

Phase Transfer Catalysis of Henry and Darzens Reactions

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Abstract

We describe in this work the influence of the addition of phase transfer catalyst in heterogeneous medium liquid/liquid on the output of the reactions of Darzens and Henry. It proves that the reaction of Darzens is favoured in the presence of low base such as K_2CO_3 and Et_3N . Phase transfer catalysis is an efficient activation method in Darzens and Henry reactions. Thus, the Ethylene Diammonium Diacetate (EDD) has a comparable catalytic activity has that of quaternary ammonium salts in the reaction of Darzens.

Keywords: Darzens, Henry, Phase Transfer Catalysis, Mechanism

1. Introduction

The formation of a carbon-carbon bond is the fundamental reaction in organic synthesis [1-5]. To this respect, Henry [6-9] and Darzens [10-12] reactions can be considered as excellent tools to give access to multifunctional compounds [13,14]. The Darzens reaction gives α,β -epoxy carbonyl compounds, whereas the Henry reaction leads to nitroaldols.

The Henry reaction [15] consists of the addition of a nitronate nucleophile on the double bond of a carbonyl compound. It proceeds usually at room temperature in the presence of a base to afford a β -nitroalcohol. The preferred bases are alkali hydroxides [16], carbonates [17], bicarbonates [18] and alkali oxides. The reaction, however, is often carried out in protic media such as methanol or, even, water [19]. Henry adducts are very useful in organic synthesis as precursors for pharmaceutical and biological purposes [20,21]. In order to improve the efficiency of the reaction, new catalytic or non-catalytic methods have been devised such as alumina [22], potassium fluoride on alumina as support [23], lanthanides [24], high pressures [25] and microwaves [26]. In the same way, the Darzens reaction permits the synthesis of adducts simultaneously involving the formation of a carbon-carbon bond and a carbon-oxygen bond [12]. Several authors have tried to improve the enantioselectivity and the yields. Arai *et al.* [27] showed that the enantioselectivity of the Darzens reaction can be excellent when using a chiral auxiliary such as cinchonine, an alkaloid structurally close to quinine. Later on, the same

group [28] introduced a phase transfer catalyst derived from cinchonine to synthesize Darzens products. In the same way, Ku *et al.* [29] reported the asymmetric synthesis of *trans- α,β* -epoxysulfones by the catalytic phase-transfer Darzens reaction of chloromethyl phenyl sulfone with various aromatic aldehydes in the presence of the *cinchona* alkaloid-derived chiral phase-transfer catalysts.

In the goal to continue our works on the activation by the phase transfer catalysis of organic reactions such as: Wittig reaction [30], Baylis-Hillman reaction [31,32], Michael reaction [32,33], Knoevenagel reaction [34], Heck reaction [35,36]. In this work, we study the activation of Henry and Darzens reactions by means of phase transfer catalysis (PTC).

2. Experimental

2.1. Henry Reaction

Procedure A: A solution of nitroalkane (7.5 mmol), solvent (15 mL), and base (5 mmol) was introduced in a 25 mL flask equipped with a magnetic stirrer. 5 mmol of carbonyl compound was added. The mixture was stirred during 24 h at ambient temperature. The organic phase was extracted with diethyl ether. When the carbonyl compound was an aldehyde, the organic phase was washed with a saturated solution of anhydrous sodium hydrogensulfite to remove the unreacted aldehyde. The organic phase was dried over anhydrous sodium sulphate. After evaporation of the solvent the product was purified on silicagel column chromatography with hexane-ether

mixtures as eluent.

Procedure B: As procedure A with addition of 2 mmol of the phase transfer catalyst.

2.2 Darzens Reaction

Procedure C: A solution of α -chloroester or α -chloroacid or α -chloronitrile (3.6 mmol), solvent (15 mL), base (3.6 mmol) was introduced in a 25 mL flask equipped with a magnetic stirrer. 3 mmol of carbonyl compound was added. The mixture was stirred during 24h at ambient temperature. The organic phase was extracted with diethyl ether and dried over anhydrous sodium sulphate. After evaporation of the solvent the product was purified on silicagel column chromatography with hexane-ether mixtures as eluent.

Procedure D: As procedure C with tetrahydrofuran as solvent and potassium hydroxide as the base with addition of 2mmol of the phase transfer catalyst.

2.3. Synthesis of Ethylene Diammonium Diacetate (EDD)

Ethylene diamine (3 g) in anhydrous diethylether was introduced in a 50mL flask. The flask was immersed into a liquid bath maintained at 35°C. Then, glacial acetic acid (6 g) was added. The mixture was stirred until boiling of ether. After 24 h cristallization occurred. The solid product was filtered and washed with ether. Finally, it was recrystallized in methanol.

2.4. Recording of Spectra

^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra are recorded on a Bruker spectrometer in $\text{DMSO-}d_6$, with tetramethylsilane as internal reference.

The products were analysed by GC-MS (Hewlett-Packard computerised system consisting of a 5890 gas chromatograph coupled to a 5971A mass spectrometer) ionisation mode used was electronic impact at 70 eV.

Microanalyses were performed using a C, H, N Analyzer Model 185 from Hewlett-Packard. I.R. spectra are recorded in KBr on a Bruker Tensor 27 spectrometer in the range 4000 - 400 cm^{-1} .

All the products were confirmed by comparing their IR, MS, ^1H NMR and ^{13}C NMR data with literature data [9,10,12,37,38].

3. Results and Discussion

3.1. Henry Reaction

Effect of the base:

We have examined the nature of the base in the Henry

reaction involving benzaldehyde and various nitroalkanes in aqueous solution (**Table 1**).

Inspection of the results of **Table 1** shows that the reactivity is modest in the presence of bases such as triethylamine and weak in the presence of carbonate anions such as K_2CO_3 . There is no reaction with sodium alchoolates.

This may be explained by the formation of secondary products issued from Cannizzaro reactions or hydrolysis in the presence of alchoolates on the contrary of reactions involving triethylamine or alkali carbonates. The results are in agreement with those of Zhou *et al.* [39] who found that Henry reaction of aromatic and aliphatic aldehydes with nitromethane is promoted by triethylamine in water. (**Figure 1**.)

Effect of the carbonyl compound:

The effect of the carbonyl compound was studied in a next step using nitromethane and various carbonyl compounds (**Figure 2**, **Table 2**).

As shown in **Table 2**, the reaction does not occur with ketones. Apparently this is due to the very weak reactivity of ketones toward the carbanion formed by deprotonation of nitromethane. Steric effects and the positive inductive effect lead in the case of ketones to a reduction

Table 1. Effect of the base in the Henry reaction.

R ¹	R ²	Product	Base	Yield (%)
			CH_3ONa	0
			EtONa	0
	H	1a	Et_3N	46
			K_2CO_3	21
			CH_3ONa	0
			EtONa	0
H	CH_3	1b	Et_3N	42
			K_2CO_3	18
			CH_3ONa	0
			EtONa	0
	C_2H_5	1c	Et_3N	47
			K_2CO_3	24
			CH_3ONa	0
CH_3	CH_3	1d	EtONa	0
			Et_3N	32
			K_2CO_3	17

Procedure A

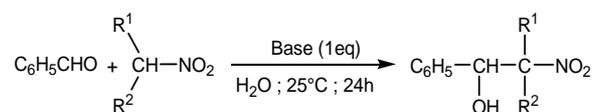


Figure 1. Henry reaction of benzaldehyde with nitroalkane.

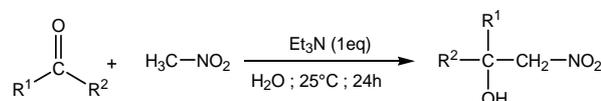


Figure 2. Henry reaction of nitromethane with carbonyl compound.

Table 2. Effect of the carbonyl compound in the Henry reaction.

R ¹	R ²	Product	Yield (%)
H	C ₆ H ₅	1a	46
H	C ₃ H ₇	1e	48
H	Cl-C ₆ H ₄	1f	54
CH ₃	C ₂ H ₅	1g	0
CH ₃	C ₆ H ₅	1h	0
-(CH ₂) ₅ -		1i	0
-(CH ₂) ₄ -		1j	0

Procedure A.

of the electrophilicity of the carbon in the carbonyl group. This makes the attack of the resulting carbanion more difficult.

Effect of phase transfer catalysis:

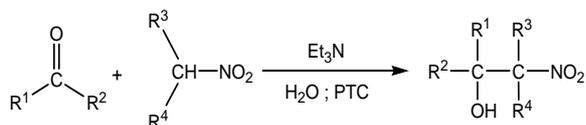
In the following step we examined the nature of the phase transfer catalyst in Henry reactions involving various aldehydes and ketones. (Figure 3.)

The results of Table 3 show that

1) There is no reaction in the absence of PTC with C5 and C6 cyclic ketones. With the addition of PTC catalysts, the reaction occurs in fair yields.

2) In the other reactions, the reaction occurs whatever the addition or not of phase transfer catalysts. The catalyst, however, leads to an improvement of yields. This can be explained by the stability of the reaction intermediate formed by the addition of the PT catalyst to the carbanion. Such intermediate inhibits any possible retro Henry reaction.

3) Among the quaternary ammonium salts listed in Table 3, the most appropriate seems to be Aliquat-336. The catalytic activity of the ammonium salt depends on

**Figure 3. Henry reaction of nitroalkanes with carbonyl compounds.****Table 3. Effect of the PT catalysts in the Henry reaction.**

R ¹	R ²	R ³	R ⁴	Prod- uct	Yield %			
					no PTC	TBAB	TEBAC	Aliquat -336
C ₆ H ₅	H	H	H	1a	46	52	53	70
C ₆ H ₅	H	H	CH ₃	1b	36	-	55	68
C ₃ H ₇	H	H	H	1c	48	51	60	72
C ₆ H ₅	H	CH ₃	CH ₃	1d	16	-	56	39
(CH ₂) ₅	H	H	H	1i	0	17	22	44
(CH ₂) ₄	H	H	H	1j	0	12	24	47
C ₃ H ₇	H	H	CH ₃	1k	38	-	63	41
C ₃ H ₇	H	CH ₃	CH ₃	1l	18	-	-	42

Procedure B. TBAB: bromure de tétrabutylammonium; TEBAC: chlorure de benzyltriéthylammonium; Aliquat-336: chlorure de méthyltriocetylammunium.

the structure of the alkyl or aryl groups on the nitrogen atom and, also, on the nature of the counter-ion. It may also be noticed that the presence of a lipophilic group (this is the case of Aliquat-336) is beneficial for the formation of the Henry adduct as it facilitates the nucleophilic attack on the aldehyde [31].

4) At last, the yield depends on the nature of the anion associated with the ammonium cation. It is higher with tetrabutylammonium chloride than with the corresponding bromide. The same result was also found by D'Incan in his study examining the effect of the phase transfer agent on the Horner-Emmons reaction between benzaldehyde and 1-cyanoethyl diethylphosphonate [40].

We propose the following mechanism of the Henry reaction involving benzaldehyde and nitromethane under PTC conditions (Figure 4).

3.2. Darzens Reaction

Effect of solvent:

The effect on the nature of the solvent in the Darzens reactions was studied in condensations between benzaldehyde and a α -chloroester, α -chloroacid or α -chloroacetonitrile in the presence of potassium hydroxide as the base. (Figure 5.)

According to the results of Table 4, there is no reaction in aqueous solution in reactions involving α -chloroesters or α -chloroacetonitrile. In organic phase, the reactivity remains low. With an acidic α -chloroacetate, however, there is no reactivity at all whatever the medium, aqueous or organic. This may be ascribed to a decomposition of the acidic function supported by the release of carbon dioxide.

Tetrahydrofuran seems to be the most adequate solvent for the Darzens reactions between benzaldehyde and

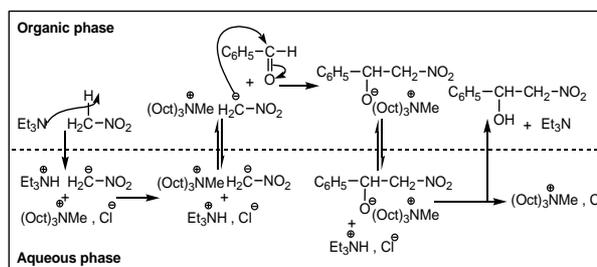
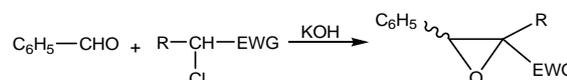
**Figure 4. Mechanism of the Henry reaction between nitromethane and benzaldehyde under PTC conditions (liquid-liquid heterogeneous catalysis).****Figure 5. Darzens reaction of benzaldehyde with a α -chloroester, α -chloroacid or α -chloroacetonitrile.**

Table 4. Effect of the base in the Henry reaction.

R	EWG	Product	Solvent	Yield (%)
	CN	2a	T.H.F	36
			CH ₂ Cl ₂	22
			Water	0
H	COOEt	2b	T.H.F	28
			CH ₂ Cl ₂	18
			Water	0
	COOH	2c	T.H.F	0
			CH ₂ Cl ₂	0
			Water	0
CH ₃	COOEt	2d	T.H.F	21
			CH ₂ Cl ₂	12
			Water	0

Procedure C.

α -chloroester or α -chloroacetonitrile, in agreement with the results given by Wang *et al.* [12].

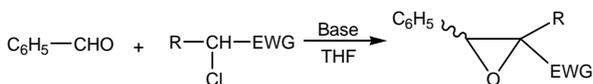
Effect of the base:

Using THF as the solvent we have studied the effect of the base in the Darzens reaction at ambient temperature (**Figure 6**).

Table 5 shows that the Darzens reaction of benzaldehyde and α -chloroesters or α -chloroacetonitrile is favoured in the presence of KOH. Sodium hydroxide, however, is not indicated. This is probably due to the opening of the epoxy cycle with NaOH, a result also given by Wang *et al.* [12].

Effect of the carbonyl compound

From **Table 6**, we note that the Darzens reaction proceeds better with aldehydes than with ketones. The latter do not react with α -chloroacetonitrile. This seems to be due to the weak reactivity of ketones toward the carbanion formed by deprotonation of α -chloroacetonitrile. Steric

**Figure 6. Darzens reaction: effect of the base.****Table 5. Effect of the base in the Darzens reaction.**

R	EWG	Product	Base	Yield (%)
	CN	2a	K ₂ CO ₃	16
			NaOH	0
			KOH	36
			Et ₃ N	10
H	COOEt	2b	K ₂ CO ₃	12
			NaOH	0
			KOH	28
			Et ₃ N	12
	COOH	2c	K ₂ CO ₃	0
			NaOH	0
			KOH	0
			Et ₃ N	13
CH ₃	COOEt	2d	K ₂ CO ₃	14
			KOH	0
			Et ₃ N	14

Table 6. Effect of the carbonyl compound in the Darzens reaction.

R ¹	R ²	Product	Yield (%)
H	C ₆ H ₅	2a	36
	C ₃ H ₇	2e	32
CH ₃	C ₂ H ₅	2f	0

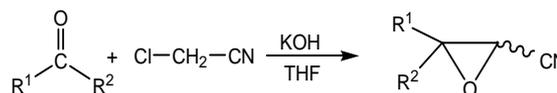
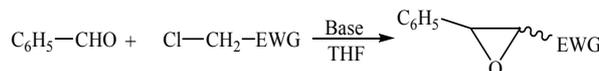
effects and the inductive effect (+I) lead in the case of ketones to a reduction of the electrophilic character of the carbon in the carbonyl group making the attack of the generated carbanion more difficult (**Figure 7**).

Effect of phase transfer catalysts

All the above results reveal that the yield in the investigated Darzens reactions is generally low. In order to improve such yields, we have turned to the use of phase transfer catalysts (**Figure 8**).

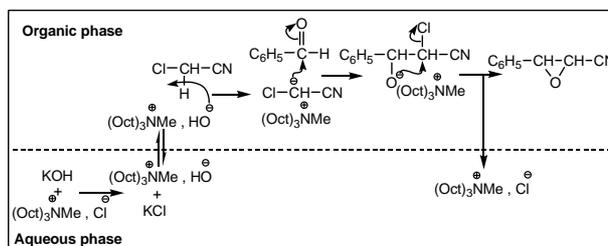
There is no reaction in the condensation between benzaldehyde and α -chloroacetate even under PTC conditions (**Table 7**).

The addition of a phase transfer catalyst on the medium noticeably enhances the reactivity (**Table 7**). This may be ascribed to the exaltation of the nucleophilicity of the carbanion formed by the addition of the PTC catalyst on the carbanion (**Figure 9**).

**Figure 7. Darzens reaction of α -chloroacetonitrile with various carbonyl compounds.****Figure 8. Effect of phase transfer catalyst in the Darzens reaction of benzaldehyde with α -chloroacetonitrile, α -chloroacetic acid and ethyl α -chloro-acetic acid.****Table 7. Effect of PT catalyst in the Darzens reaction**

EWG	Product	Yield %		
		no PTC	Aliquat-336	EDD*
CN	2a	36	60	64
COOEt	2b	28	41	48
COOH	2c	0	0	0

Procedure D. *EDD: Ethylene Diammonium Diacetate

**Figure 9. Mechanism of the Darzens reaction involving benzaldehyde and α -chloroacetonitrile under PTC conditions.**

4. Conclusions

The anionic activation in Henry and Darzens reactions has been achieved by the addition of quaternary ammonium salts leading to an exaltation of the reactivity of the generated anions. The addition of a phase transfer catalyst in the reaction medium leads to an increase in the yield for the Henry reaction involving nitromethane and various ketones as well as a remarkable reactivity in the Darzens reaction. On the contrary, there is no reaction with a α -chloroacetate acid whatever the medium, even under PTC conditions.

5. References

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