmagnesium bromide is added to a stirred THF suspension of (2*S*)-N-diphenylphosphinoyl-2-phenylmethylaziridine (**1**) and copper (I) bromide-diethylsulfide complex at -40°C, a deep yellow colour is generated. Upon warming to room temperature and then heating at reflux a black suspension is formed and ring-opening takes place: (2*S*)-N-diphenylphosphinoyl-2-amino-1-phenylpentane (**2**) is produced in 73% yield (after chromatographic purification) as the only product of the reaction (scheme 2). No trace of regioisomeric product of ring-opening is observed and, equally importantly, no dephosphinoylation is observed.



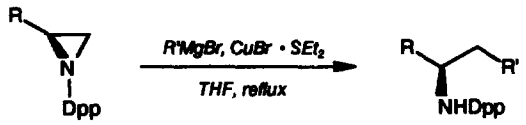
(1) (2)

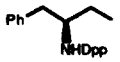
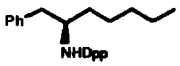
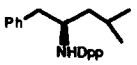
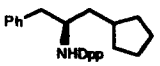
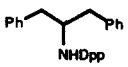
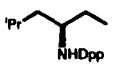
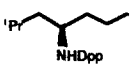
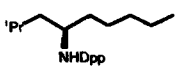
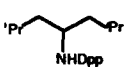
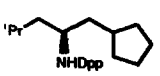
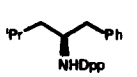
SCHEME 2

The reaction is of general utility, as shown in the table.[4,5] Primary and secondary Grignard reagents are suitable nucleophiles and there is no trace of products arising from reductive ring-opening of aziridine, often a side-reaction in the reaction of such organometallics with N-tosyl aziridines.[6] The reaction of methylmagnesium iodide under these conditions is, however, unproductive. Using a range of copper (I) salts, the process either delivers starting material or the ring-opened product arising from nucleophilic attack by iodide. Fortunately, this is not a drawback to the utility of these aziridines, due to the regiospecificity and good yield of the ring-opening reaction with dimethylcopperlithium, as previously reported.[3]

Having demonstrated the utility of phosphinyl activation in ring-opening of unfunctionalized aziridines, we then sought to extend the reactions to encompass ring-opening of 2-carboalkoxyaziridines derived from serine. Thus, aziridine (**3**) was prepared from N-trityl-2-methoxycarbonylaziridine in two steps. When (**3**) was reacted with Grignards under the conditions previously employed, however, we did not observe ring-opening reaction (scheme 3).

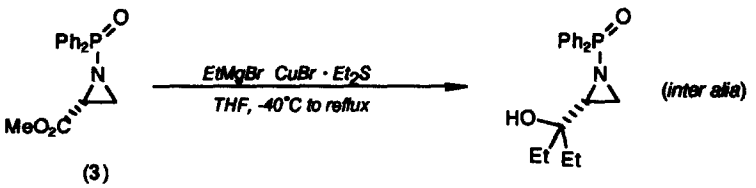
TABLE - RING-OPENING OF DPP AZIRIDINES BY GRIGNARD REAGENTS



R	R'	Product[a]	Yield[5]
$PhCH_2$	Me		67%
$PhCH_2$	Et		73%
$PhCH_2$	^{n}Bu		89%
$PhCH_2$	^{i}Pr		88%
$PhCH_2$	$^{c}C_5H_9$		53%
$PhCH_2$	Ph		83%
Me_2CHCH_2	Me		73%
Me_2CHCH_2	Et		80%
Me_2CHCH_2	^{n}Bu		76%
Me_2CHCH_2	^{i}Pr		84%
Me_2CHCH_2	$^{c}C_5H_9$		84%
Me_2CHCH_2	Ph		86%

[a]Dpp = diphenylphosphinoyl

Several products were isolated from these reactions and the major components of these low-yielding reactions were compounds arising from attack at the ester, again a commonly observed side-reaction in attempted ring-openings of similar aziridines.[6] The use of more sterically demanding esters did not encourage successful ring-opening. We are presently attempting to overcome these serious limitations in our laboratories



(3)

SCHEME 3

Acknowledgement

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1. Howson, W.; Osborn, H.M.I.; Sweeney, J.B.; *SynLett*, **1993**, 675
2. Kenner, G. W.; Moore, G. A.; Ramage, R;. *Tetrahedron Letters*, **1976**, 3623; Ramage, R.; Hopton, D.; Parrott, M. J.; *J. Chem. Soc., Perkin Trans I*, **1984**, 1357.
3. Howson, W.; Osborn, H.M.I.; Sweeney, J.B.; *SynLett*, **1993**, in press
4. Representative procedure for ring-opening of N-diphenylphosphinoyl aziridines with Grignard reagents: To CuBr.Et_2S (2 mol%), under N_2, at room temperature was added a solution of N-Dpp aziridine in THF (typically 0.3 mmol in 5 ml THF). The solution was then cooled to -40°C and a solution of Grignard reagent (5 equivalents) in THF added dropwise. The solution was warmed to room temperature over 10 minutes and then heated under reflux until tlc indicated the reaction to have gone to completion (typically 4 hours). The reaction was then quenched by the addition of a saturated aqueous solution of NH_4Cl (5 ml), and the aqueous layer extracted with EtOAc (3 x 15 ml). The combined organic layers were washed with brine (10 ml), dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The crude products were purified by column chromatography using EtOAc as the eluting solvent.
5. All new compounds gave satisfactory analytical data (^1H, ^{13}C nmr, IR, m/z, combustion analysis {C, H and N}).
6. Baldwin, J.E.; Spivey, A.C.; Schofield, C.J.; Sweeney, J.B.; *Tetrahedron*, **1993**, *49*, 6309.

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