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An Unusual Dependency of Counterion During Wittig Methylenation of Bis-Heteroaryl Ketones¹

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Abstract: Attempted Wittig methylenation of some bis-heteroaromatic ketones (8, 11 and 13) using MeP⁺Ph₃Br⁻ and n-BuLi gave none of the desired olefin. However, when KtBuO was used as the base for generation of the ylide, efficient olefination of these ketones was observed. A possible mechanistic pathway for this interesting but unprecedented observation is proposed.

Recently, we reported the discovery of dihydrobenzo[b]quinolizinium cations (4) which are potent and selective N-methyl-D-aspartate (NMDA) antagonists.³ The general synthetic route to these compounds involved an inverse electron demand Diels-Alder reaction between the benzo[b]quinolizinium cation (3) and 1,1-diaryl ethylenes (2). The latter were prepared via Wittig methylenation⁴ of the corresponding ketones 1.



During the course of this investigation, we found that among the three bis-pyridyl ketones,⁵ only the 3,3' and 4,4' derivatives (compounds 5, 6) reacted readily with the ylide generated from MeP+Ph₃Br⁻ and *n*-BuLi to give the desired olefins 7a,b. Under identical conditions, the bis-2,2'-pyridyl ketone 8 gave none of olefin 7c.



A survey of the literature revealed that there are no reports of olefination of either ketone 5 or 6. But, there was one example of Wittig methylenation ketone 8.⁶ Interestingly, these authors have reported that olefination of 8 using MeP+Ph₃Br⁻ and PhLi led to very low yield of olefin 7c. They, however, found that treatment of 8 with the ylide generated from MeP+Ph₃Br⁻ and dimsyl anion (DMSO/NaH) at 80 °C gave the desired ethylene 7c in moderate yield. Although no explanation was offered by these researchers for this dichotomy, the results

reported here show that the presence of ortho nitrogens in $\mathbf{8}$ is playing a crucial role for this interesting but yetunprecedented observation. In order to better understand this anomaly, a detailed investigation of the Wittig methylenation of $\mathbf{8}$ and other bis-azole ketones (wherein the carbonyl group is attached to the carbon next to the nitrogen) was undertaken.

Due to the pioneering efforts of Vedejs,⁷ Schlosser,⁸ and Maryanoff,^{9,10} there is a better understanding of the mechanism of the Wittig reaction to-day. Although most of these studies have focused primarily on the stereo-chemical outcome of the reaction of unstabilized phosphorous ylides with aldehydes, they have given us unequivocal evidence which suggests that 1,2-oxaphosphetanes are the principal intermediates in various Wittig reactions. They have also reported that in presence of added salt (or salt that is formed during the generation of the ylide) such as LiBr, the oxaphosphetanes are converted to the betaine-lithium bromide adducts. If oxaphosphetane generation is absolutely necessary for the formation of olefins, then perturbing its formation via stabilization of the betaine-lithium halide complex should result in lower yield of the olefins. We believe that this is the scenario with ketone **8**. Since the initial reactions were carried out under conditions wherein an equimolar amount of LiBr is present, the dominant species after the reaction would be intermediate **10**. Such a chelated intermediate is plausibly formed via cleavage of the initially formed oxaphosphetane **9**¹¹ by LiBr with the aid of pyridyl chelation. Moreover, intermediate **10** might not convert back to the oxaphosphetane **9** readily, which could then lead to olefin **7c (Scheme 1)**. If this mechanistic hypothesis is correct, then changing the



counterion to one that is less likely to participate in the proposed formation of the chelate **10** should result in olefin **7c**. The results reported by Eckhard et al for the olefination of **8** using the ylide generated from MeP+Ph₃Br and dimsyl anion would argue in favor of this hypothesis. However, to overcome both the solvent and temperature effects in the reaction conditions reported by Eckhard, the olefination of **8** under milder conditions was attempted. Thus treatment of MeP+Ph₃Br with KtBuO in THF (0 °C, 1.5 h) followed by reaction of the resulting ylide with **8** gave >90% yield of olefin **7c** (Scheme 2).¹² These results support the mechanistic hypothesis proposed in Scheme **1**.

Having successfully demonstrated the validity of the rationale proposed in **Scheme 1**, the generality of this counterion dependency on the Wittig methylenation was studied using the isomeric bis-azole ketones 11-16.¹³ As the data in **Table 1** reveal, in every instance, wherein the carbonyl group is attached to the carbon next





to the nitrogen (compounds 11, 13 and 15) no olefination was observed when *n*-BuLi was used for generation of the ylide from MeP+Ph₃Br. However, moderate to good yields of the desired alkenes could be isolated when KtBuO was used as the base.

Table 1: Wittig Olefination of bis-heteroaromatic ketones 11-16

	O MeP⁺Ph ₃ Br⁻ / Base / THF		
Het	Het	Het	Het
· · · · · · · · · · · · · · · · · · ·		% Yield of Olefin ^b	
Ketone ^a	Het =	MeP+Ph3Br / n-BuLi	MeP+Ph3Br / KtBuO
11		0	70
12	N N PMB	60	c
13		<10	90
14	N. N. N. PMB	90	c
15	₹ ^N	d	d
16	N_	75	c

PMB = 4-Methoxybenzyl. ^aKetone 14 was prepared as described in reference 13. Ketones 11 and were prepared via a methodology similar to the one used for the preparation of 14. Ketones 13, 15 and 16 were prepared as described in reference 3. ^bAll olefination reactions were performed at 25 °C in THF at 0.1 M concentration. ^cOlefination under these conditions was not carried out. ^dKetone 15 decomposed readily under these reaction conditions and no trace of the olefin was observed.

During the course of the reaction of 11 with $CH_2=PPh_3$ (from MeP+Ph₃Br and *n*-BuLi) the fragmentation product 17 was isolated in 50% yield. Analysis of the crude reaction mixture from this reaction by FAB-MS clearly showed the presence of the mass ion for the β -keto phosphorane 18. These observations further validate



the contention that stabilization of the betaine-LiBr adduct via strong chelation (and hence prevention of equilibration to the oxaphosphetane) is responsible for the lack of formation of the desired olefins from ketones **8**, **11** and **13**. Studies are currently underway to further define the mechanistic rationale proposed in this paper.

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References and Notes:

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