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Solvent-Free Passerini Reactions

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Solvent-Free Passerini Reactions

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Abstract: The influence of the substrate structure and concentration on the yield of the Passerini reaction was studied. A new, solvent-free methodology for a convenient preparation of α-acyloxyamides **4** was established and compared to the classical methodology. A higher reaction yield was obtained in shorter time, especially in the case of aromatic aldehydes.

Keywords: α-acyloxyamides, aromatic aldehydes, Passerini reaction, solvent free

Multicomponent reactions (MCRs) are synthetically useful organic transformations in which three or more different starting materials react together to form a final product in a one-pot procedure.[1–4] For that reason, the optimization of MCRs is one of the crucial factors in drug-design development.

One of the most widely used MCRs is the Passerini three-component condensation, in which an aldehyde **1**, a carboxylic acid **2**, and an isocyanide **3** react to form an α-acyloxyamide **4** (Scheme 1).[5]

The Passerini reaction is simple, performed in one pot, gives products in high yields, and has a 100% atom economy, which nearly satisfies the definition of an ideal synthesis, as given by P. A. Wender et al.[6] The common problems in the Passerini reactions are associated with purification of the product and low reaction yields when aromatic aldehydes are used.[7–9]

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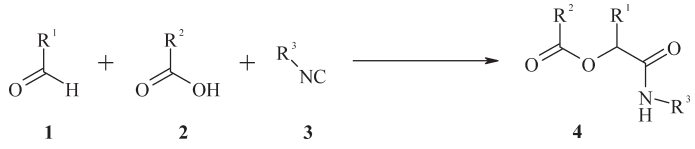


Scheme 1. Passerini reaction.

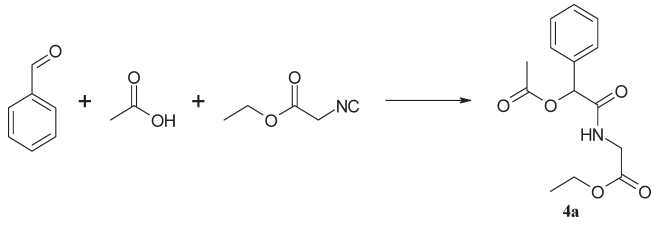
Several solutions for the latter problem were established: application of water as a reaction solvent, which makes purification easier, or use of high pressure, which improves the outcome of the sterically congested Passerini reactions.[10,11] Sometimes, the use of metal catalysts gives good results.[12]

During our studies, we were interested in an efficient synthesis of the α-acyloxyamide **4a**, derived from benzaldehyde (Scheme 2). This compound is an important building block in the synthesis of biodegradable polymers[13,14] and the drugs related to Parkinson's Disease.[15]

An initial experiment was performed under classic conditions in the methylene chloride solution, and the desired product was obtained after 24 h in 14% yield. A two-fold increase of the substrate concentrations doubled the yield. This result encouraged us to study systematically the influence of the substrate concentrations on the yield of the Passerini reaction.

The results depicted in Fig. 1 show that there is a linear correlation between the substrate concentrations and the yield of reactions studied. It is important to note that the product **4a** precipitates from the reaction mixture if the reaction is performed at a concentration of substrates greater than 2.5 mol/L. A simple crystallization of the obtained product yields the analytically pure compound. The concentration of 3.0 M is the maximum attainable if a solvent is used.

In the next step, the same reaction was performed without any solvent. The product was obtained in 86% yield after crystallization, which greatly improved the efficiency of this synthesis. The same reaction performed in a DCM solution under the classical conditions led to the desired product in 22% yield (Table 1, entry 1). The concentration of the substrates was 1 mol/L.



Scheme 2. Model reaction.

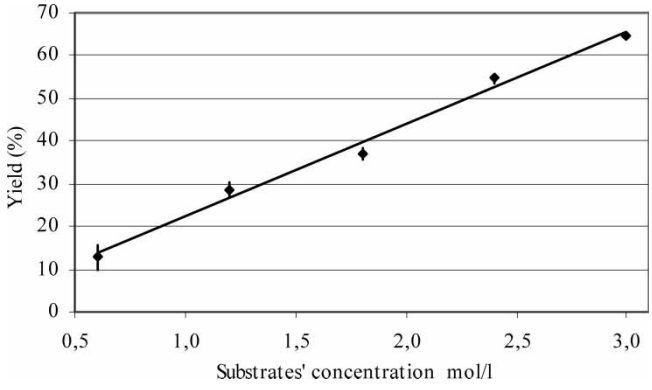


Figure 1. Influence of the substrate concentrations on the yield of the model Passerini reaction.

These results encouraged us to perform a systematic study in which the yields of the classical and solvent-free approaches were compared (see Table 1).

The solvent-free procedure resulted in a considerable increase of yield in the case of both aromatic and aliphatic acids (entries 1–3, Table 1). When an aromatic isocyanide was used for the reaction (entry 4, Table 1), an increase of the yield in the solvent-free procedure was also observed, compared to the classical conditions (55% vs. 36%). On the other hand, the products derived

Table 1. Influence of the substrate structures and the reaction condition on the yield of the Passerini reaction

Entry	Compound	R^1	R^2	R^3	Yield (%) (solvent-free)	Yield (%) (DCM)
1	**4a**	Ph	CH_3	CH_2CO_2Et	86	22
2	**4b**	Ph	CH_2Br	CH_2CO_2Et	56	30
3	**4c**	Ph	Ph	CH_2CO_2Et	82	29
4	**4d**	Ph	CH_3	$PhCH_2$	55	36
5	**4e**	$PhCH_2$	CH_3	CH_2CO_2Et	89	90
6	**4f**	C_2H_5	CH_3	CH_2CO_2Et	57	88
7	**4g**	$(CH_3)_2CHCH_2$	CH_3	CH_2CO_2Et	53	96
8	**4h**	C_7H_{15}	CH_3	CH_2CO_2Et	65	89
9	**4i**	4-MeO-Ph	4-MeO-Ph	CH_2CO_2Et	0	0
10	**4j**	4-MeO-Ph	4-NO_2-Ph	CH_2CO_2Et	23	11
11	**4k**	4-NO_2-Ph	4-NO_2-Ph	CH_2CO_2Et	44	42
12	**4l**	4-F-Ph	4-NO_2-Ph	CH_2CO_2Et	55	12
13	**4m**	4-F-Ph	4-MeO-Ph	CH_2CO_2Et	20	3

from aliphatic aldehydes were obtained in good yields when the reaction was performed in dichloromethane (88–90%, entries 6–8, Table 1), although the purification procedure was much more difficult. Regardless of the protocol used, the reaction between *p*-anisaldehyde, *p*-methoxybenzoic acid, and isocyanoacetic acid ethyl ester failed (entry 9, Table 1).

For aromatic substrates, the influence of the functional group present on phenyl rings was investigated. The highest yield enhancement was obtained when one of these substrates bears an electron-withdrawing group, while the other had an electron-donating group (entries 10 and 13, Table 1). When the electron densities of the aldehyde and the acid were altered in the same direction, no yield enhancement was observed (entry 11, Table 1), although the product purification was very easy in the solvent-free procedure.

CONCLUSIONS

The Passerini reaction, which is widely used in the synthesis of peptidomimetics, can be efficiently carried out under solvent-free conditions. Even in the case of aliphatic aldehydes, for which the reaction proceeds less efficiently, it is an interesting alternative to the classical approach, simplifying the isolation and purification of the product. According to the best of our knowledge, this is the first example of a solvent-free approach to the Passerini reaction, which is a standard of green chemistry and a characteristic of an ideal synthesis.

EXPERIMENTAL

General Solvent Procedure

Aldehyde **1** (3.0 mmol) and isocyanide **3** (3.3 mmol) were added to the solution of a carboxylic acid **2** (3.3 mmol) in methylene chloride (3 mL) at room temperature. The reaction mixture was stirred at ambient temperature for 24 h and then concentrated in vacuo. The crude product was purified by silica-gel flash chromatography using hexane/ethyl octane 6:4 as an eluent to afford the corresponding product **4**.

General Solvent-Free Procedure

Isocyanide **3** (3.3 mmol) was added to the suspension of the carboxylic acid **2** (3.3 mmol) and the aldehyde **1** (3.0 mmol) at room temperature. The reaction mixture was stirred at ambient temperature for 24 h and then concentrated in vacuo. The crude product was purified by crystallization from ethyl octane/hexane to afford the corresponding product **4**.

Data

Compound **4a**: mp 95–97 °C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.1$ Hz, 3H), 2.19 (s, 3H), 4.06 (d, $J = 5.1$ Hz, 2H), 4.22 (q, $J = 7.1$ Hz, 2H), 6.13 (s, 1H), 6.72 (s, 1H), 7.33–7.497 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.7$, 21.6, 41.8, 62.3, 75.9, 128.0, 129.3, 129.4, 129.6, 135.8, 168.9, 169.6, 170.0. Anal. calcd. for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.01. Found: C, 60.14; H, 6.22; N, 5.12, HRMS (ESI): m/z calcd. for $C_{14}H_{17}NO_5Na$ $[M + Na]^+$: 302.1004, Found: 302.0999.

Compound **4b**: mp 94–95 °C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.1$ Hz, 3H), 3.95 (s, 2H), 4.06 (dd, $J = 3.0$ Hz, $J = 5.7$ Hz, 2H), 4.21 (q, $J = 7.1$ Hz, 2H), 6.17 (s, 1H), 6.80 (s, 1H), 7.36–7.48 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.7$, 25.9, 41.9, 62.3, 76.7, 127.9, 129.1, 129.7, 134.9, 165.6, 167.9, 169.6. Anal. calcd. for $C_{14}H_{16}BrNO_5$: C, 46.95; H, 4.50; N, 3.91. Found: C, 46.94; H, 4.62; N, 3.78. HRMS (ESI): m/z calcd, for $C_{14}H_{16}BrNO_5Na$ $[M + Na]^+$: 380.0109, Found: 380.0104.

Compound **4c**: mp 101–103 °C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.26$ (t, $J = 7.1$ Hz, 3H), 4.08 (dd, $J = 5.3$ Hz; $J = 7.1$ Hz, 2H), 4.21 (q, $J = 7.1$ Hz, 2H), 6.39 (s, 1H), 6.80 (s, 1H), 7.25–8.14 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.4$, 41.6, 62.0, 76.1, 127.8, 128.9, 129.1, 129.4, 130.1, 134.0, 135.6, 165.3, 168.7, 169.7. Anal. calcd. for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.61; H, 5.82; N, 4.11. HRMS (ESI): m/z calcd. for $C_{19}H_{19}NO_5Na$ $[M + Na]^+$: 364.1160. Found: 364.1155.

Compound **4d**: mp 88–90 °C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.13$ (s, 3H), 4.43 (d, $J = 5.6$ Hz, 2H), 6.09 (s, 1H), 6.55 (s, 1H), 7.17–7.44 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 21.6$, 43.9, 76.2, 127.9, 128.1, 129.2, 129.3, 129.5, 136.0, 138.2, 168.8, 169.7. Anal. calcd. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.95. Found: C, 72.07; H, 6.16; N, 4.91. HRMS (ESI): m/z calcd. for $C_{17}H_{17}NO_3$ $[M + Na]^+$: 306.1106, Found: 306.1101.

Compound **4e**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.1$ Hz, 3H), 2.08 (s, 3H), 3.04–3.34 (m, 2H), 3.99 (dd, $J = 3.6$ Hz, $J = 5.1$ Hz, 2H), 4.21 (q, $J = 7.1$ Hz, 2H), 5.42 (dd, $J = 4.7$ Hz, $J = 7.5$ Hz, 1H), 6.48 (s, 1H), 7.13–7.35 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.7$, 21.4, 38.3, 41.6, 62.2, 74.7, 127.5, 128.9, 129.9, 130.0, 136.4, 169.7, 169.9, 171.1. Anal. calcd. for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.62; H, 6.64; N, 4.81. HRMS (ESI): m/z calcd. for $C_{15}H_{19}NO_5Na$ $[M + Na]^+$: 316.1161. Found: 316.1155.

Compound **4f**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 7.4$ Hz, 3H), 1.23 (t, $J = 7.1$ Hz, 3H), 1.84–2.08 (m, 2H), 2.12 (s, 3H), 3.98 (dd, $J = 2.5$ Hz, $J = 5.1$ Hz, 2H), 4.16 (q, $J = 7.1$ Hz, 2H), 5.07–5.13 (m, 1H), 6.59 (s, 1H). ^{13}C NMR (50 MHz, CDCl3): $\delta = 8.9$, 14.1, 20.9, 25.0, 40.9,

61.6, 74.7, 169.5, 169.5, 169.8. Anal. calcd. for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.82; H, 7.46; N, 5.91, HRMS (ESI): m/z calcd. for $C_{10}H_{17}NO_5Na$ $[M + Na]^+$: 254.1004. Found: 254.0999.

Compound **4g**: mp 44–46 °C. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.94$ (d, $J = 3.9$ Hz, 6H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.71–1.98 (m, 3H), 2.16 (s, 3H), 4.01–4.05 (m, 2H), 4.22 (q, $J = 7.1$ Hz, 2H), 5.25–5.52 (m, 1H), 6.71 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.6$, 17.4, 19.2, 31.2, 41.5, 62.1, 78.4, 170.1, 170.2, 176.0. Anal. calcd. for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.57; H, 8.34; N, 5.38. HRMS (ESI): m/z calcd. for $C_{12}H_{21}NO_5Na$ $[M + Na]^+$: 282.1317. Found: 282.1312.

Compound **4h**: ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 7.0$ Hz, 3H), 1.25–1.32 (m, 15H), 1.85–2.05 (m, 2H), 2.17 (s, 3H), 4.01–4.07 (m, 2H), 4.22 (q, $J = 7.1$ Hz, 2H), 5.20–5.37 (m, 1H), 6.61 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.6$, 14.6, 21.4, 23.1, 25.2, 29.5, 29.7, 32.2, 32.4, 41.5, 62.1, 74.4, 170.0, 170.1, 170.6. Anal. calcd. for $C_{15}H_{27}NO_5$: C, 59.78; H, 9.03; N, 4.65. Found: C, 59.61; H, 8.95; N, 4.63. HRMS (ESI): m/z calcd. for $C_{15}H_{27}NO_5Na$ $[M + Na]^+$: 324.1787. Found: 324.1798.

Compound **4i**: The substrates were recovered instead.

Compound **4j**: ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.2$ Hz, 3H), 3.81 (s, 3H), 4.08 (dd, $J = 3.6$ Hz, $J = 4.9$ Hz, 2H), 4.22 (q, $J = 7.1$ Hz, 2H), 6.32 (s, 1H), 6.54 (s, 1H), 6.94 (d, $J = 8.8$ Hz, 2H), 7.49 (d, $J = 8.8$ Hz, 2H), 8.15–8.45 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 14.5$, 41.7, 55.7, 62.1, 76.6, 114.7, 123.9, 126.8, 129.7, 131.2, 163.6, 168.3, 169.7. Anal. calcd. for $C_{20}H_{20}N_2O_8$: C, 57.69; H, 4.84; N, 6.73. Found: C, 57.72; H, 4.71; N, 6.73. HRMS (ESI): m/z calcd. for $C_{20}H_{20}N_2O_8Na$ $[M + Na]^+$ 439.1117. Found: 439.1126.

Compound **4k**: ^1H NMR (200 MHz, $CDCl_3$ + DMSO): $\delta = 1.16$ (t, $J = 7.0$ Hz, 3H), 3.96–4.02 (m, 2H), 4.16 (q, $J = 7.4$ Hz, 2H), 6.51 (s, 1H), 7.9 (d, $J = 8.8$ Hz, 2H), 8.26 (d, $J = 8.8$ Hz, 2H), 8.30–8.38 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$ + DMSO): $\delta = 13.8$, 60.9, 65.3, 74.8, 123.2, 123.3, 128.2, 130.8, 134.0, 141.7, 147.6, 150.3, 162.9, 167.0, 168.8. Anal. calcd. for $C_{19}H_{17}N_3O_9$: C, 52.90; H, 3.97; N, 9.74. Found: C, 53.05; H, 4.16; N, 9.53. HRMS (ESI): m/z calcd. for $C_{19}H_{17}N_3O_9Na$ $[M + Na]^+$: 454.0862. Found: 454.0879.

Compound **4l**: ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.2$ Hz, 3H), 4.09 (dd, $J = 4.0$ Hz, $J = 4.9$ Hz, 2H), 4.22 (q, $J = 7.1$ Hz, 2H), 6.35 (s, 1H), 6.72 (s, 1H), 7.06–7.15 (m, 2H), 7.50–7.63 (m, 2H), 8.30–8.36 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 14.5$, 41.7, 62.2, 76.1, 116.1, 116.6, 124.0, 130.0, 130.1, 130.7, 130.7, 131.2, 134.6, 151.1, 163.4, 167.9, 169.6. Anal. calcd. for $C_{19}H_{17}FN_2O_7$: C, 56.44; H, 4.24; N, 6.93. Found: C, 55.99; H, 4.56; N, 6.54. HRMS (ESI): m/z calcd. for $C_{19}H_{17}FN_2O_7Na$ $[M + Na]^+$: 427.0917. Found: 427.0906.

Compound **4 m**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.1$ Hz, 3H), 3.87 (s, 3H), 4.09 (dd, $J = 5.2$ Hz, $J = 11.7$ Hz, 2H), 4.22 (q, $J = 7.1$ Hz, 2H), 6.35 (s, 1H), 6.85–7.20 (m, 5H), 7.50–7.63 (m, 2H), 8.20–8.40 (m, 2H). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 14.5$, 41.6, 55.8, 62.0, 75.0, 114.2, 115.8, 116.2, 121.4, 129.6, 129.7, 129.8, 129.9, 131.8, 132.2, 132.6, 164.2, 168.8, 169.9. Anal. calcd. for $C_{20}H_{20}FNO_6$: C, 61.69; H, 5.18; N, 3.60. Found: C, 61.40; H, 5.17; N, 3.74. HRMS (ESI): m/z calcd. for $C_{20}H_{20}FNO_6Na$ $[M + Na]^+$: 412.1172. Found: 412.1181.

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