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# Salt-Controlled Selectivity in "on Water" and "in Water" Passerini-Type Multicomponent Reactions

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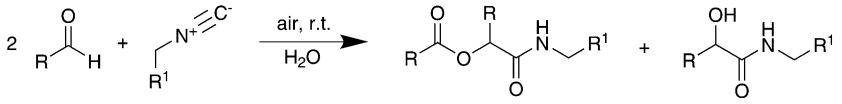
**Abstract:** We have demonstrated that simple sodium salts can completely reverse the product ratios of the Passerini reaction in aqueous media. Furthermore, the use of the "salting-in" salt and a small excess of the nucleophile gives significantly higher yields than the use of the saturated solution of the nucleophile alone.

**Keywords:** Hofmeister series; in water; on water; Passerini reaction; salt effect

In addition to the environmentally benign nature of water, its beneficial effects on a variety of organic transformations have been widely recognized.[1,2] Particularly, poor hydration of the most of the organic compounds often leads to higher reactivity and/or selectivity when compared with reactions in organic media. Since the initial publications on the favorable kinetics and selectivity in the Diels–Alder cycloaddition performed in aqueous media,[3] many new examples of the advantages of water in various organic reactions were reported in the literature.[4–6] In parallel, the mechanistic aspects of these reactions were studied in much detail. The high cohesion energy density of water, hydrogen bonding-stabilized transition state, enhanced hydrophobic effect in the ground *vs.* transition state, were proposed as factors responsible for the reaction acceleration in aqueous media.[7–10] Oft times, the addition of inorganic salts or co-solvents was used to vary the reaction rates by either enhancing or reducing the hydrophobic interactions.[3–5,11] While the added salt can also influence the *selectivity* of organic reactions, there are only few reports of such studies showing a moderate effect on the ratio between isomeric products.[12] Still, much work is necessary to establish aqueous solutions as the media of choice in organic synthesis. Herein, we report the dramatic salt effect on both rate and selectivity of Passerini-type reactions with water as the reaction medium.

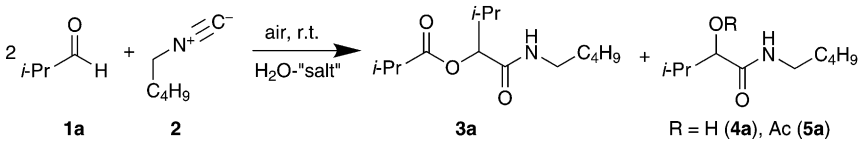
While the majority of the established "on water" reactions was related to cycloaddition, Pirrung and co-workers demonstrated that mutlicomponent transformations can also greatly benefit from using water as the reaction medium.[13] We recently reported a highly efficient aqueous three-component Passerini reaction where one of the components – carboxylic acid – is produced *in situ via* the aerobic oxidation of hydrophobic aldehydes upon stirring with water in an open vessel.[14] The reaction products distribution showed strong dependency on the hydrophobicity of the reactants, with more hydrophobic ones producing the typical Passerini product – ester incorporating two molecules of the aldehyde. Less hydrophobic starting materials gave also the corresponding alcohol, the product of addition of water rather than the carboxylate (Scheme 1). These results suggested that the reactivity "on water" might differ from that in water. To verify this and explore the possibility of using this difference in organic synthesis, we decided to investigate the "salting-out" and "salting-in" effects on the product distribution in the Passerini reaction.

To this end, we tested concentrated solutions of common salts in accordance with the Hofmeister series.[15] While derived from protein solubility studies,[16] the series can give an indication of the position-




**Scheme 1.** "On water" Passerini reaction with two equivalents of the aldehyde.




**Scheme 2.** Competitive formation of "on water" and "in water" products in the presence of sodium salts.

**Table 1.** Effect of sodium salts on the product ratios in the reaction of **1a** and **2**.[a]

| Entry | Salt | **3a**:**4a** ratio[b] | Entry | Salt | **3a**:**4a** ratio[b] |
|---|---|---|---|---|---|
| 1 | $H_2O$ | 40:60 | 6 | NaOAc | 26:74[c] |
| 2 | $Na_2SO_4$ | 100:0 | 7 | $NaClO_4$ | 49:51 |
| 3 | $Na_2SO_4$[d] | 98:2 | 8 | $NaBF_4$ | 65:35 |
| 4 | $Na_2SO_4$[e] | 99:1 | 9 | $NaPF_6$ | 15:85 |
| 5 | NaCl | 85:15 | 10 | NaOTs | 8:92 |

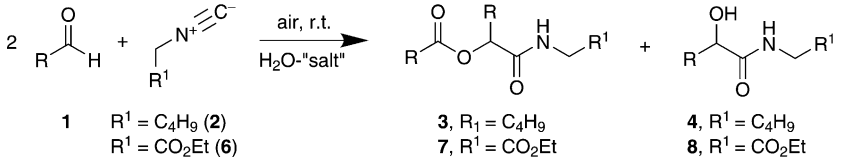
[a] *Typical conditions:* a suspension of aldehyde (0.51 mmol) and isocyanide (0.17 mmol, 3:1 ratio) in a saturated salt solution (3–4 M, 3 mL water) was stirred at 1100 rpm for 7 h at room temperature in the presence of air in a 50-mL glass reactor.
[b] 80–96% overall yield.
[c] The **3a** to **5a** ratio is reported. No **4** was observed in this reaction.
[d] Stirring rate 300 rpm.
[e] Shaker was used to agitate the reaction with a 30 Hz frequency. Overall yield of only 50% was obtained in this case.

ing of the salt with regard to the organic compounds salting-out or -in.[17] Upon the reaction with pentyl isonitrile (**2**) by stirring with water at room temperature, isobutyraldehyde **1a** gave the mixture of **3a** and **4a** in a 40:60 ratio (Scheme 2).[14] By performing the same reaction in a 3 M $Na_2SO_4$, only **3a** was obtained in a quantitative yield (Table 1). Compound **3a** was also the major product when the reaction was performed in 4 M NaCl and $NaBF_4$, the **3a**:**4a** ratios being 85:15 and 65:35, respectively. In contrast, the 4 M $NaPF_6$ solution provided **4a** as the major product (85%), while using 4 M NaOTs (OTs = *p*-$CH_3C_6H_4SO_3$, tosylate) led to **4a** in a 92% yield relative to **3a**. Thus, changing the nature of the simple sodium salts and expanding their spectrum to include the sulfate and *p*-toluenesulfonate anions can completely reverse the selectivity. Previously, only small-to-moderate changes in the isomer ratios of the Diels–Alder reaction upon the addition of common salts were reported.[12]

Unexpectedly, running the reaction with 4 M of NaOAc gave **3a** in a reasonably high quantity, 26%, while giving the acetate **5a** as the major product. Although there is a nearly 70-fold excess of a carboxylate (acetate) that possesses a similar nucleophilicity, the isobutyrate **3a** is still formed in a high yield suggesting that the salting-out properties of sodium acetate work against the acetate anion in the reaction with the water-insoluble Passerini intermediate (*vide infra*).

Encouraged by these results, we explored the salt effect on the reactivity of other aliphatic aldehydes with **2** as well as isocyanoacetate (**6**) (Scheme 3). While using the salting-out sodium sulfate led to the Passerini products **3** and **7**, the salting-in tosylate led to the complete reversal of the reactivity providing the hydrolysis products **4** and **8** almost exclusively (Table 2). In particular, reacting **6** with hexanal or valeraldehyde could lead to the quantitative yields of either **7** or **8** when performed in 3 M $Na_2SO_4$ or 4 M NaOTs, respectively. Importantly, the aqueous salt solutions could be re-used multiple times without changes in the reaction rates or product ratios.

The reactions "on $Na_2SO_4$" were significantly faster than the reactions with 4 M NaOTs. While **3** was observed in a nearly quantitative yield already after 15 min "on $Na_2SO_4$", the formation of **4** took about 2 hours to complete in the case of NaOTs. Furthermore, after 15 min, the reaction showed *ca.* 3:7 ratio between **3** and **4** before giving over 90% of **4** after 2 hours. As two molecules of the aldehyde are required to prepare **3**, its formation rate should be faster at the beginning of the reaction. Noteworthy, the initial oxidation of 1 equivalent of the aldehyde to give the carboxylic acid does not appear to limit the reaction rate or selectivity. The same rates and product ratios were obtained when the reactions were performed under the standard Passerini conditions (aldehyde:acid:isonitrile ratio of 1:1:1) with aqueous salt solutions as the reaction media. These observations suggest that



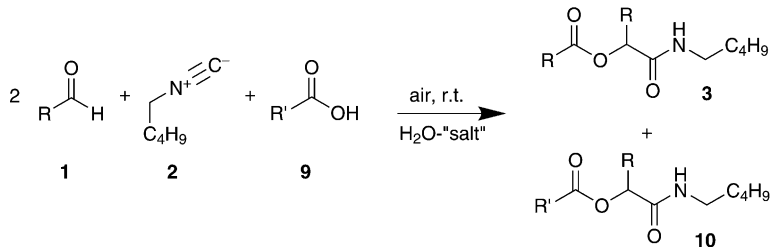

**Scheme 3.** Salting-in and salting-out effect on the product distribution

**Table 2.** Salting-in and salting-out effect on "on water" *vs.* "in water" product ratio.[a]

| Entry | Aldehyde RCHO, R = | Isonitrile $R^1NC$, **2** or **6** | **3**:**4** ratio (**7**:**8** ratio) | | |
|---|---|---|---|---|---|
| | | | $Na_2SO_4$ (3 M) | $H_2O$ | NaOTs (4 M) |
| 1 | *i*-Pr (**1a**) | **2** | 100:0 | 40:60 | 8:92 |
| 2 | *i*-Pr (**1a**) | **6** | 96:4 | 15:85 | 4:96 |
| 3 | $C_4H_9$ (**1b**) | **2** | 99:1 | 74:26 | 5:95 |
| 4 | $C_4H_9$ (**1b**) | **6** | 96:4 | 22:78 | 0:100 |
| 5 | $C_5H_{11}$ (**1c**) | **2** | 100:0 | 97:3 | 7:93 |
| 6 | $C_5H_{11}$ (**1c**) | **6** | 98:2 | 77:23 | 0:100 |
| 7 | *cyclo*-$C_6H_{11}$ (**1d**) | **2** | 96:4 | 91:9 | 6:94 |
| 8 | *cyclo*-$C_6H_{11}$ (**1d**) | **6** | 99:1 | 82:18 | 2:98 |
| 9 | $C_7H_{15}$ (**1e**) | **2** | 100:0 | 100:0 | 16:84 |
| 10 | $C_7H_{15}$ (**1e**) | **6** | 100:0 | 99:1 | 5:95 |

[a] The reactions were performed under the conditions described for Table 1.




**Scheme 4.** External carboxylic acid incorporation under the "on water" conditions.

the partitioning of the reactants between the two phases determines the outcome of the reaction as *i*-PrCOOH is partially soluble in water (5.6% mass).[18] To verify this, we performed the reactions shown in Scheme 3 in the presence of 1 equivalent of competing carboxylic acids. When the NaOTs solution was used as the medium, **4** was the dominant product (generally well over 85%) regardless of the carboxylic acids. "On $Na_2SO_4$", the Passerini product was dominant, its composition being dependent on the hydrophobicity of the added acid (**9**) (Scheme 4, Table 3). For example, with cyclohexanecarboxaldehyde **1d** and **2**, the Passerini product incorporated 90%, 80%, 30% and 20% of two cyclohexyl groups (**3d**) upon the addition of 1 equivalent of acetic, propionic, valeric and octanoic acid, respectively. The considerable hydration of shorter carboxylic acids likely prevents their efficient transfer to the organic phase necessary for the competition in the Passerini reaction to give **10**. The results also suggest that the product-forming step takes place in the organic phase and not at the interface between the two liquids. The necessity for the nucleophile to penetrate the organic phase is more obvious when $Na_2SO_4$ is used as it significantly reduces the solubility of organic reactants in water. For example, the $^1H$ NMR spectra showed that the solubility of hexanal was *ca.* 30 times higher in $D_2O$ than in $D_2O$-3 M $Na_2SO_4$.

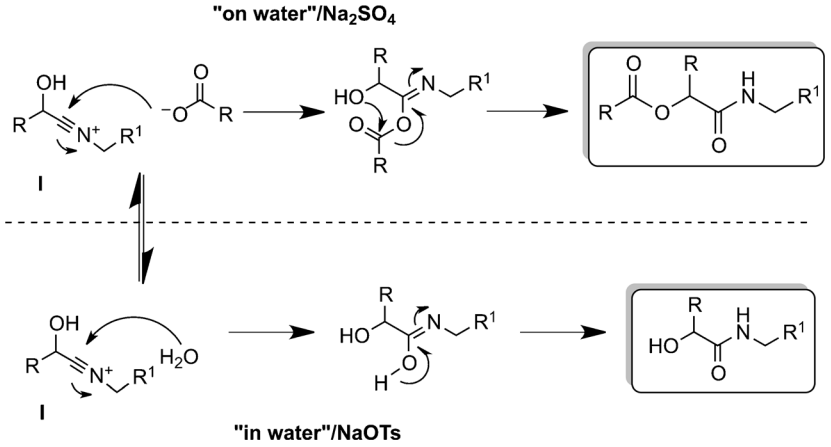
**Table 3.** Hydrophobicity-dependent incorporation of external carboxylic acids in the Passerini reaction product.

| Entry | Aldehyde (**1**) | Acid (**9**) | **3**:**10** ratio[a] |
|---|---|---|---|
| 1 | *cyclo*-$C_6H_{11}CHO$ | $CH_3COOH$ (**9a**) | 91:9[b] |
| 2 | (**1d**) | $C_2H_5COOH$ (**9b**) | 80:20 |
| 3 | | $C_4H_9COOH$ (**9c**) | 29:71 |
| 4 | | $C_7H_{15}COOH$ (**9d**) | 20:80 |
| 5 | $C_7H_{15}CHO$ (**1e**) | $CH_3COOH$ (**9a**) | 96:4[c] |
| 6 | | $C_2H_5COOH$ (**9b**) | 85:15 |
| 7 | | $C_4H_9COOH$ (**9c**) | 54:46 |
| 8 | | $C_5H_{15}COOH$ (**9e**) | 46:54 |

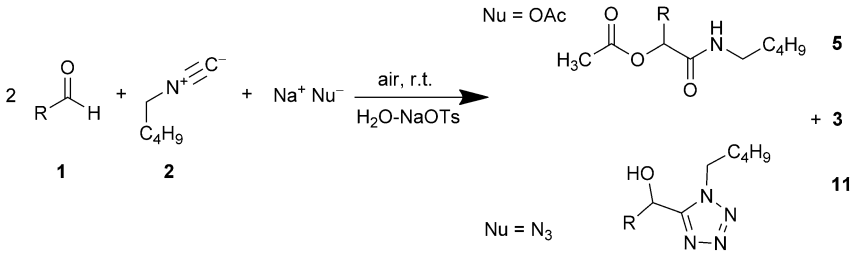
[a] The reactions were performed under the conditions described for Table 1. 1 equivalent of acid and 2 equivalents of aldehyde were used.
[b] **3**:**5d** ratio.
[c] **3**:**5e** ratio.

While the "self-reactivity" in the Passerini reaction is enhanced upon salting-out, the salting-in properties of NaOTs can be used to facilitate reactions between the postulated intermediate (**I**, Scheme 5) and various water-soluble nucleophiles "in NaOTs". As mentioned earlier, the use of 4 M sodium acetate in the combination with **1a** and **2** led to 74% yield of **5a**. With the more hydrophobic **1d**, only *ca.* 10% of the acetate was incorporated in the Passerini product




**Scheme 5.** Proposed competition reactions between the postulated intermediate **I** and nucleophilies in water and "on water".




**Scheme 6.** Reactive intermediate trapping under the "in water" or "in NaOTs" conditions.

upon the reaction with **2** in 4 M NaOAc. However, **5d** was obtained with over 59% selectivity when the reaction was performed in 3 M NaOTs in the presence of only 10 equivalents of NaOAc. Using the 4 M NaOTs and 35 equivalents of KOAc led to the increase in the yield of **5d** to 80%. Furthermore, when the azide was used as the intercepting nucleophile, the tetrazole **11d** was obtained in a 45% yield (*vs.* 53% of **3d**) in 4 M $NaN_3$, and in over 95% yield when performed in 3.8 M NaOTs with only 10 equivalents of $NaN_3$ (Scheme 6).

Thus, synthetically relevant yields of complex molecules can be obtained by using a combination of a nucleophile and salting-in reagent while the use of high concentrations of the nucleophile gives poorer results. These results demonstrate that the reaction product is formed in the aqueous phase when concentrated NaOTs is used.

Interestingly, the reaction between **1b** and cyclohexyl isonitrile in 3.8 M NaOTs and 10 equivalents of $NaN_3$ produced the corresponding tetrazole (**12**) with over 90% selectivity. As the reaction intermediate **I** incorporating these aldehyde and isonitrile partners is expected to have very similar solubility to the intermediate of the reaction between **1d** and **2**, the resulting similarity in the selectivity (compared with *ca.* 95% of **11d**) supports the solubility being a crucial factor in determining the reaction path.

In conclusion, our findings highlight the difference between the reactions "on water" and in aqueous solutions. The addition of simple salts to the aqueous phase can dramatically reverse the selectivity of the Passerini-type multicomponent reactions by shuttling the reactants between the two phases. The obtained information can be used in the development of new synthetic methodologies in aqueous media. Studies on other synthetically useful transformations under the "on water" and in water conditions are currently underway.

## Experimental Section

All reactions were performed in standard deionized water. The reagents were purchased from Sigma-Aldrich and used as received. The aldehydes were purified by distillation. The reactions were performed in test tubes with the Radleys Carousel Workstation.

### General Experimental Procedures

A suspension of aldehyde (0.51 mmol) and isocyanide (0.17 mmol, 3:1 ratio) in a saturated salt solution (3–4 M, 3 mL water) was stirred for 7 h at room temperature in the presence of air in a 50-mL glass reactor. For Table 3, 1 equivalent of acid and 2 equivalents of aldehyde were used. The organic products were extracted with $CH_2Cl_2$, the

solvent was dried on $MgSO_4$ and evaporated. The crude mixture was analyzed by $^1H$ NMR spectroscopy and gas chromatography. The aqueous phase could be recycled multiple times.

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