Tetrahedron Letters 53 (2012) 306–308

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Fast and efficient solvent-free Passerini reaction

Till Bousquet [a,b,c,*], Mouhamad Jida [a,c,d], Mohamad Soueidan [a,b,c], Rebecca Deprez-Poulain [a,c,d], Francine Agbossou-Niedercorn [a,b,c], Lydie Pelinski [a,b,c,*]

[a] *Université Lille Nord de France, Lille, France*
[b] *UMR CNRS 8181, Unité de Catalyse et de Chimie du Solide, Université de Lille 1, 59655 Villeneuve d'Ascq Cedex, France*
[c] *PRIM, Pôle de Recherche Interdisciplinaire sur le Médicament, Lille F-59000, France*
[d] *Biostructures and Drug Discovery, INSERM U761, Faculté de Pharmacie, 3 rue du Pr Laguesse, Lille F-59006, France*

ARTICLE INFO

Article history:
Received 14 October 2011
Revised 28 October 2011
Accepted 4 November 2011
Available online 12 November 2011

Keywords:
Passerini reaction
Solvent free
High temperature

ABSTRACT

A Passerini three component condensation between a carboxylic acid, an aldehyde, and an isocyanide at high temperature under solvent-free conditions was developed. This methodology allows the formation of a broad range of α-acyloxyamides in excellent yields in short reaction times.

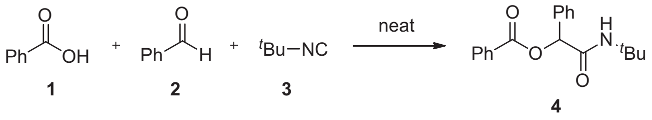
Multicomponent reactions (MCRs) are convergent reactions in which three or more reagents are combined to react in a one pot procedure.[1] They have been extensively studied over the past few years, leading to products exhibiting a great structural diversity in an environmentally friendly way with regards to the concept of atom economy.[2] Among these processes, the Passerini reaction is classified as an isocyanide multicomponent reaction (IMCR) and deals with the condensation of an isocyanide, an aldehyde, and a carboxylic acid.[3] This reaction is typically carried out with high concentrations of starting materials in an inert aprotic solvent (usually methylene chloride).[3,4] Depending on the nature of the substrate, reaction times ranging from hours to several days are often required.

In the last decade, several optimizations have been achieved to improve the yield, reduce the cost, the ecological impact, and the reaction times of the Passerini reaction. Thus, processes have been described in aqueous solution,[5] ionic liquid,[6] without solvent either at room temperature,[7] or under microwave irradiation activation.[8] However, the solvent-free method at room temperature gives products in low to moderate yields when aliphatic aldehydes were reacted.[7] Although this limitation can be overcome by a microwave-assisted procedure,[8] an alternative could be interesting since this irradiation process is not easy to scale up. On the other side, ionic liquids are interesting solvents for organic transformations, however they are not as green as expected and are usually quite expensive.[9] In addition, carrying out a very efficient reaction followed by an effective isolation of highly functionalized products from ionic liquids remains still a challenge.

Given our ongoing interest in MCRs[10] and considering the high potential of the Passerini reaction, we wish to report herein a new green protocol to perform the reaction at high temperature under solvent-free conditions on a broad range of substrates.

Initial experiments were performed to determine the temperature and reaction times required to complete the transformation under solvent-free conditions (Table 1).

Table 1
Optimization of Passerini reaction conditions under solvent-free conditions



Entry	Temperature (°C)	Reaction time (min)	Conversion (%)[a]	Yield (%)[b]
1	80	20	88	70
2	100	20	100	86
3	120	15	100	85
4	150	10	100	84
6	180	4	100	88
7	200	2	100	77

[a] Determined by ^{1}H NMR.
[b] Isolated yields.

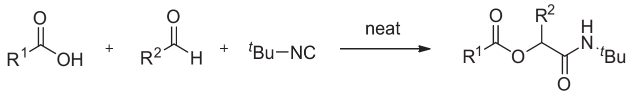
---

* Corresponding authors.
E-mail address: till.bousquet@univ-lille1.fr (T. Bousquet).

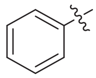
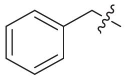
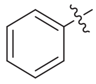
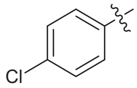
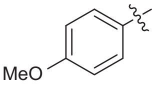
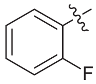
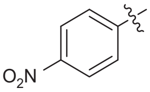
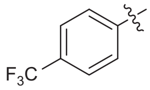
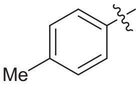
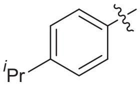
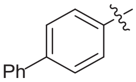
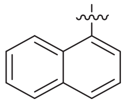
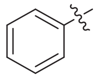
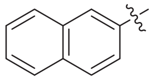
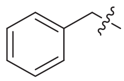
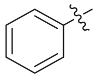
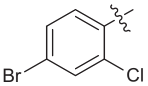
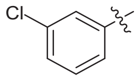
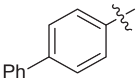
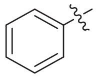
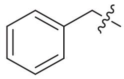
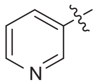
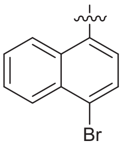
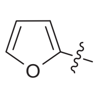
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.11.028

First, 1.1 equiv of benzoic acid **1**, 1 equiv of benzaldehyde **2,** and 1 equiv of *tert*-butyl isocyanide **3** were combined and reacted at 80 °C[11] for 10 min providing the α-acyloxy amide **4** with 88% conversion and in a 70% yield (entry 1, Table 1). Increasing the temperature to 100 °C for 20 min resulted in higher conversion (100%) and yield (86%) (entry 2). Although these reaction conditions are already interesting, we have investigated the limits of the method by increasing further the temperature. As expected, shorter reaction times were required to reach full conversions (180 °C, 2 min, 100% conversion, entry 6) At 200 °C, the product was isolated in lower yield (77%) suggesting degradation due to overheating (entry 7).

Table 2
Passerini reaction under solvent-free conditions with *tert*-butyl isocyanide



5 **6** **3** **7**

Entry	R¹	R²	Product	Yields (%)[a]
1			**7a**	80
2			**7b**	86 (70[b])
3			**7c**	82
6			**7d**	88
7			**7e**	83
8			**7f**	86
9			**7g**	92
10			**7h**	85
11			**7i**	83
12			**7j**	90
13			**7k**	78
14			**7l**	76

[a] Isolated yields.
[b] Under microwave irradiation at 120 °C for 1 min (40 W).

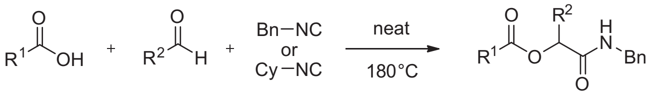
Thus, this optimization has highlighted a range of temperatures where the target product **4** can be isolated in good yields. For the following experiments, the temperature was set to 180 °C and the reaction time to 4 min.[12]

The scope of the process has been demonstrated by the evaluation of a large array of reagents by varying the isocyanide, the carboxylic acid, and the aldehyde.

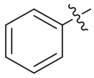
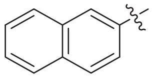
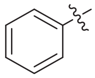
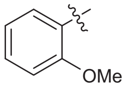
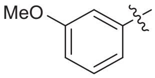
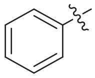
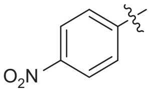
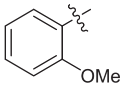
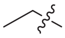
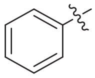
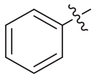
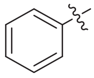
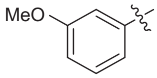
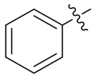
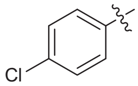
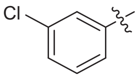
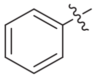
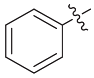
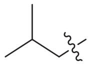
In the first series of experiments, *tert*-butyl isocyanide was condensed with various carboxylic acids and aldehydes bearing electron-donating or -withdrawing groups (Table 2).

In all cases, the desired products **7a–j** were isolated in good yields ranging from 76 to 92% (Table 2). When compared to the literature data, the reaction promoted by microwave irradiation provided product **7b** in a 70% yield at 120 °C,[8] while the classical thermal heating procedure applied here allowed a significant improvement of the yield (86% vs 70%) (entry 2). Thus, although microwave–assisted organic synthesis has been demonstrated to usually increase the rate of MCR with the reduction of reaction times and improvement of the yields,[13] the protocol described herein seems to be more efficient for the Passerini reaction. Additionally, it is noteworthy that the reactions were successfully performed with heterocyclic aldehydes as well (entries 13 and 14).

Table 3
Scope of the Passerini reaction under solvent-free conditions with benzyl and cyclohexyl isocyanide



6 **7** **8**

Entry	R¹	R²	Isocyanide	Product	Yields (%)[a]
1			Bn-NC	**8a**	86
2			Bn-NC	**8b**	81
3			Bn-NC	**8c**	80
4			Bn-NC	**8d**	93
5			Bn-NC	**8e**	75
6		Me	Bn-NC	**8f**	64 (36[b]) (55[c])
7			Cy-NC	**8g**	85
8			Cy-NC	**8h**	85
9			Cy-NC	**8i**	88
10			Cy-NC	**8j**	79

[a] Isolated yields.
[b] In CH_2Cl_2 at room temperature for 24 h.
[c] Under solvent-free conditions at room temperature for 24 h.

A second set of experiments with benzyl and cyclohexyl isocyanide is reported in Table 3. Once again, whatever the nature of the aldehydes and carboxylic acids used, products **8a–j** were obtained in excellent yields (64–93%). When the reaction involving substrates of entry 6 was performed in dichloromethane at room temperature, product **8f** was obtained in a 36% yield.[7] The yield rises up to 55% when the reaction is achieved under solvent free conditions.[7] The present system provided **8f** in a 64% yield highlighting the higher efficiency of our protocol.

In conclusion, a convenient and efficient Passerini multicomponent reaction under solvent-free conditions at high temperature was achieved with a broad range of reagents. Additionally, this procedure is interesting as it shows that microwave heating is not always necessary to reach high conversions and excellent yields. In this work, whatever the reagent used, the yields were all over 75%. Possible adjustments of the temperature would allow the extension of scope of this protocol.

Acknowledgments

The authors thank Pr B. Deprez for fruitful discussions. We want to thank institutions supporting our laboratories (Centre National de la Recherche Scientifique and Université de Lille Nord de France). This project was supported by the Conseil Régional Nord-Pas de Calais, DRRT PRIM 2008-07 PRIM-SP.

Supplementary data

Supplementary data (typical reaction procedure, spectral data and copies of NMR data of compounds **7j,k,g** and **8a,d,h**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.028.

References and notes

1. Zhu, J.; Bienaymé, H. *Multicomponent reactions*; Wiley-VCH: Weinheim, 2005; (b) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602.
2. Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51.
3. (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
4. Ugi, I.; Meyer, R. *Angew. Chem., Int. Ed.* **1962**, *1*, 8.
5. Pirrung, M. C.; Das Sarma, K. *J. Am. Chem. Soc.* **2004**, *126*, 444.
6. (a) Andrade, C. K. Z.; Takada, S. C. S.; Suarez, P. A. Z.; Alves, M. B. *Synlett* **2006**, 1539; (b) Fan, X.; Li, Y.; Zhang, X.; Qu, G.; Wang, J. *Can. J. Chem.* **2006**, *84*, 794.
7. Koszelewski, D.; Szymanski, W.; Krysiak, J.; Ostaszewski, R. *Synth. Commun.* **2008**, *28*, 1120.
8. Barreto, A. F.; Vercillo, O. E.; Andrade, C. K. Z. *J. Braz. Chem. Soc.* **2011**, *22*, 462.
9. (a) Zhang, Q.; Zhang, S.; Deng, Y. *Green Chem.* **2011**, *1*, 12; (b) Coleman, D.; Gathergood, N. *Chem. Soc. Rev.* **2010**, *39*, 600; (c) Docherty, K. M.; Kulpa, C. F., Jr *Green. Chem.* **2005**, *7*, 185; (d) Garcia, M. T.; Gathergood, N.; Scammells, P. J. *Green. Chem.* **2005**, *7*, 9.
10. (a) Pellegrini, S.; Grad, J. N.; Bousquet, T.; Pélinki, L. *Tetrahedron Lett.* **2011**, *52*, 1742; (b) Jida, M.; Soueidan, M.; Willand, N.; Agbossou-Niedercorn, F.; Pélinki, L.; Laconde, G.; Déprez-Poulain, R.; Deprez, B. *Tetrahedron Lett.* **2011**, *52*, 1705.
11. A regular silicon oil bath was used for heating with a thermocouple temperature control.
12. General experiment procedure: the reaction vessel containing a mixture of isocyanide (0.5 mmol, 1 equiv), aldehyde (0.55 mmol, 1.1 equiv) and carboxylic acid (0.55 mmol, 1.1 equiv) is placed in a preheated oil bath at 180 °C for 4 min. After being diluted in dichloromethane/MeOH (90:10), the organic layer was washed twice with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$ and concentrated in vacuo. The crude product was dissolved in ethanol (3 mL) before being poured into water. The resulting thick precipitate was collected by filtration furnishing the Passerini product. As an example, product **7j** was obtained as an off-white solid in 90% yield (Table 2, entry 12); mp = 136–138 °C; Purity >99% (measured by LC/MS); ^{1}H NMR (300 MHz, DMSO) δ 8.10 (d, *J* = 8.7 Hz, 2H), 7.99 (br s, 1H, NH), 7.85 (d, *J* = 8.7 Hz, 2H), 7.74 (d, *J* = 6.9 Hz, 2H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.46–7.36 (m, 4H), 6.09 (s, 1H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, DMSO) δ 167.50, 165.24, 145.44, 139.29, 136.73, 130.54, 129.59, 128.92, 128.64, 127.66, 127.48, 75.96, 50.94, 28.83; rt (LCMS) = 3.19 min; (M+H$^+$) = 388.
13. (a) Kappe, C. O. *Chem. Soc. Rev.* **2008**, *37*, 1127; (b) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250; (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.