Carbon-carbon bond formation in aqueous media. 
Benzamidomethylation of some carbon nucleophiles

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Abstract

C-C bond formation reactions between (benzamidomethyl)triethylammonium chloride (1) and some carbon nucleophiles (2a-f) were performed smoothly in aqueous media, under mild reaction conditions and ambient temperature. Mono-C-alkyl (3a, 3b, 3c) and di-C-alkyl (3d, 3e, 3f) derivatives were obtained without using a catalyst. Crystals of the products were easily isolated by simple filtration, in moderate yields and with no apparent contamination due to the formation of O-alkyl products.

Keywords: C-C Bond formation, carbon nucleophiles, aqueous medium

Introduction

Carbon-carbon bond formation is the essence of organic synthesis and provides the foundation for generating more complicated organic compounds from the simpler ones. In the latest decade, there has been increased recognition that organic reactions can proceed well in aqueous media and offer advantages over those occurring in organic solvents. Organic synthesis in water have attracted much attention, not only because unique reactivity is often observed in water but also because water can significantly shorten the synthetic route, increase product selectivity and reduce the volatile organic consumption.\textsuperscript{1}

In this trend, Manabe and Kobayashi\textsuperscript{2} made a step forward in palladium-catalyzed allylic substitution with carbon nucleophiles as one of the most important and useful carbon-carbon bond-forming reactions. They disclosed a new catalytic system for substitution in aqueous...
medium. Also, the key of the catalytic system was the use of a catalytic amount of a carboxylic acid, which greatly accelerates the reactions.

Recently, similar catalyzed nucleophilic reactions were reported, but polar organic solvents were used as a medium. Allylic substitution of alcohols with some C-nucleophiles such as β-diketones, catalyzed by Pd-complexes, gives an excellent result for forming new C-C bonds.\(^3\) Pd-complexes also were found to catalyze nucleophilic benzylic substitution of benzylic esters, with high generality.\(^4\) In this reactions two different types of products were demonstrated, mono-C and di-C substituted products. Catalytic allylation with anilines, nitrogen compounds and 1,3-dicarbonyl compounds takes place with Pd-complexes\(^5\) and H-mont (or other solid Bronsted acid)\(^6,7\) as a catalyst. Direct substitution of alcohols with allyl-, propargyl- and alkynyl- silanes catalyzed by InCl\(_3\)\(^8,9\) or with active methylene compounds catalyzed by Pd-complexes\(^10\) was also reported as a good synthetic approach that gives moderate to high yields of the products.

Literature data for the C-C bond formation by the S\(_2\)2 reactions of enolate intermediates in aqueous medium\(^11\) are sparse. This motivated our research to be primary focused on investigating the possibility for building new C-C bonds in the reaction of nucleophilic substitution in aqueous media without using a catalyst and secondary, on the synthesis of new benzamidomethyl derivatives, which may have a great application as constituent moieties for the intermediates within the synthesis of different biologically active compounds. It has already been demonstrated in the past and recently.\(^12-16\) For example, synthesis of benzamidomethyl ester, such as 2-benzamidomethyl-3-oxybutanoates which are used as intermediates in preparation of (2R,3S)-2-benzamidomethyl-3-hydroxybutanoates\(^17,18\) as chiral building blocks for synthesis of biologically active carbapenems.\(^19-21\) Also, new 1,3-diketones as synthons for preparation of new pyrazole, isooxazole or diazepine derivatives were synthesized, which had been obtained in the past and recently in the reactions with hydrazines\(^22-24\), hydroxylamine\(^25\) or in reactions with phenylenediamines,\(^26-27\) accordingly. Many of this type compounds can show different microbiological activity. Furthermore, synthesis of new benzamidomethyl cyanacetamides, as synthons for building of quinazolines,\(^28\) pyridinones,\(^29\) chromones\(^30\) and other heterocycles\(^23,24\) has been performed.

Our previous results\(^31-33\) show that triethylamino group in (benzamidomethyl)triethylammonium chloride 1 can be easily replaced by different nucleophiles. In aqueous media these reactions were performed relatively fast, under mild conditions, giving almost pure products which can be easily isolated by simple filtration.
In this paper we present the formation of C-C bonds in the reactions of nucleophilic substitution between 1 and different carbon nucleophiles, in aqueous media, without using a catalyst.

**Results and Discussion**

Reactions of 1 with the carbon nucleophiles as dibenzoylmethane 2a, benzoylacetone 2b, ethyl 4-nitrobenzoylacacetate 2c, 1,3-indanedione 2d, 2-cyanoacetamide 2e and 2-cyano-N-phenylacetamide 2f were performed in stirred aqueous (or H₂O/acetone) media, at ambient temperature and in a presence of small quantities of triethylamine (TEA) to pH ≥ 9. Mixed solvent media (H₂O/acetone) was used in the cases where the corresponding nucleophile compound was insoluble or sparingly soluble in water. In the reactions with 2a-c, mono-C-alkylation products 3a-c were obtained (Scheme 1).

\[
\text{R}_1 \text{O} \quad \text{O} \quad \text{R}_2 \\
\text{H}_2\text{O} \\
\text{1} \\
\text{O} \quad \text{O} \\
\text{R}_1 \text{O} \quad \text{R}_2 \quad \text{BAM} \\
\text{3}
\]

**Scheme 1**

In the case of reactions with 2d-f, di-C-alkylation derivatives 3d-f were obtained (Scheme 2 and Scheme 3). Mono-C-alkylation products in the reactions of 1 and 2d, 2e, 2f have not been isolated, despite the attempts of changing the mole ratio of reactants from 1:1 to 2:1, 3:1 on the
side of the nucleophile, changing the reaction solvent mixture or by controlling the increase of pH.

Scheme 2

All products 3a-f were isolated with no apparent contamination due to the formation of O-alkyl products.  

Scheme 3

In the UV spectra of the reactants 2a, 2b, 2c in alcoholic solution (Table I), three different bands with maxima at ~200 nm, ~250 nm and 310 (340) nm appeared. The peak at the longest wavelength (310 or 340 nm) originates from the enol-form, and the peak at 250 nm could be prevalently related to keto-form and also some minor contribution of the enol-form. To illustrate the effect of mono C-benzamidomethylation on the keto-enol equilibrium, we compared the UV-visible spectra of the reactants with analogous products. In the case of 3a, 3b and 3c the maxima at the longer wavelength disappeared, as a result of C-C bond formation, which disabled or significantly inhibited the tautomeric enol-form of the products. Without enol-form, newly formed monobenzamidomethyl products considerably lose nucleophilic nature and further reaction with 1 does not occur. Good example for this is UV spectra of 2b and 3b presented in Figure 1. Monobenzamidomethyl derivative of 2d was not isolated to measure UV-VIS spectrum.
Figure 1. UV-visible spectra of 2b and 3b.

Table 1. UV data for compounds 2a-f and 3a-f

<table>
<thead>
<tr>
<th>React.</th>
<th>c/mol dm$^3$</th>
<th>$\lambda_{\text{max}}$/nm</th>
<th>log ${\varepsilon}$</th>
<th>Product</th>
<th>c/mol dm$^3$</th>
<th>$\lambda_{\text{max}}$/nm</th>
<th>log ${\varepsilon}$</th>
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<tr>
<td>2a</td>
<td>2.20 $\cdot 10^{-5}$</td>
<td>206</td>
<td>5.04</td>
<td>3a</td>
<td>5.85 $\cdot 10^{-5}$</td>
<td>206</td>
<td>4.51</td>
</tr>
<tr>
<td></td>
<td>248</td>
<td>5.09</td>
<td></td>
<td>248</td>
<td>342 (sh)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>2.12 $\cdot 10^{-5}$</td>
<td>202</td>
<td>4.04</td>
<td>3b</td>
<td>6.67 $\cdot 10^{-5}$</td>
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<td>4.39</td>
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<td></td>
<td>246</td>
<td>3.93</td>
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<td>246</td>
<td>310 (sh)</td>
<td>2.48</td>
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<td>2c</td>
<td>1.20 $\cdot 10^{-4}$</td>
<td>202</td>
<td>4.09</td>
<td>3c</td>
<td>5.43 $\cdot 10^{-5}$</td>
<td>202</td>
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<tr>
<td></td>
<td>260</td>
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<td>311 (sh)</td>
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<tr>
<td>2d</td>
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<td>200</td>
<td>3.98</td>
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<td>2e</td>
<td>1.91 $\cdot 10^{-3}$</td>
<td>204</td>
<td>2.83</td>
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<td>229 (sh)</td>
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<td>250</td>
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<td>2f</td>
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<td>201</td>
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<td>1.38 $\cdot 10^{-5}$</td>
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<td>233</td>
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</table>

$\varepsilon =$ dm$^3$ mol$^{-1}$ cm$^{-1}$; (sh) – shoulder
In the $^1$H-NMR spectra of monobenzamidomethyl derivatives 2a, 2b and 2c, the signal from \( CH \) appears as triplet at 6.1 ppm, 5.06 ppm and 5.03 ppm, respectively. As expected, this signal is absent in the $^1$H-NMR spectra of dibenzamidomethyl derivatives.

The reason why 2a, 2b and 2c gives monobenzamidomethyl derivatives, and 2d dibenzamidomethyl derivative, probably was due to the differences in the acidity of the nucleophilic compounds: pKa $2a = 15.2$, $2b = 14.2$, $2c = 11$; pKa $2d = 7.2$. More acidic the nucleophile is (e.g. 2d) greater the activity of the firstly formed mono-C-alkylated derivative which is most likely existing in enol-form. Therefore, the reaction proceeds immediately, by attaching the second nucleophile group to the salt, thus forming di-C-alkylated derivative. For this reason, monobenzamidomethyl derivative of 2d (which might be expected as intermediate) was not isolated, regarding this or similar reaction conditions. Weaker acids 2a, 2b and 2c give monobenzamidomethyl derivatives as much weaker nucleophiles.

The last type of the carbon nucleophiles that were included in this research were the $\beta$-ketonitriles. In the reaction of 1 with 2e, 2f, di-C-alkyl derivatives were isolated. pKa $2e = -1.27$ and pKa $2f = -1.03$ show similarity with the reaction of 1 with 2d. Most likely, firstly formed monobenzamidomethyl derivatives are still good nucleophiles and the kinetics of the reaction is so high, that di-C-alkylated products are the only possible derivatives synthesized under this reaction conditions.

Conclusions

This research demonstrates that C-C bond forming processes can occur in aqueous media in the reaction between quaternary ammonium salt 1 and different carbon nucleophiles. Depending on the acidity of the nucleophilic compounds mono- and di-C-alkylation products were isolated. More acidic the nucleophile is, the process of second deprotonation is predominant, giving di-products without any possibility of isolating mono products under this or similarly modified reaction conditions. During this research some new benzamidomethyl derivatives were synthesized, which can be used as intermediates for the synthesis of potential biologically active compounds.

Experimental Section

General Procedures. Melting points were determined with Reichert heating plate and were uncorrected. Carbon-hydrogen elemental analysis was carried out with Coleman Model 33. Nitrogen elemental analysis was carried out by the Dumas method. Mass spectra were measured on a API QSTAR PULSAR I. NMR spectra were recorded on a Bruker 400 using DMSO-$d_6$ and CDCl$_3$ as solvents. Infrared spectra were measured on a Perkin-Elmer System 2000 FT IR, by
the method of KBr pellets. UV-visible spectra were recorded on a Varian Cary 50 Spectrophotometer in 1 cm quartz cells. All the reagents and solvents were obtained from commercial sources and were used without further purification.

(Benzamidomethyl) triethylammonium chloride 1 was obtained in manner described in previous work.32

**General procedure for synthesis of 3a-f**

A water solution of 1 was added to a water solution (or H₂O/acetone solution in all cases needed) of 2 with TEA to pH = 9-11. The mixture was stirred for 1h at ambient temperature and all the products 3a-f were collected by filtration.

**N-(2-Benzoyl-3-oxo-3-phenylpropyl) benzamide (3a).** 1 (0.9 g, 3.1 mmol), 2a (0.5 g, 2.1 mmol) and TEA (0.3 ml, pH=9) in acetone/water. Yellow crystals, recrystallized from acetone. Mp:157-158 °C (lit.1 158-160 °C); Yield 53.4 % Anal.Calcd. for C₂₃H₁₉NO₃: C, 77.3 %; H, 5.4 %; N, 3.9 %. Found: C, 77.1 %; H, 5.6 %; N, 3.8 %. FTIR(KBr)/cm⁻¹: 3428(s) and 3398(s) (νNH); 1697(vs),1684(vs) and 1670(vs) (νCO); 1651(vs) Amide I; 1529(vs) Amide II;

**N-(2-Benzoyl-3-oxobutyl) benzamide (3b).** 1 (1.5 g, 6.0 mmol), 2b (0.45 g, 3.0 mmol) and TEA (0.1 ml, pH=9) in water. White crystals, recrystallized from acetone. Mp:105-107 °C (lit.1 108-109 °C); Yield 33.9 % Anal.Calcd. for C₁₇H₁₇NO₃: C, 73.2 %; H, 5.8%; N, 4.5 %. Found: C, 72.9 %; H, 6.1 %; N, 4.6 %. FTIR(KBr)/cm⁻¹: 3430(s) and 3324.0(m) (νNH); 1724(vs) and 1661(s) (νCO);1637(vs) Amide I; 1534(s) Amide II;

**Ethyl 2-(4-nitrophenyl)-3-[(phenylcarbonyl)amino]propanoate (3c).** 1 (1 g, 3.7 mmol), 2c (0.67 g, 2.8 mmol) and TEA (0.5 ml, pH=9) in water. Yellow crystals, recrystallized from acetone. Mp: 158-160 °C; Yield 37 %.Anal.Calcd. for C₁₉H₁₈N₂O₆: C, 61.6 %; H, 4.9 %; N, 7.6 %. Found: C, 61.4 %; H, 4.7 %; N, 7.5 %. FTIR(KBr)/cm⁻¹: 3430(s) (νNH); 1743(vs) (νCOOC);1686(s) (νCO); 1656(s) Amide I; 1527(vs) Amide II; 1H-NMR(400MHz; CDCl₃)/ppm 8.14-7.41 (9H, 2Ph); 5.06 (1H, t, J 6.0, CH); 4.10 (2H, q, J = 7.2, CH₂CH₃); 3.84 (2H, t, J = 6.0, NCH₂); 1.06 (3H, t, J 7.2, CH₃); 13C-NMR(100 MHz; DMSO-d₆)/ppm 150.2, 140.4, 133.9, 131.3, 129.8, 128.2, 127.1 and 127.6. MS (EI POS. Temp): m/z 371.1 (M+H)^⁺.

**N-[1,3-Dioxo-2,3-dihidro-1H-inden-2-yl)methyl]benzamide (3d).** 1 (0.9 g, 3.3 mmol), 2d (0.3 g, 2.3 mmol) and TEA (0.1 ml, pH=9) in water/acetone. Purple crystals, recrystallized from
acetone. Mp: 200-203 °C Yield 42.2 %. Anal. Calcd. for C_{25}H_{20}N_{2}O_{4}: C, 72.8 %; H, 4.9 %; N, 6.8 %. Found: C, 72.7 %; H, 5.1 %; N, 6.9 %. FTIR(KBr)/cm\(^{-1}\): 3336(m) and 3278(m) (\(\nu_{NH}\)); 1743(m) and 1705(vs) (\(\nu_{CO}\)).

**N-(3-Amino-2-cyano-3-oxopropyl)benzamide (3e).** 1 (1 g, 3.7 mmol), 2e (0.3 g, 2.9 mmol) and TEA (0.1 ml, pH=9) in water. White crystals recrystallized from water. Mp: 166-169°C; Yield 24 %. Anal. Calcd. for C_{19}H_{18}N_{4}O_{3}: C, 65.1 %; H, 5.2 %; N, 16.0 %. Found: C, 64.9 %; H, 5.3 %; N, 15.8 %. FTIR(KBr)/cm\(^{-1}\): 3423(s), 3387(s), 3332(s) and 3277(s) (\(\nu_{NH}\)); 2246(w) (\(\nu_{CN}\)); 1681(vs) and 1654(vs) Amide I; 1536(vs) Amide II; \(^{13}\)C-NMR(100 MHz; DMSO-d\(_{6}\))/ppm 199.3 C=O; 166.9 CONH; 68.4 CH\(_{2}\); 58.4 C; Aromatic: 141.5, 135.8, 133.9, 131.3, 128.2, 127.1 and 122.9. MS (ESI, positive ion mode): m/z 413.1 (M+H\(^{+}\)).

**N-(3-Anilino-2-cyano-3-oxopropyl)benzamide (3f).** 1 (0.9 g, 3.14 mmol), 2f (0.5 g, 1.7 mmol) and TEA (0.2 ml, pH=11-12) in water/acetone. White crystals recrystallized from ethanol. Mp: 178-181°C; Yield 32.6 %. Anal. Calcd. for C_{25}H_{22}N_{4}O_{3}: C, 69.6 %; H, 5.2 %; N, 14.3 %. Found: C, 69.5 %; H, 5.0 %; N, 14.5 %. FTIR(KBr)/cm\(^{-1}\): 3334(s) and 3279(m/sh) (\(\nu_{NH}\)); 2254(w) (\(\nu_{CN}\)); 1699(s) and 1654(vs) Amide I; 1539(vs) Amide II; \(^{1}H\)-NMR(400 MHz; DMSO-d\(_{6}\))/ppm 10.17 (1H, s, NHPh); 8.91 (2H, t, J = 6.3, NHCH\(_{2}\)); 7.88-7.13 (15H, 3Ph); 4.12 dd and 4.02 dd (4H, AB from ABX, J 14.0 and 6.3, 2xNHCH\(_{2}\)); \(^{13}\)C-NMR(100 MHz; DMSO-d\(_{6}\))/ppm 167.2 C=O; 166.8 C=O; 118.4 CN; 51.8 CH\(_{2}\); 41.5 CCN; Aromatic: 138.0, 131.6, 128.4, 127.1; MS (ESI, positive ion mode): m/z 427.5 (M+H\(^{+}\)).

**Acknowledgements**

We are grateful and appreciate the technical support and hospitality from the Faculty of Chemistry and Mineralogy at the University of Leipzig, especially to Prof. Dr. Evamarie Hey-Hawkins.

**References and Notes**

37. Note: pKa values for each compound were obtained from SciFind Scholar - calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (1994-2008 ACD/Labs).
42. Aydemir, F. M.Sc. Thesis, Gazi University, **1991**.