Highly Efficient Darzens Reactions Mediated by Phosphazene Bases under Mild Conditions

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The highly basic and poorly nucleophilic phosphazene base P$_2$-t-Bu promotes the Darzens condensation of α-halo esters with aromatic aldehydes affording α,β-epoxy esters in nearly quantitative yields under mild conditions and in short reaction times. The more basic P$_2$-t-Bu phosphazene was found useful with low reactivity aldehydes. These reactions can be performed in aprotic organic solvents of low polarity, thus minimizing the hydrolysis of α,β-epoxy esters which often accompanies the base-promoted Darzens condensations.

Introduction

Polyaminophosphazenes are extremely strong, chemically and thermally stable, non-ionic Brønsted superbases with pK$_{B,H^+}$ values spanning the range from 27.6 to about 47 as determined or estimated in acetonitrile.[1–6] Besides their high basicity, the usefulness of phosphazene bases in producing highly reactive anions is due to the large size and charge delocalization of the phosphazenum ions, leading to weak cation–anion interactions.[7] In addition, the low nucleophilicity of phosphazene bases[1,3,4] and the high stability of phosphazenium cations enable smooth deprotonation processes from even very weakly acidic C–H bonds with limited side reactions.[8,9] Furthermore, the high solubility of polyaminophosphazenes in organic solvents such as hexane, toluene, DCM or THF allows conceiving the high solubility of phosphazene bases is experiencing a recent surge of interest and usefulness of phosphazene bases in producing highly reactive or catalysts in a variety of reactions requiring the formation of phospha-nucleophiles have been used as stoichiometric reagents and synthetic intermediates to construct complex organic frameworks.[20–23] The scope and synthetic significance of this reaction have enlarged as the result of the diversity of α-halo carbonyl compounds that can be used. Indeed, in addition to α-halo esters, α-halo amides,[24] α-halo nitriles[25a] and α-halo ketones[26] have been used as pro-nucleophiles. Furthermore, aza-Darzens reactions were developed using imines, sulfonimines or N-sulfonyl imines as electrophile components.[27] Other compounds with active methylene groups and bearing suitable leaving groups such as α-halosulfones[28] or ammonium[29] and sulfonium ylides[11a,13f,30] have also been successfully employed as pro-nucleophiles. Lewis and Brønsted acid-catalyzed Darzens reactions have also been reported for α-diazoamides and diazoesters.[31] Nowadays, in their base-promoted version, the Darzens reactions of α-halo esters with aromatic aldehydes are most commonly performed in the presence of anionic bases such as alkali metal hydroxides, carbonates or alkoxides,[32] sodium amide, LDA, LiHMDS or n-butyllithium,[33] very often with pre-formation of the reactive ester enolate anion. In the case of α-chloroketones and α-chloroamides, the use of phase transfer agents in association with aqueous metal hydroxides has now become a paradigm leading to α,β-epoxy carbonyl compounds in moderate-to-
excellent yields and stereoselectivity. However, with respect to \(\alpha,\beta\)-epoxy esters, their preparation by means of Darzens reactions remains far from ideal. Indeed, as far as \(\alpha\)-halo esters are concerned, hydrolysis of the trans epoxy esters has been reported, even in the case of tert-butyl esters. This reactivity has been invoked as a possible explanation for the low yields or the exclusive cis-selectivity observed in some cases. In addition, in the reactions promoted by metal alkoxides, the formation of unwanted side products such as \(\alpha\)-chlorocinnamate esters was reported and the formation of \(\alpha\)-chboro-\(\beta\)-lactones was even dominant in the case of the Darzens condensations involving phenyl esters of \(\alpha\)-chlorocarboxylic acids promoted by lithium \(N\)-cyclohexyl-\(N\)-isopropylamide.

We considered that the strength of phosphazene bases and their inertness as nucleophiles could offer some advantages in the development of a Darzens condensation in aprotic organic solvents of low polarity. Here, we describe the results so far obtained from exploring two phosphazene bases. Exploring a series of solvents and reaction conditions; the best conditions were then used to investigate the scope of the reaction, the role of the pro-nucleophile and the stereoselectivity of the process.

### Results and Discussion

To test the utility of phosphazene bases in Darzens reactions, we used the two readily available bases \(P_{1-t-Bu}\) I (\(pK_{w,s} = 26.89\)) and \(P_{t-Bu}\) II (\(pK_{w,s} = 42.7\)), as shown in Figure 1, for the condensation of methyl chloroacetate (1a) with 4-bromobenzaldehyde (2a) taken as model system (Table 1).

A preliminary solvent screening was performed considering acetonitrile, DCM, THF and toluene (Table 1); this identified acetonitrile (dielectric constant, \(\varepsilon = 37.5\)) as the optimal choice. Reaction in this solvent resulted in complete conversion of the starting materials within 6 h, affording 3aa in 92% isolated yield (Table 1, entry 1). In the numbering systems of the condensation products, the first letter refers to the \(\alpha\)-halo ester, while the second identifies the aldehyde. Lowering the reaction temperature to \(-25^\circ C\) had little impact on the outcome, and 3aa was obtained in 86% isolated yield after 10 h (Table 1, entry 2). Quite remarkably, the use of a significantly less polar solvent such as dichloromethane (\(\varepsilon = 8.93\)) provided similar results to that of acetonitrile in terms of yield although requiring a longer reaction time (Table 1, entry 3). The reactivity in DCM is also remarkable because this is a solvent usually not suitable for base-promoted Darzens reactions of \(\alpha\)-halo esters. THF, with a dielectric constant of 7.58, provided the desired epoxide 3aa in 83% yield in 24 h (Table 1, entry 4).

Given the long reaction time required using this solvent, the Darzens condensation was also performed with the stronger phosphazene base, \(P_{t-Bu}\) II, obtaining 3aa in 57% yield after 24 h (Table 1, entry 5). However, the use of \(P_{t-Bu}\) II instead of \(P_{t-Bu}\) I resulted in a relatively complex mixture with formation of unidentified byproducts likely because of the exceedingly high strength of this base. Using a solvent of even lower polarity such as toluene (\(\varepsilon = 2.38\)) gave impractically long reaction times and poor overall yield of the product (Table 1, entry 6).

In all cases, the cis and trans \(\alpha,\beta\)-epoxy esters were obtained in a ratio close to 1:1, in line with the high reactivity of the enolate anion obtained under these conditions. Not unexpectedly, other weaker organic bases such as Hünig’s base, a typical hindered tertiary amine, or Pronto Sponge\(^\text{®}\) with a \(pK_{w,s}\) of 18.62, did not result in conversion of the reagents. \(1,8\)-diazabicyclo[5.4.0]undec-7-ene (DBU), despite a \(pK_{w,s}\) of 24.34 measured in acetonitrile, very close to that of \(P_{1-t-Bu}\) I, acted as a nucleophile under these reaction conditions. Overall, the best conditions required the use of 1.5 equiv. of base I, dry acetonitrile as solvent and a 0.25 M concentration of reagents at a reaction temperature of \(25^\circ C\).

The scope of the reaction was assessed by considering a series of model aromatic aldehydes carrying different substituents at the para, meta or ortho position and methyl chloroacetate (1a) as the pro-nucleophile component (Table 2). Yields comparable to those obtained in the case of 2a were obtained with 4-chlorobenzaldehyde (2b) which gave the epoxy ester 3ab in 92% yield after 6 h, while the reaction of benzaldehyde (2c) was more sluggish, affording product 3ac in 83% yield only after 16 h. With 4-nitrobenzaldehyde (2d), the epoxide was obtained in 81% yield within one hour, while with aldehydes 2e and 2f, carrying the electron-donating 4-methyl and 4-methoxy groups, the \(\alpha,\beta\)-epoxy esters were obtained in 87%

| Entry | Base | Solvent | \(\varepsilon\) | Time [h]\(^\text{[b]}\) | Yield [%]\(^\text{[d,e]}\) | d.r.\(^\text{[d,e]}\) |
|-------|------|--------|-------------|-----------------|-----------------|--------------|
| 1     | I    | MeCN   | 37.5        | 6               | 92              | 1/0.9        |
| 2     | I    | MeCN   | 37.5        | 10              | 86              | 0.9/1        |
| 3     | I    | DCM    | 8.93        | 16              | 90              | 1/0.85       |
| 4     | I    | THF    | 7.58        | 24              | 83              | 1/0.94       |
| 5     | II   | THF    | 7.58        | 24              | 57              | 1/0.85       |
| 6     | I    | Toluene| 2.38        | 48              | 66              | 0.88/1       |

\([a]\) Unless otherwise stated, all Darzens reactions were carried out using 0.5 mmol of the aldehydes and a stoichiometry of 1.5:1:1.5 for 1a/2a/I or II in 2 mL of solvent at 25°C. \([b]\) Reaction time. \([c]\) Yield of isolated product after column chromatography. \([d]\) Average of two experiments. \([e]\) Determined by \(^1\)H NMR analysis of the crude reaction mixture. \([f]\) Reaction carried out at \(-25^\circ C\).
and 74% yield, respectively, albeit requiring a prolonged reaction time. The relatively low isolated yield of 3af arises from its reduced stability during chromatographic purification; indeed, using flash chromatography, variable amounts of the vicinal diols, formed by the opening of the epoxide ring, could be isolated. The 2-bromobenzaldehyde (2d) provided the desired epoxide 3ag in 84% yield with a d.r. of 1/1, suggesting that the steric hindrance at the ortho position did not affect the diastereoselectivity of the reaction. As expected on the basis of electronic effects, aldehyde 2h, with the methoxy group at the meta position, gave the desired product 3ah in a better yield (91%) and after a shorter reaction time with respect to aldehyde 2f. In none of the cases discussed above that involve the use of P$_2$-t-Bu I, the formation of unwanted byproducts could be observed from analysis of the crude reaction mixture. For 4-nitrobenzaldehyde (2d) and 4-methoxybenzaldehyde (2f) that are, respectively, the most and the least reactive aldehydes in the panel, the condensation reactions were also carried out by using the phosphazene base P$_2$-t-Bu II in THF at -10°C. In the former case, extensive decomposition occurred, while in the latter case, 82% yield of the product was achieved in 1 h (Table 2).

The sensitivity of the reaction yield and time on the nature of the halogen and/or alkoxy group carried by haloester 1 was assessed by using 4-bromobenzaldehyde (2a) in the presence of P$_2$-t-Bu L, considering methylbromoacetate (1b), tert-butylchloroacetate (1c) and tert-butylbromoacetate (1d) in addition to methylchloroacetate (1a) as the pro-nucleophile components.

As in the previous cases, reactions were performed in dry acetonitrile at 25°C (Table 3). Chloroesters provided faster reactions with respect to the corresponding bromoesters (Table 3, entry 1 vs. entry 2; entry 3 vs. entry 4), consistently with the expected higher acidity of the protons in the alpha position to the ester function of 1a with respect to those of 1b or those of 1c with respect to the alpha protons of 1d, and a rate-limiting deprotonation of the halo ester. The tert-butyl esters reacted at a slower rate with respect to the methyl esters (Table 3, entry 1 vs. entry 3; entry 2 vs. entry 4), and the introduction of the tert-butyl group only slightly affected the diastereoselectivity of the reaction. Overall, these data support a high reactivity of the “naked” enolate anions formed by deprotonation of esters 1a–1d which are only weakly associated with the phosphazene cations.

The low cis/trans selectivity observed in these reactions could be either the result of the high reactivity of the ester enolate anions or due to a base-catalyzed epimerization of the reaction products because of the high strength of P$_2$-t-Bu I and the acidity of the C–H proton in position 2 of epoxide 3 (Figure 2).

In order to characterize the system, we tested the diastereoisomeric stability of trans-epoxide 3ad in the presence of P$_2$-t-Bu I, Figure 2. For this study trans-epoxide 3ad with a cis/trans diastereoisomeric ratio of 1/10, obtained by reaction of 1a and 2d with cesium carbonate in acetonitrile, was co-dissolved with base II in acetonitrile at the same concentration used in the

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**Table 2. Darzens reactions of methyl chloroacetate (1a) with aromatic aldehydes 2a–2h in the presence of the phosphazene base P$_2$-t-Bu I.**

| Aldehyde | R     | Time [h] | Yield [%] | d.r. |
|----------|-------|----------|-----------|------|
| 2a       | p-Br  | 6        | 92        | 1/0.9|
| 2b       | p-Cl  | 6        | 92        | 1/0.9|
| 2c       | H     | 16       | 83        | 1/0.75|
| 2d       | p-NO$_2$ | 81  | 94        | 1/0.94|
| 2e       | p-Me  | 16       | 87        | 1/0.85|
| 2f       | p-OMe | 48       | 74        | 0.9/1|
| 2f$_1$   | p-OMe | 1       | 62        | 1/1  |
| 2g       | o-Br  | 6        | 84        | 1/1  |
| 2h       | m-OMe | 16       | 91        | 1/0.8|

[a] Yields of isolated products as the average of two experiments. [b] Determined by $^1$H NMR analysis of the crude reaction mixture. [c] Reaction performed at -10°C in THF on a 0.15 mmol scale using base II, single run.

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**Table 3. Darzens reaction of α-halo esters 1a–1d and 4-bromobenzaldehyde (2a) promoted by the phosphazene base P$_2$-t-Bu I.$^{[24]}$**

| Entry | α-halo ester | R, X | Time [h] | Yield [%] | d.r. |
|-------|--------------|------|----------|-----------|------|
| 1     | 1a           | Cl   | 6        | 92        | 1/0.9|
| 2     | 1b           | Br   | 16       | 85        | 1/0.9|
| 3     | 1c           | F    | 16       | 92        | 1/0.7|
| 4     | 1d           | Br   | 36       | 84        | 1/0.7|

[a] All Darzens reactions were carried out on a 0.5 mmol scale using a 1.5 : 1 : 1.5 1a–1d/2a/I molar ratio in 2 mL of acetonitrile at 25°C. [b] Reaction time. [c] Yield of isolated product after column chromatography. [d] Average of two experiments. [e] Determined by $^1$H NMR analysis of the crude reaction mixture.

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**Figure 2. Time course of the degradation of trans-epoxide 3ad in the presence of P$_2$-t-Bu I.**
Darzens reactions and, after given time intervals, the reaction mixture was analyzed by $^1$H NMR spectroscopy. This analysis showed that trans-epoxide $3\text{ad}$ does not undergo epimerization in four hours, which is four times larger than the time required for the synthesis of $3\text{ad}$ under the conditions reported in Table 2. The apparent increase in the cis/trans ratio observed at 16 h was thus due to the selective degradation to unidentified products of the trans-epoxide as evidenced by $^1$H NMR analyses.

**Conclusion**

In summary, the Darzens reactions of $\alpha$-halo acetate esters with aromatic aldehydes proceed smoothly in the presence of phosphazene bases, affording $\alpha,\beta$-epoxy esters without side products. Acetonitrile, DCM or THF are suitable solvents for these reactions, and reaction times are inversely correlated to the dielectric constants of the solvents. The experimental results suggest that base $\text{P}^+\text{t-Bu}^\text{I}$ should be preferred over base II when the reaction involves aromatic aldehydes carrying electron- withdrawing groups. In contrast, base II is more suited when the aldehydes carry electron-donating substituents. In all of the cases analyzed, and with a proper selection of the base, the reaction afforded $\alpha,\beta$-epoxy esters with a cis/trans ratio of 1 to 1 in nearly quantitative yields and with short reaction times. Moreover, the reaction work-up is straightforward.

**Experimental Section**

**General Information.** Unless otherwise noted, all reactions were performed in oven-dried or flame-dried glassware. All reactions were performed in dry solvents under a nitrogen atmosphere. Air-sensitive reagents and solutions were transferred via a syringe and were used to introduce the apparatus through rubber septa. All reagents were purchased from Sigma-Aldrich and used as received. Analytical thin layer chromatography (TLC) was performed on silica gel 60 RP-18F254S pre-coated plates with visualization under short-wavelength UV light and by dipping the plates with Pancaldi solution (ammonium molybdate HPLC grade and used as received. Analytical thin layer chromatography including cyclohexane and ethyl acetate were performed in dry solvents under a nitrogen atmosphere. Air-sensitive reagents and solutions were transferred via a syringe and were purchased from Sigma-Aldrich and used as received.

**General procedure for the preparation of compounds (4h–3)** In nearly quantitative yields and with short reaction times. Moreover, the reaction work-up is straightforward.

1. **Acknowledgements**

The authors would like to thank Dr. Livius Cotarca for rising our attention on Darzens reactions and for helpful discussions during the development of this work. C. L. wishes to thank Dr. Luca Raveglia for the possibility of carrying out experimental work at Aptuit.

**Conflict of Interest**

The authors declare no conflict of interest.

**Data Availability Statement**

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** $\alpha,\beta$-epoxy esters · $\alpha$-haloesters · carbon nucleophiles · polyaminophosphazenes · superbases

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