Available online at www.sciencedirect.com

Tetrahedron Letters 46 (2005) 3957–3960

Tetrahedron Letters

Acceleration of the Passerini reaction in the presence of nucleophilic additives

Maxim A. Mironov,* Maria N. Ivantsova, Maria I. Tokareva and Vladimir S. Mokrushin

Department of Technology of Organic Synthesis (TOSLab), Urals State Technical University, 620002 Ekaterinburg, Russian Federation

Received 14 March 2005; revised 7 April 2005; accepted 12 April 2005

Abstract—An accelerating effect of nucleophilic additives was revealed for the Passerini multi-component reaction. The influence of aqueous solutions on the reaction rate was studied in detail and the direct involvement of water in the bond-making step was attributed as the basis of an accelerating effect. Other nucleophiles were tested as alternatives to water; as a result *N*-hydroxysuccinimide is proposed as an accelerant of the Passerini reaction.

© 2005 Elsevier Ltd. All rights reserved.

Water is known to be an irreplaceable solvent and reagent for biochemical transformations, which are notable for high selectivity and atom efficiency. In the past, synthetic organic chemistry did not use water as a solvent due to poor solubility and, in some cases, the instability of organic reagents in aqueous solutions. Now, it has been recognized that chemical reactions in mixed aqueous solutions or two-phase systems often give better results than in organic solvents and the insolubility of the final products facilitates their isolation.[1] It is also known that several bimolecular reactions are dramatically accelerated in water, but only the Diels–Alder reaction has been studied in detail.[2] In most cases, a reduction of the hydrophobic surface of the reactants during the activation process accounted for the acceleration effect, although polarization of the reactants, complex formation and direct involvement of water in the bond-making step were also discussed.[3] Multi-component reactions (MCR), where a final product is formed from several starting materials, are more complex topics for the study of these effects.[4] In fact, aqueous solutions could have a contrary influence on the rates of sub-reactions and the resulting rate change could be positive as well as negative. Recently, Pirrung and Das Sharma have described the profound rate accelerating effect of aqueous solutions when compared to organic solvents in the case of the Ugi and Passerini multi-component reactions.[5] This acceleration was attributed to a combination of hydrophobic and cohesive energy density effects. In contrast, when carrying out our investigation of the Ugi reaction in water we did not observe this effect and in several cases a considerable decrease in the reaction rate was registered.[6]

Due to the popularity of the Ugi and Passerini reactions as powerful tools for the synthesis of diverse and complex organic compounds it would be useful to study the influence of water on the reaction rates of one example in detail. We would like to present our work devoted to the Passerini multi-component reactions in the presence of water and other hydroxyl-containing compounds. We expect our results to be important for the development of catalysis in the area of isocyanide-based chemistry.

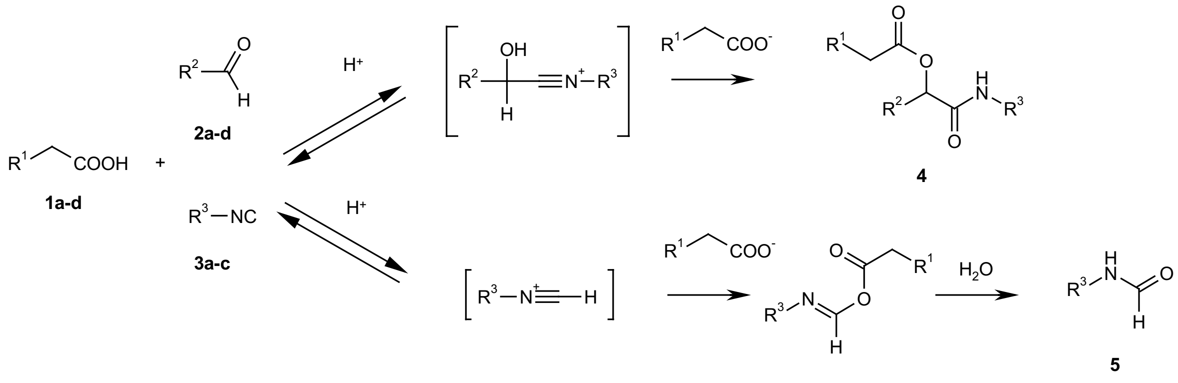
Previously, three main factors, which have an influence on the rate of the Passerini reaction, were evaluated: acidity of the medium, concentration of the reagents and the polarity of the solvents.[4] Thus, in the presence of strong mineral acids the reaction was complete in 1 min.[7,8] It was also established that, in contrast to the Ugi reaction, the Passerini reaction is accelerated in aprotic solvents.[9] Another important factor is the concentration of reagents, because all MCRs including the Passerini reaction proceed better if the reactants are present in high concentration, that is 0.5–1 M.[4] In the case of the Passerini reaction, dilution favours two component side reactions as illustrated in Scheme 1. It

---

Keywords: Passerini reaction; Catalysis; Aqueous solutions; Nucleophilic additives; Isocyanides.

* Corresponding author. Tel.: +7 343 3754888; fax: +7 343 3754135; e-mail: mir@htf.ustu.ru

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.04.050



R^1 = a) H; b) CH_3; c) Ph; d) Phthalimido

R^2 = a) C_2H_5; b) 4-Cl-C_6H_4; c) 3-CH_3O,4-HO-C_6H_3; d) 4-*i*Pr-C_6H_4

R^3 = a) 3-Picolinyl; b) 4-Morpholinyl-C_6H_4; c) *t*-Bu

Scheme 1. The Passerini reaction and competing hydrolysis.

should be noted that these side processes make a study of hydrophobic effects practically impossible. In fact, the low solubility of the reactants in water enhances the influence of the hydrophobic effect on the reaction rate, but the yield of three component products is decreased with dilution. Recently, the accelerating effect of high pressure was discovered for a sterically demanding Passerini reaction.[10]

Taking into account the principal obstacles to the study of the Passerini reaction in dilute aqueous solutions, we chose a relatively concentrated (0.25 M) solution of reactants in pure water and also mixed aqueous solutions as reaction media: water–acetonitrile mixtures (3:1, 1:1 and 1:3). Acetonitrile was used as a solvent mixed with water and, in comparison with benzene, had only an insignificant negative effect on the reaction rate. In the course of this investigation, we also used weak organic acids **1a**–**d**, various aldehydes **2a**–**d**, water-soluble isocyanides **3a** and **b** and water-insoluble isocyanide **3c**. The conversion of starting materials was determined by reverse-phase HPLC monitoring.[11]

The results summarized in Table 1 reveal that the reaction is accelerated in mixed aqueous solutions and even a small addition (up to 10 equiv) of water results in a significant acceleration of the reaction. The reaction time depends strongly on the structure of the aldehydes. Thus, the use of aliphatic aldehyde **2a** results in shortening the reaction time in aqueous solutions. In contrast, the choice of the aromatic aldehyde **2b** leads to an increase in the reaction rate and a decrease of the yields in aqueous solution. Moreover, due to competing hydrolysis of the isocyanide, no products could be isolated using the aromatic aldehyde **2c**, which contains an electron-donating group. It should be noted that due to the hydrolysis of isocyanides, the yields of the target products **4** in aqueous solution were lower than in pure acetonitrile. In addition, we have noted a correlation between the concentration of the reactants and the observed ratio of products **4/5**. For example, reaction of aromatic aldehydes with isocyanides and organic acids failed in pure water at a concentration lower than 0.1 M. On the other hand, we found that the ratio of **4/5** can be improved if both isocyanide and aldehyde are liquids, which are poorly soluble in water, so they form a separate phase, whilst the acid has good solubility in water (combination **1b**; **2d**; **3c**). In contrast, the use of water-soluble isocyanides **3a** and **b** in combination with insoluble aldehydes and acids has a negative effect (combi-

Table 1. The Passerini reaction in aqueous solutions at 0.25 M concentrations

Combination	Reaction time[a] (h)/isolated yields of the Passerini products after 72 h (%)				
	Acetonitrile	Acetonitrile–water, 3:1	Acetonitrile–water, 1:1	Acetonitrile–water, 1:3	Water
1a; **2a**; **3a**	92/80	47/92	18/90	5/85	3/78
1a; **2a**; **3b**	65/93	34/90	13/86	3.5/82	2/75
1a; **2b**; **3a**	225/41	112/15[b]	94/12[b]	89/10[b]	87/9[b]
1a; **2b**; **3b**	160/55	89/11[b]	82/9[b]	76/8[b]	75/8[b]
1a; **2c**; **3b**	>300/12	95/0[b]	70/0[b]	70/0[b]	69/0[b]
1b; **2d**; **3c**[c]	193/42	—	74/24[b]	—	11/62
1c; **2d**; **3a**[c]	182/49	—	85/10[b]	—	88/9[b]
1d; **2b**; **3b**[c]	167/46	—	79/11[b]	—	74/7[b]

[a] This time indicates 90% conversion of starting isocyanide for aliphatic aldehydes and 75% for aromatic aldehydes (HPLC monitoring).

[b] Hydrolysis of isocyanides is the predominant process.

[c] The system is heterogeneous.

nations **1c**; **2d**; **3a** and **1d**; **2b**; **3b**). These data are also summarized in Table 1. It should be noted that the reaction times for the heterogeneous systems are not accurate because the reaction rates are correlated with intensity of shaking or magnetic stirring. In addition, these systems were sensitive to the addition of surfactants. For example, addition of a 0.1 M amount of cetylpyridinium chloride results in a nearly 30-fold decrease of reaction time for the combination **1b**; **2d**; **3c**. Taking this into account, we suggest that the Passerini reaction might be taking place on the boundary surface. Indeed, at high concentrations of isocyanide and aldehyde, which are favourable for formation of an adduct, effective protonation of this adduct on the phase boundary can promote the Passerini reaction.

In summary, despite a pronounced accelerating effect, aqueous solutions can only be used in organic synthesis as a media for the Passerini reaction occasionally due to the known reactivity of water towards isocyanides and the sensitivity of the process in water due to the solubility of starting reagents.

Thus, water seems to be not only a solvent for the Passerini reaction but its influence can be explained through direct involvement in the bond-making step. We suggest that water plays the role of nucleophilic additive increasing the addition rate of the isocyanide as a second nucleophile. Therefore, reagents used in peptide chemistry as nucleophilic additives (*N*-hydroxybenzotriazole, *N*-hydroxysuccinimide and 4-nitrophenol) have been tested to verify this theory.[12] All the reagents exhibited a profound rate accelerating effect, but *N*-hydroxysuccinimide was selected as a more conventional additive due to its good solubility in water, facilitating isolation of the target products.[13] Selected results of the Passerini reaction in the presence of *N*-hydroxysuccinimide are summarized in Table 2. These data reveal the fact that the reaction time in the presence of 1 equiv of *N*-hydroxysuccinimide can be compared with the reaction time in 50–75% aqueous solutions. On the other hand, no side hydrolysis was observed with *N*-hydroxysuccinimide. In addition, the effect did not depend on the comparative solubility of the starting reagents in water. In this way, our attempt to separate the accelerating effect from its solvent component was successful. As a result, the independent finding of an 'ideal' solvent and accelerator is now possible for each combination of the starting reagents in the Passerini reaction. Interestingly it was found that nucleophiles with a donating group like mercaptans have a negative effect on the reaction rate opening the way to the development of inhibitors for the Passerini reaction.

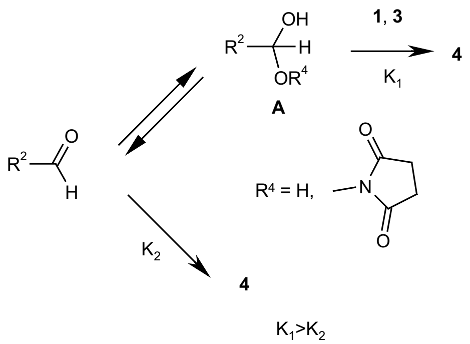
Table 2. The Passerini reaction in the presence of *N*-hydroxysuccinimide

Combination	Reaction time[a] (h)	Isolated yields (%)
1a; **2a**; **3a**	12	93
1a; **2a**; **3b**	9	95
1b; **2d**; **3c**	65	89
1d; **2b**; **3b**	56	86

[a] This time indicates 90% conversion of starting isocyanide for aliphatic aldehydes and 75% conversion of starting aldehydes (HPLC monitoring).

Despite its long study, the mechanism of the Passerini reaction is still a matter for discussion, because kinetic and preparative investigations have led to different mechanistic suggestions.[4] As intermediates in this reaction hemiacetals,[14] *N*-protonated isocyanides,[7] zwitter ionic[15] and hydrogen-bonded adducts[9] have been proposed. It is also not known which step determines the reaction rate. Analysis of published data allows discrimination between reactions in the presence of strong and weak acids. Therefore, it is correct to consider the formation of a hydrogen-bonded adduct of the carbonyl compound with organic acids to be a rate-determining step, if we discuss the Passerini reaction promoted by weak acids. This mechanism can explain the significantly slower rates observed in protic, hydrogen-bonding solvents. On the other hand, the effective protonation of an isocyanide–carbonyl adduct seems to be possible for strong acids and so, the formation of this adduct is a rate-determining step in the present instance. This supposition is corroborated by the observation[7] that, using aqueous solutions of mineral acids, it is impossible to carry out the Passerini reaction without a great excess (5–10 equiv) of carbonyl compound due to the side protonation of isocyanides. In this way, the mechanism of the reaction depends on the nature of the starting materials and can also be changed through solvent replacement. Using this idea as a basis we propose the following mechanism for reaction acceleration in aqueous solutions or in the presence of hydroxyl-containing additives (Scheme 2). The first step is the reversible formation of adduct **A** with water or *N*-hydroxysuccinimide, which can react with isocyanide faster than the starting carbonyl compound. We consider such a model to be good for an explanation of the more pronounced effect in the case of aliphatic aldehydes. The formation of adduct **A** is less preferable for aromatic aldehydes because the sp^2–sp^2 bond is converted into the less stable sp^2–sp^3 bond. The proposed mechanism is a rough model, which requires improvement. Multicomponent condensations involve a set of reversible sub-reactions and many factors have an influence on chemical equilibriums.[16]

The investigations presented in this work allow us to predict further development of our method for



Scheme 2. Proposed mechanism of the effect.

acceleration of isocyanide-based multi-component reactions (IBMCRs). In our opinion, the most promising area is the discovery of new IBMCRs.[17] The discovery of novel IBMCRs in the presence of nucleophilic additives is in progress and results will be published in due course. We also hope that chiral nucleophilic additives may be used for stereochemical induction in the Passerini reaction.[18]

In summary, we have found that the rate accelerating effect for the Passerini reaction in aqueous solutions cannot be explained only through the properties of water as a solvent. This effect has been attributed to the direct involvement of water in a bond-making step and this was collaborated by the similar influence of other nucleophiles. Using nucleophilic additives, we have discovered a novel method for the acceleration of the reaction. These observations will be useful for the creation of practical and mild procedures for obtaining diverse compounds using the Passerini reaction.

Acknowledgement

This work was supported in part by CRDF (REC-005).

References and notes

1. *Organic Synthesis in Water*; Grieco, Ed.; Blackie Academic & Professional: Glasgow, 1998; *Green Chemistry, frontiers in benign Chemical Synthesis and Processes*; Anastas, P., Williamson, T. C., Eds.; Oxford University Press: New York, 1998.
2. Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816; Grieco, P. A.; Garner, P.; Zhen-min, He. *Tetrahedron Lett.* **1983**, *24*, 1897; Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901.
3. Blokzijl, W.; Engberts, J. B. F. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1545.
4. Ugi, I.; Dömling, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.
5. Pirrung, M. C.; Das Sarma, K. *J. Am. Chem. Soc.* **2004**, *126*, 444; Pirrung, M. C.; Das Sarma, K. *Synlett* **2004**, 1425.
6. Mironov, M. A.; Ivantsova, M. N.; Mokrushin, V. S. *Mol. Divers.* **2003**, *6*, 193.
7. Hagedorn, I.; Eholzer, U. *Chem. Ber.* **1965**, *98*, 936; Hagedorn, I.; Eholzer, U.; Winkelmann, H. D. *Angew. Chem.* **1964**, *76*, 583.
8. König, S.; Klösel, R.; Karl, R.; Ugi, I. *Z. Naturforsch B.* **1994**, *49*, 1586.
9. Ugi, I.; Meyer, R. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8.
10. Jenner, G. *Tetrahedron Lett.* **2002**, *43*, 1235.
11. HPLC analysis of the reaction products. The mixtures were analyzed by reversed-phase HPLC with detection at 230 nm. Chromatography was performed on a Hewlett-Packard HP 1090 apparatus equipped with a diode-array detector. A reverse-phase column was used (Hypersil® BDS C18, 3 μ, 50 × 4.6 mm) under an optimized binary gradient acetonitrile/water, flow 0.5 mL/min. To validate the analytical method, some products and starting materials were characterized separately. The peaks were assigned to the corresponding products by comparison of the retention time and UV profiles.
12. Anderson, G. W.; Zimmerman, J. E.; Gallahan, F. M. *J. Am. Chem. Soc.* **1963**, *85*, 3039; König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788.
13. General procedure. A mixture of 0.3 mmol of each of the compounds: aldehyde, acid and anhydrous *N*-hydroxysuccinimide were stirred in 0.5 mL of acetonitrile for 2 h at 20 °C. Then 0.3 mmol of isocyanide was added to the mixture. After the reaction was complete, solutions were evaporated to dryness and the residue was washed with water. The crude mixture was purified by crystallization or flash-chromatography. A typical ^{1}H NMR spectrum of a Passerini product (combination **1d**; **2b**; **3b**). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.55$ (s, 1H, NH), 7.93–7.84 (m, 4H, phthaloyl), 7.61 (d, $J = 8.6$ Hz, 2H, C_6H_4Cl), 7.43 (d, $J = 8.6$ Hz, 2H, C_6H_4Cl), 6.83 (d, $J = 8.9$ Hz, 2H, C_6H_4-4-morpholinyl), 6.69 (d, $J = 8.9$ Hz, 2H, C_6H_4-4-morpholinyl), 6.12 (s, 1H, CH), 4.78 (d, $J = 17.8$ Hz, 1H, CH_2), 4.49 (d, $J = 17.8$ Hz, 1H, CH_2), 3.72 (t, $J = 4.7$ Hz, 4H, $O(CH_2)_2$), 3.02 (t, $J = 4.7$ Hz, 4H, $N(CH_2)_2$). Anal. Calcd for $C_{28}H_{24}ClN_3O_6$: C, 62.98; H, 4.53; N, 7.87. Found: C, 62.83; H, 4.62; N, 8.01.
14. Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126.
15. Baker, R. H.; Stanonis, D. *J. Am. Chem. Soc.* **1951**, *73*, 699.
16. Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366.
17. Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306; Mironov, M. A.; Mokrushin, V. S.; Maltsev, S. S. *Synlett* **2003**, 943.
18. Kusebauch, U.; Beck, B.; Messer, K.; Herdweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 4021; Frey, R.; Galbraith, S. G.; Guelfi, S.; Lamberth, C.; Zeller, M. *Synlett* **2003**, 1536; Denmark, S.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825.