Tetrahedron Letters 50 (2009) 4833–4837

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Chloride ion pairs as catalysts for the alkylation of aldehydes and ketones with C–H acidic compounds

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ARTICLE INFO

Article history:
Received 4 March 2009
Revised 2 June 2009
Accepted 3 June 2009
Available online 7 June 2009

Keywords:
Organocatalysis
C–C bond forming reactions
Ionic liquids
Lewis bases

ABSTRACT

Chloride anions associated with various soft cations (like tetraalkyl ammoniums, alkyl imidazoliums or pyridiniums) were shown to be able to promote the alkylation of carbonyl derivatives with acidic compounds, as exemplified on Knoevenagel and aldol condensations under relatively mild conditions. This activity was attributed to an enhanced nucleophilicity of the chlorine anion, originating from a softness/hardness mismatch between the anion and the cation.

While Lewis acidic catalysts have been used for a long time especially in heterogeneous catalysis,[1] Lewis basic catalysts only recently started unfolding their potentialities.[2] Nevertheless, numerous applications of Lewis basic catalysts can already be found in the literature. This can be exemplified for the case of two important archetypical C–C bond forming reactions, namely the Knoevenagel and the aldol condensations. Knoevenagel condensations, the reaction of aldehydes or ketones with C–H acidic malonates (like malonodinitrile or diethylmalonate), are usually catalysed by Brönsted bases, typically amines (Scheme 1a). Charles however reported as early as 1963[3,4] an alternative mechanism involving the attack of a primary amine on an aldehyde to form an imine, which then reacts with the methylene moiety (Scheme 1b). The possibility to promote Knoevenagel condensations with nucleophilic compounds was also evidenced by the use of triphenyl phosphine as a catalyst for this reaction.[5] Aldol condensations, the reaction of two aldehydes or ketones to yield an enone, can be catalysed by Brönsted acids or strong bases, but also by basic solids.[6,7]

Lewis basic catalysts also proved very effective for enantioselective aldol condensation; this includes the use of amino acids, especially proline, phosphoramides and phosphine oxides.[8–11]

It was recently shown that halides associated with very soft cations (like tetraalkyl ammoniums or alkyl imidazoliums) were able to act as catalysts in various reactions. This property was attributed to the fact that ion pairs with mismatching softness and hardness were forming weakly associated ion pairs even in relatively non polar solvents. The resulting unshielded and, thus, nucleophilic anions were used to promote the conversion of epoxides and CO_2 into organic carbonates[12] and the aromatisation of partially unsaturated 6-rings.[13] In an attempt to test the versatility of this property of halides, we investigated their activity in C–C bond forming reactions. Quite interestingly, there already have been some reports on the use of halides to promote Knoevenagel condensations. LiBr was employed as a heterogeneous catalyst for this reaction under solvent free conditions.[14] The authors of this report did not make any statement on the mechanism of the described reactions. However it can be assumed that the strong oxophilicity of the lithium was promoting the reaction and that the bromide anion only played a minor role. Iodine[15] and tetrabutylammoniumbromide[16] were also reported to promote Knoevenagel reactions in water. However, in both cases the reactions were carried out in the presence of K_2CO_3, making it difficult to assess exactly what was the role of the halogen. This contribution, thus, aims at demonstrating the possibility to catalyse the alkylation of carbonyl groups with C–H acidic compounds with chlorine ions, avoiding any other co-reactant.

In the first part of this work, it was assessed whether halide ion pairs were able to promote one of the easiest Knoevenagel condensations, namely the reaction of benzaldehyde with malonodinitrile to yield benzylidenemalononitrile (Scheme 2) at 80 °C in 4 h. Figure 1 displays the obtained conversions for various ion pairs (calculated as the amount of formed product determined by GC–MS

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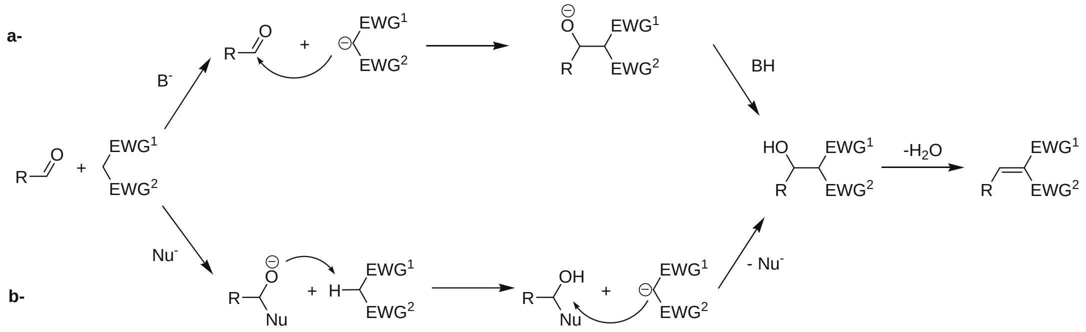
doi:10.1016/j.tetlet.2009.06.013



Scheme 1. Accepted mechanisms for the (a) basic and (b) nucleophilic pathways for the Knoevenagel condensation.

relative to a toluene reference). These investigations were facilitated by the fact that many ion pairs with organic cations are commercially available because of their use as ionic liquids.

In our previous study on the aromatisation of Diels–Alder reaction products[13] we noticed that: (i) the anions have to be halides to promote the reaction but the nature of the halide did not strongly affect the reaction; (ii) the cation did not strongly impact the reaction rates as soon as solubility was provided. In the case of Knoevenagel condensations, a given solubility of the ion pair was also required. Indeed NaCl, which is not soluble in acetonitrile at this temperature, failed to provide any rate acceleration as compared with the test without catalyst. But, contrary to our previous work, even with good solubility, the nature of the cation and the nature of the halide affected the outcome of our test reaction. Indeed, while hexadecyltrimethyl ammonium chloride (CTAC), hexadecylmethyl imidazolium chloride (C_{16}mimCl) and ethylmethyl imidazolium chloride (EmimCl) featured almost the same activity, the pyridinium-based salts (butylmethylpyridinium chloride and hexadecylpyridinium chloride) featured a stronger catalytic activity, reaching 54% and 37% of conversion. These observations are in agreement with our hypothesis that the activity of the tested ion pairs correlates with the softness/hardness mismatch of our ions. Indeed, pyridinium species can be regarded as softer cations as alkylammoniums or even imidazoliums. Unfortunately we were not able to find any comprehensive study on the dissociation constants of these ion pairs in organic solvents in the literature and further experimental work is required to measure it.

Hexadecyltrimethylammonium bromide (CTAB) did not yield any detectable rate enhancement nor did ethylmethylimidazolium tetrafluoroborate ($EmimBF_4$), showing that only chlorine was the active anion for this reaction. It is also worth being noticed that the obtained conversions are relatively low (a primary amine would perform much better under such conditions) and are only interesting from an academic point of view as hints on the actual mechanism.

Although butylmethyl pyridinium chloride showed the best activity in this catalysts screening, its low miscibility with many solvents prompted us to pursue our study with ion pairs featuring long alkyl chains. We thus selected C_{16}pyrCl and CTAC as they were the second and third best choices (with respect to the measured activity).

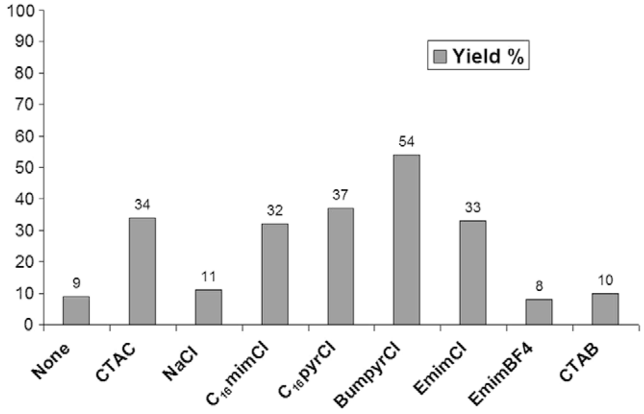
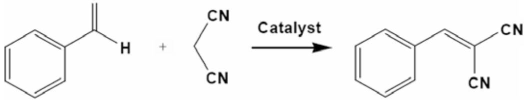


Figure 1. Results of the reaction of benzaldehyde with malononitrile in the presence of various catalysts. (i) General reaction conditions: 0.2 mmol of catalyst, 2 mmol of aldehyde, 2 mmol nitrile, in 5 mL of acetonitrile, 80 °C for 4 h. (ii) CTAC stands for cetyltrimetylammonium chloride, CTAB for cetyltrimetylammonium bromide, C_{16}mimCl for cetylmethylimidazolium chloride, C_{16}pyrCl, for cetylpyridinium chloride EmimCl for ethylmethylimidazolium chloride, $EmimBF_4$ for ethylmethylimidazolium tetrafluoroborate and BumpyrCl for butylmethylpyridinium chloride. (iii) The yields were determined by GC–MS as the amount of formed benzylidene with toluene as an internal standard. Reaction of benzaldehyde with malononitrile.

In a second step, we decided to investigate the impact of the solvent on the observed conversion enhancements. Indeed, if the activity of our chlorine-based ion pairs originates from the fact that they are weakly associated, then increasing the dielectric constant of the used solvent should help increasing the conversion rates. For this investigation, C_{16}pyrCl was selected as a catalyst, because it features a good solubility in a wide range of solvents. We tested the Knoevenagel condensation of benzaldehyde and malononitrile at 80 °C for 12 h with C_{16}pyrCl in heptane, toluene, diisopropyl ether, THF, isopropanol and acetonitrile. Figure 2 displays the ob-



Scheme 2. Reaction of benzaldehyde with malononitrile.

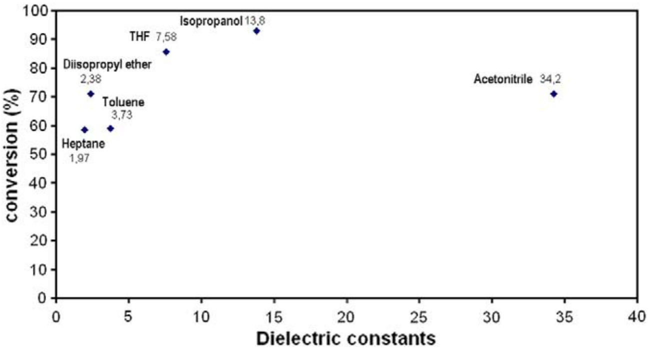
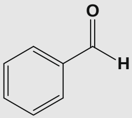
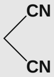
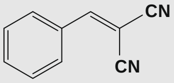
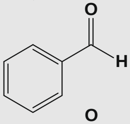
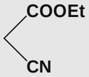
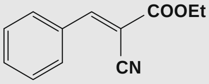
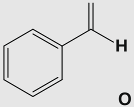
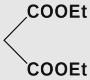
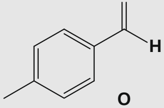
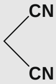
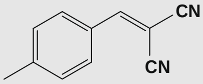
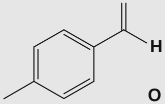
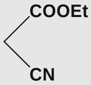
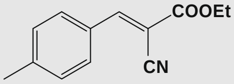
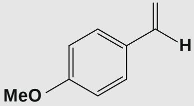
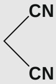
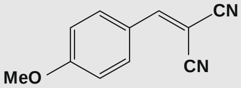
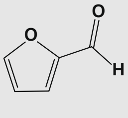
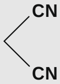
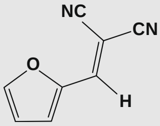
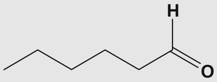
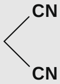
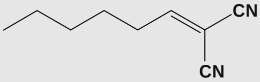
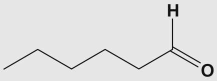
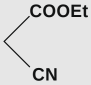
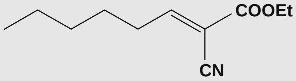
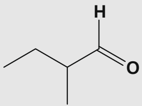
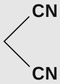
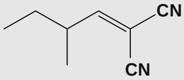
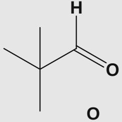
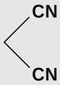
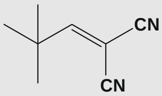
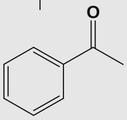
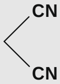
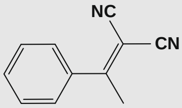
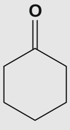
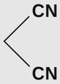
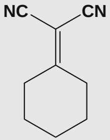
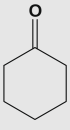
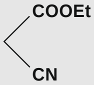
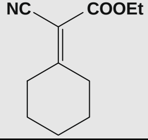


Figure 2. Influence of the dielectric constant of the solvent on conversion of rate of the Knoevenagel condensation.

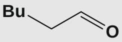
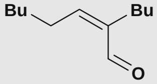
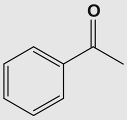
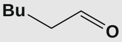
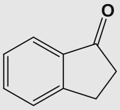
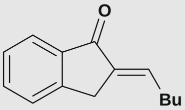
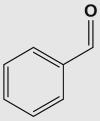
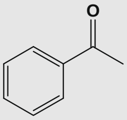
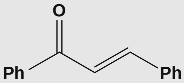
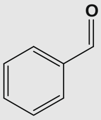
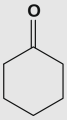
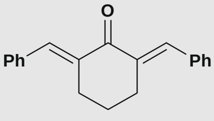
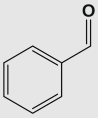
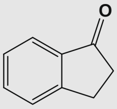
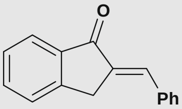
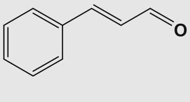
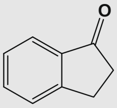
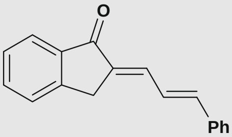
Table 1
Results of various Knoevenagel condensations catalysed by CTAC[a]

Entry	Aldehyde	Nucleophile	Product	Conv.[b] (%)			
				CTAC		C_{16}PyrCl	
				THF	CH_3CN	THF	CH_3CN
1				91	64	98	71
2				54	46	69	50
3			/	0	0	0	0
4				81	100	97	82
5				56	100	82	87
6				50	50	73	15
7				71	47	74	54
8			 Also traces of aldol condensation product	61	44	41	34
9				6	0	40	<1
10				41	43	38	13
11				65	21	32	<1
12				13	0	26	0
13				15	10	51	28
14				31	32	43	30

[a] General reaction conditions: 0.2 mmol of CTAC, 2 mmol of aldehyde, 2 mmol of donor, in 5 mL of acetonitrile, at 80 °C for 12 h.

[b] Conversions were determined as the consumption of donor as measured per GC–MS using toluene as an internal standard.

Table 2
Results of various Knoevenagel condensations catalysed by CTAC[a]

Entry	Electrophile	Nucleophile	Products	Conv.[b] (%)	
				CTAC	C_{16}pyrCl
1		/	 (Traces of the E-isomer)	74	100
2		/	/	0	0
3			 (Traces of the hexanal dimmer)	85	58
4				0	28
5[c]				96	70
6				95	60
7				91	40

[a] General reaction conditions: 0.2 mmol of CTAC, 4 mmol of pure aldehyde or ketone or a mixture of 2 mmol of aldehyde and 2 mmol of ketone, without solvent, at 120 °C for 20 h.

[b] The conversion rates were determined as the amount of consumed reactant by GC–MS using biphenyl as an internal standard.

[c] In this case only 1 mmol of ketone was used.

tained conversion rates as a function of the dielectric constant of the solvents. As can be seen an initial increase in the conversion rates with increasing ε was observed reaching a maximum with THF and isopropanol (with 86% and 93% of conversion). These data fit well with the hypothesis that ion pair dissociation is the reason for the activity of our chlorides. Nevertheless acetonitrile, which is the most polar solvent we tested, gave a lower conversion rate of 71%. It is relatively difficult to decide at this stage, whether this little loss of activity is due to a second order effect (e.g., a shielding of the chlorine by very polar solvents), or just has to be considered as non relevant (because of experimental error). Although isopropanol gave the best result, it proved difficult to deal with in the rest of the study due to the formation of small amounts of acetals. The next reactions were thus tested in both acetonitrile and THF.

We then investigated the activity of CTAC and C_{16}pyrCl for a broad range of Knoevenagel substrates. We thus heated various combinations of electrophile and nucleophile in the presence of catalytic amounts of CTAC and C_{16}pyrCl both in acetonitrile and THF at 80 °C for 12 h. Table 1 displays some of the results we obtained.

A quick look at the results reported in Table 1 shows that both CTAC and C_{16}pyrCl can actually act as catalysts for a large range of Knoevenagel substrates. A closer look at the reactions however shows surprising features. Indeed, while in the case of benzaldehyde the usual decrease of conversion when passing from malononitrile, to ethyl cyanoacetate to diethyl malonate is observed (Table 1, entries 1–3) the yields with *p*-tolualdehyde are much better (Table 1, entries 4 and 5,) than with benzaldehyde. This is unusual as *p*-tolualdehyde, being more electron rich, is a worse electrophile. In the case of *p*-methoxy benzaldehyde, however, the conversion decreases, as expected (Table 1, entry 6). A moderate conversion is also observed in the case of furaldehyde (Table 1, entry 7, up to 74%). The great advantage of using chlorine-based ion pairs as catalysts for Knoevenagel reactions, however, seems to be the fact that relatively unreactive electrophiles can be used. Indeed non aromatic aldehydes such as hexanal, 2-methylbutanal or pivaldehyde (Table 2, entries 8, 10 and 11) and even ketones (cyclohexanone, Table 2, entries 13 and 14) could yield the condensation product in low to moderate yields. Here again, strong deviations from the expected activities are observed. Acetophenone, for instance is a relatively active ketone and shows very poor yields (Table 2, entry 12, 26% at best). Cyclohexanone, on the contrary is deactivated through both sigma donation and sterical hindrance, but reacts with malononitrile and even better with ethyl cyanoacetate (Table 1, entries 13 and 14 up to 51% of conversion). These unusual reactivities confirm that the Knoevenagel reactions do not proceed via the usual basic mechanism (Scheme 1a). They also indicate that the reaction is probably concerted. Regarding the activity of both ion pairs, the pyridinium proves more active than the ammonium in most cases. This is consistent with our hypothesis that a softness/hardness mismatch is governing the catalytic activity. The influence of the solvent remains moderate, but THF tends to be the better solvent. Theoretical investigations are currently running to find a suitable explanation for these observations.

As aldol condensations are, in principle, closely related to Knoevenagel reactions, we also attempted to promote various condensations between aldehydes and/or ketones with CTAC and C_{16}pyrCl at 120 °C for 20 h. Table 2 summarises the results we obtained.

As can be seen, our two ion pairs also proved to act as effective promoters for aldol condensations. Interestingly, while the nature of the aldehyde did not strongly impact the conversion rate (hexanal, benzaldehyde and cinnamaldehyde were converted from 74% to 96% with CTAC), the nature of the ketones proved to be determining. Acetophenone, which is a typical aldol substrate, did only poorly react (Table 2, entries 2 and 4). On the contrary, 1-indanone, which is more sterically hindered, or cyclohexanone, which is very electron rich and thus usually a relatively bad nucleophile, both did react (Table 2, entries 5–7) even yielding the highest conversion rates in this study (from 85% to 96%). In the case of aldol reactions, CTAC performed better than C_{16}pyrCl. These observations again have to be rationalised.

In this work, it has been evidenced that chlorine, when associated with soft organic cations, could act as an effective catalyst to promote Knoevenagel and aldol condensations in, sometimes, high yields under mild conditions. Interestingly, the use of CTAC and C_{16}PyrCl as a catalyst for these reactions enabled to use relatively unreactive aldehydes such as hexanal, 2-methylbutanal and pivaldehyde. Detailed experimental and theoretical work is required to shed some light on the reasons for these observations. We also currently focus on immobilised chlorine ion pairs in order to yield stable heterogenous aldol condensation catalysts, which would be of interest for industrial applications.

Acknowledgements

The Max-Planck Society and the CEA are gratefully acknowledged for financially supporting this work.

Supplementary data

Supplementary data (experimental procedures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.013.

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