

Continuous-Flow Synthesis of 4-(2-Nitrophenyl) Morpholine Coiled Tube Microreactor

Kundan A. Borse¹, Nilesh B. Patil², Shekhar S. Sawant³, Arunkumar D. Pati¹, Madhukar D. Tayade¹,
Ashutosh D. Shinde¹, Nilesh S. Pawar^{*1}

¹Department of Chemistry, KES's Pratap College Amalner (M.S.), INDIA

²Department of Chemistry, JET's Z. B. Patil College, Deopur, Dhule (M.S.), INDIA

³Institute of Chemical Technology, Matunga, Mumbai (M.S.), INDIA

*Corresponding Author

DOI: <https://doi.org/10.51584/IJRIAS.2026.11060245>

Received: 29 June 2026; Accepted: 04 July 2026; Published: 15 July 2026

ABSTRACT

The continuous-flow synthesis of 4-(2-nitrophenyl) morpholine was investigated using a coiled tube microreactor to evaluate the influence of reaction temperature and residence time on product yield and purity. Solutions of 2-fluoronitrobenzene and morpholine in the presence of potassium carbonate were continuously pumped through a 100 mL flow reactor equipped with a back-pressure regulator. Reaction temperatures between 140 and 170 °C and residence times from 20 to 50 min were systematically examined. Increasing the reaction temperature from 140 to 160 °C significantly improved the isolated yield from 69.9% to 94.6%, while a further increase to 170 °C resulted in a slight decline in yield to 93.2%. Similarly, increasing the residence time from 20 to 50 min enhanced the product yield from 72.2% to 95.5%, with only marginal improvement beyond 40 min. The optimized reaction conditions were established at 160 °C with a residence time of 40–50 min, affording the desired product in up to 95.5% isolated yield and 99% purity. Structural confirmation was achieved using ¹H NMR, ¹³C NMR, and mass spectrometry. The study demonstrates that continuous-flow processing provides excellent temperature control, enhanced mass transfer, high product quality, and an efficient, scalable alternative to conventional batch synthesis for aromatic nucleophilic substitution reactions.

Keywords: Continuous-flow chemistry; Microreactor technology; Nucleophilic aromatic substitution (S_NAr); Process optimization; 4-(2-Nitrophenyl)morpholine

INTRODUCTION

Organic synthesis has conventionally been carried out using batch processes, typically in round-bottom flasks, test tubes, or sealed vessels. In recent years, however, continuous flow techniques have attracted significant interest among synthetic organic chemists [1]. Until only a few years ago, continuous flow processes were largely confined to the petrochemical and bulk chemical industries. Until recently, specialized continuous plants have demonstrated high economic efficiency. More recently, however, the use of these systems for the synthesis of fine chemicals, including natural products [2] and active pharmaceutical ingredients (APIs), has gained considerable popularity, particularly in academic research. Although the pharmaceutical industry continues to depend primarily on multipurpose batch or semi-batch reactors, there is a clear and growing shift toward the adoption of continuous flow techniques for API production [3]. The example clearly demonstrates the significant potential of flow systems. The growing interest in continuous flow processes can be attributed to the inherent features of flow reactors. Typically, on a laboratory scale, a continuous flow process is carried out in what is commonly referred to as a “microreactor” [4]. It is a narrow-channel device in which reactions occur under strictly regulated conditions within a limited volume. A key feature of flow systems is their highly efficient heat and mass transfer, which accelerates reaction rates and typically results in significantly enhanced productivity compared to conventional batch processes [5]. Flow chemistry is now regarded as a dependable

method for the preparation of simple organic molecules [6-11] as well as complex, high-molecular-weight pharmaceutical compounds [12-17].

Flow chemistry derives its advantages from superior heat and mass transfer efficiency along with fast mixing, which are difficult to achieve using traditional synthetic methods [18]. In general, continuous flow synthesis seeks to perform reactions under intrinsic kinetic conditions. This enables the use of reactors with reduced volumes, making them inherently safer. Owing to the low processing volumes and operation at intrinsic rates with minimal human involvement, it becomes feasible to carry out hazardous reactions and operate at significantly higher temperatures, which are often not achievable with conventional techniques [19-20]. An automated flow synthesis strategy also markedly lowers labor expenses, and operations can continue for extended periods without interruption or notable downtime for maintenance [14, 21]. A wide range of reactions has been carried out using flow synthesis and has been demonstrated to be superior to conventional synthetic methods [22-25]. A few examples of experimental setups for the successful flow synthesis of multiple organic molecules were presented in this paper.

Experimental:

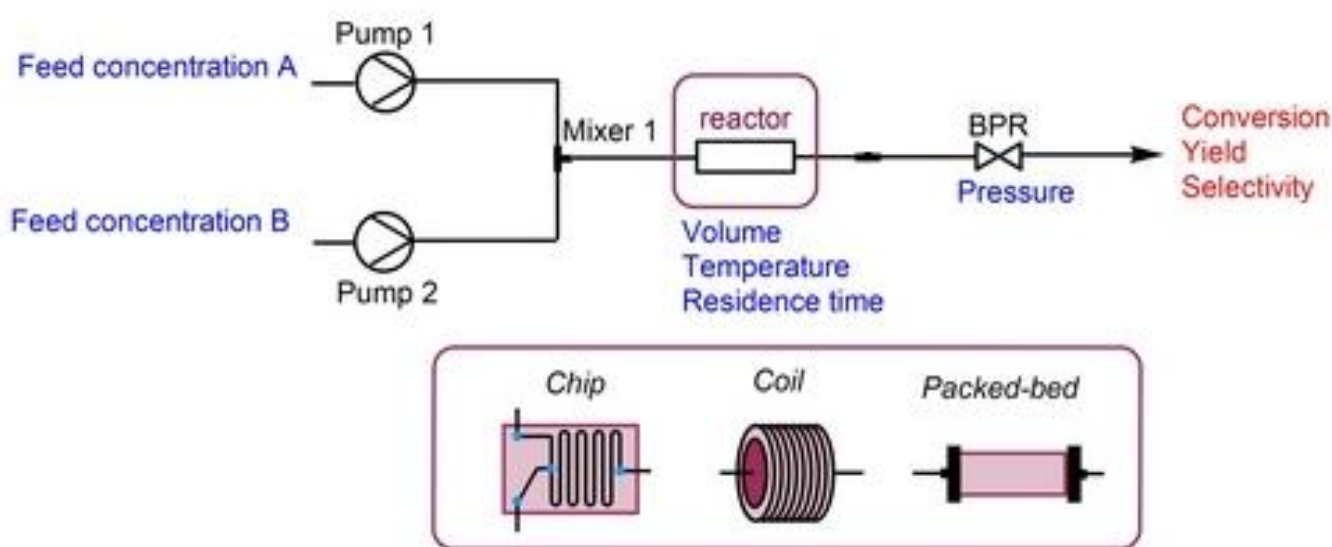
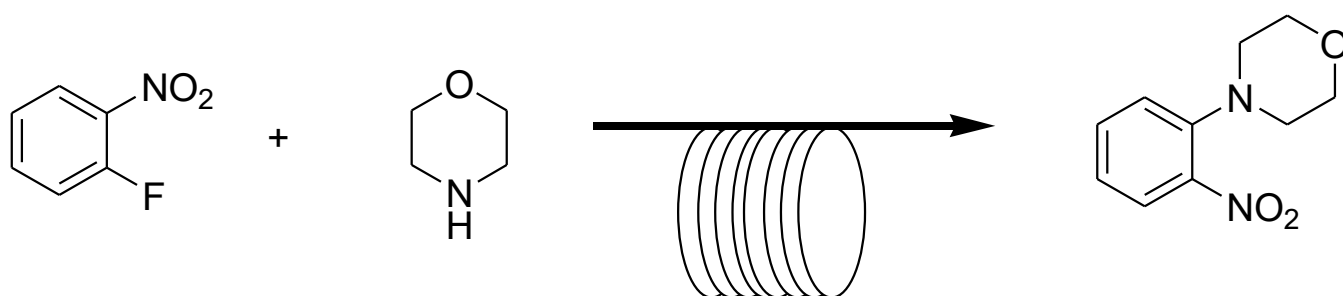


Figure 1: Common Flow Reactor Scheme



Scheme 1: Reaction of 2-fluoronitrobenzene with morpholine in ROS and flow reactor

Solution A: - In a clean bottle prepared solution of 141.1 g (1.0 mole) 2-fluoronitrobenzene and 500 g DMF as solvent.

Solution B: - In a clean bottle prepared solution of 87.1 g (1.0 mole) of Morpholine and 138.2 g (1.0 mole) K_2CO_3 in 1000 g DMF as solvent. A well-stirred suspension of potassium carbonate in DMF finely dispersed was pumped.

Specifications of coiled tube reactor:

- Inner diameter (ID): 2.0 mm
- Outer diameter (OD): 3.175 mm (1/8 in)
- Tubing length: 31.83 m
- Internal volume: approximately 100 mL

Experiment no.1: In a coiled tube reactor (100 mL coil volume) followed by BPR, the solution A and B is pumped with rate of 0.86 gm/min solution A and 1.64 gm/min of solution B maintaining 140°C reactor temperature and 40 min residence time. After achieving steady state aliquots of samples were collected (20gm) and further quench the reaction mass into cold water in next coil and extract the quench mass with ethyl acetate twice (100*2) separate the layers, combined all organic and wash with water twice (50*2). Distilled out the organic layer under reduced pressure and purified the material by column chromatography using ethyl acetate: hexane (1:20) as the eluent. The desired product was obtained 1.56 g (69.9% yield) with 99% purity.

Experiment no.2: In a coiled tube reactor (100 mL coil volume) followed by BPR, the solution A and B is pumped with rate of 0.86 gm/min solution A and 1.64 gm/min of solution B maintaining 150°C reactor temperature and 40 min residence time. After achieving steady state aliquots of samples were collected (20gm) and further quench the reaction mass into cold water in next coil and extract the quench mass with ethyl acetate twice (100*2) separate the layers, combined all organic and wash with water twice (50*2). Distilled out the organic layer under reduced pressure and purified the material by column chromatography using ethyl acetate: hexane (1:20) as the eluent. The desired product was obtained 1.80 g (80.7% yield) with 99% purity.

Experiment no.3: In a coiled tube reactor (100 mL coil volume) followed by BPR, the solution A and B is pumped with rate of 0.86 gm/min solution A and 1.64 gm/min of solution B maintaining 160°C reactor temperature and 40 min residence time. After achieving steady state aliquots of samples were collected (20gm) and further quench the reaction mass into cold water in next coil and extract the quench mass with ethyl acetate twice (100*2) separate the layers, combined all organic and wash with water twice (50*2). Distilled out the organic layer under reduced pressure and purified the material by column chromatography using ethyl acetate: hexane (1:20) as the eluent. The desired product was obtained 2.11 g (94.6% yield) with 99% purity.

Experiment no.4: In a coiled tube reactor (100 mL coil volume) followed by BPR, the solution A and B is pumped with rate of 0.86 gm/min solution A and 1.64 gm/min of solution B maintaining 170°C reactor temperature and 40 min residence time. After achieving steady state aliquots of samples were collected (20gm) and further quench the reaction mass into cold water in next coil and extract the quench mass with ethyl acetate twice (100*2) separate the layers, combined all organic and wash with water twice (50*2). Distilled out the organic layer under reduced pressure and purified the material by column chromatography using ethyl acetate: hexane (1:20) as the eluent. The desired product was obtained 2.08 g (93.2% yield) with 99% purity.

Table-01 Results showing the impact on yield by changing the temperature.

Temp (°C)	RT (min)	Total Flow/min	Solution A/min	Solution B/min	TY	Product (gm)	Yield %
140	40	2.50	0.86	1.64	2.231	1.56	69.9
150	40	2.50	0.86	1.64	2.231	1.80	80.7
160	40	2.50	0.86	1.64	2.231	2.11	94.6
170	40	2.50	0.86	1.64	2.231	2.08	93.2

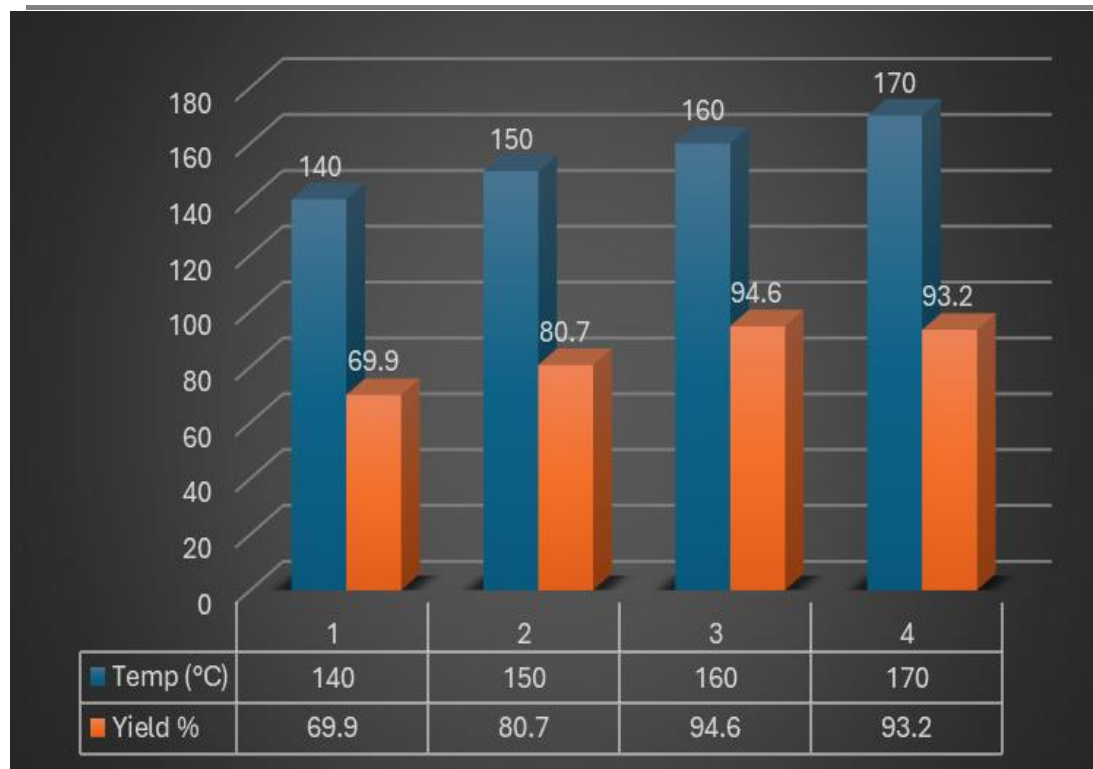


Figure 2: Chart-01 Graph showing the impact on yield by changing the temperature.

Experiment no.5: In a coiled tube reactor (100 mL coil volume) followed by BPR, the solution A and B is pumped with rate of 1.72 gm/min solution A and 3.28 gm/min of solution B maintaining 160°C reactor temperature and 20 min residence time. After achieving steady state aliquots of samples were collected (20gm) and further quench the reaction mass into cold water in next coil and extract the quench mass with ethyl acetate twice (100*2) separate the layers, combined all organic and wash with water twice (50*2). Distilled out the organic layer under reduced pressure and purified the material by column chromatography using ethyl acetate: hexane (1:20) as the eluent. The desired product was obtained 1.61 g (72.2% yield) with 99% purity.

Experiment no.6: In a coiled tube reactor (100 mL coil volume) followed by BPR, the solution A and B is pumped with rate of 1.14 gm/min solution A and 2.19 gm/min of solution B maintaining 160°C reactor temperature and 30 min residence time. After achieving steady state aliquots of samples were collected (20gm) and further quench the reaction mass in to cold water in next coil and extract the quench mass with ethyl acetate twice (100*2) separate the layers, combined all organic and wash with water twice (50*2). Distilled out the organic layer under reduced pressure and purified the material by column chromatography using ethyl acetate: hexane (1:20) as the eluent. The desired product was obtained 1.85 g (82.9% yield) with 99% purity.

Experiment no.7: In a coiled tube reactor (100 mL coil volume) followed by BPR, the solution A and B is pumped with rate of 0.86 gm/min solution A and 1.64 gm/min of solution B maintaining 160°C reactor temperature and 40 min residence time. After achieving steady state aliquots of samples were collected (20gm) and further quench the reaction mass into cold water in next coil and extract the quench mass with ethyl acetate twice (100*2) separate the layers, combined all organic and wash with water twice (50*2). Distilled out the organic layer under reduced pressure and purified the material by column chromatography using ethyl acetate: hexane (1:20) as the eluent. The desired product was obtained 2.12 g (95.0% yield) with 99% purity.

Experiment no.8: In a coiled tube reactor (100 mL coil volume) followed by BPR, the solution A and B is pumped with rate of 0.69 gm/min solution A and 1.31 gm/min of solution B maintaining 160°C reactor temperature and 50 min residence time. After achieving steady state aliquots of samples were collected (20gm) and further quench the reaction mass into cold water in next coil and extract the quench mass with ethyl acetate twice (100*2) separate the layers, combined all organic and wash with water twice (50*2). Distilled out the organic layer under reduced pressure and purified the material by column chromatography using ethyl acetate: hexane (1:20) as the eluent. The desired product was obtained 2.13 g (95.5% yield) with 99% purity.

Table-02 Results showing the impact on yield by changing the residence time.

Temp (°C)	RT (min)	Total Flow/min	Solution A/min	Solution B/min	TY	Product (gm)	Yield %
160	20	5.00	1.72	3.28	2.231	1.61	72.2
160	30	3.33	1.14	2.19	2.231	1.85	82.9
160	40	2.50	0.86	1.64	2.231	2.12	95.0
160	50	2.00	0.69	1.31	2.231	2.13	95.5

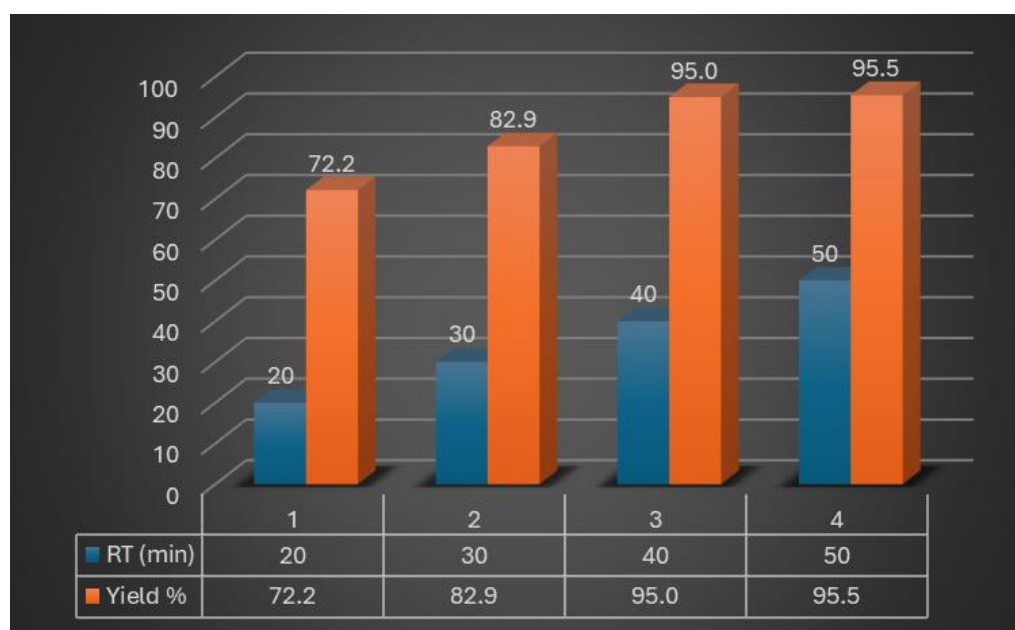
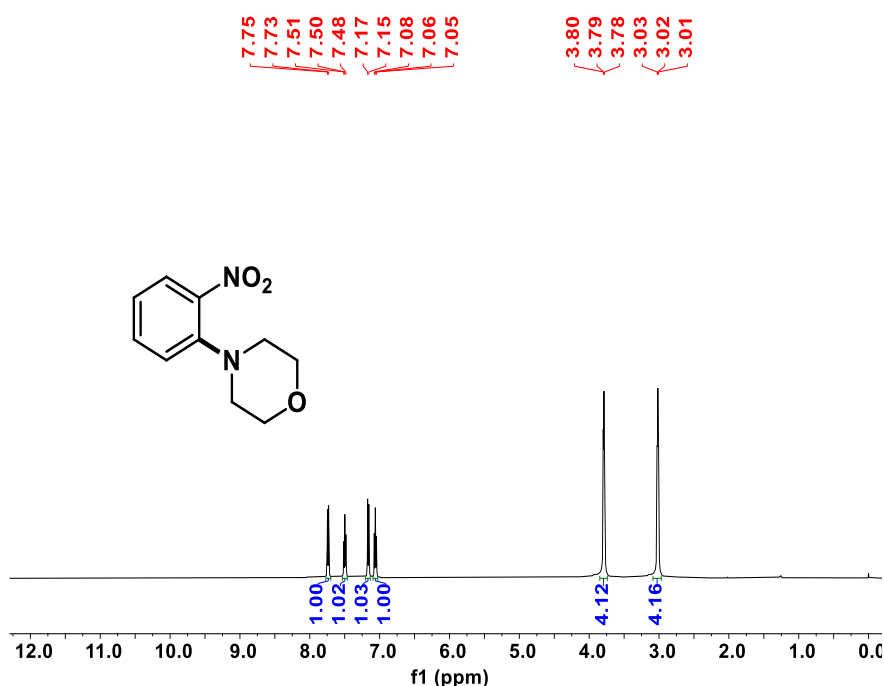


Figure 3: Chart-02 Graph showing the impact on yield by changing the residence time.

Isolated Product ^1H NMR, ^{13}C NMR, Mass graphs.


Figure 4: ^1H NMR of 4-(2-Nitrophenyl) Morpholine

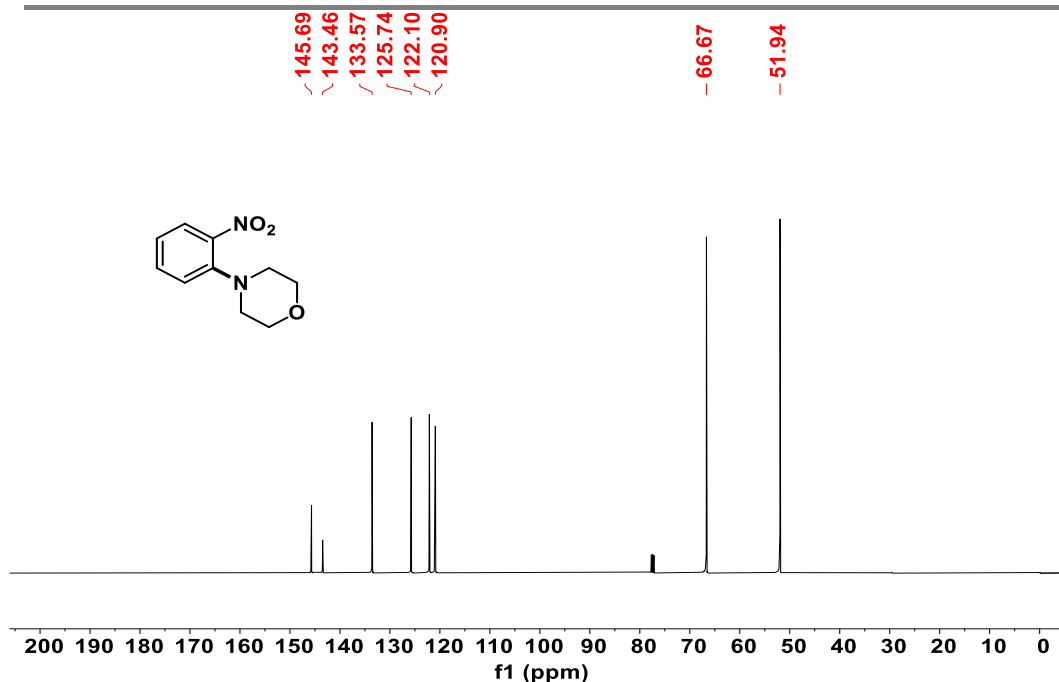


Figure 5: ^{13}C NMR of 4-(2-Nitrophenyl) Morpholine

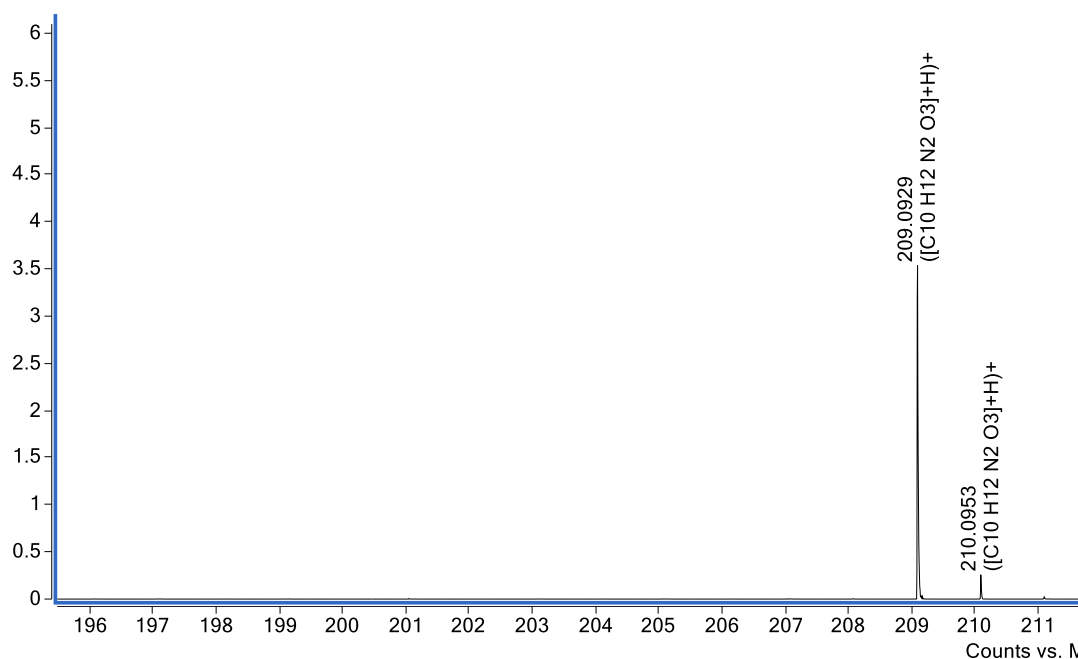
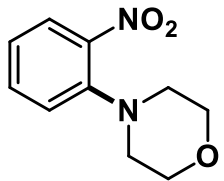


Figure 6: Mass Spectra of 4-(2-Nitrophenyl) Morpholine

Table 3: Isolated Product ^1H NMR, ^{13}C NMR, Mass.

4-(2-nitrophenyl) morpholine	
	^1H NMR (500 MHz, CDCl_3): δ 7.74 (d, J = 8.1 Hz, 1H), 7.54 – 7.46 (m, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.11 – 7.03 (m, 1H), 3.79 (t, 1H), 3.02 (t, 4H).
	^{13}C NMR (126 MHz, CDCl_3): δ 145.69, 143.46, 133.57, 125.74, 122.10, 120.90, 66.67, 51.94.
	HRMS (ESI) m/z calculated for $\text{C}_{10}\text{H}_{13}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 209.0926; found 209.0929.

RESULTS AND DISCUSSION

The nucleophilic aromatic substitution of 2-fluoronitrobenzene with morpholine was successfully performed in a continuous-flow microreactor. The effects of reaction temperature and residence time were systematically evaluated to determine the optimum operating conditions for maximizing product yield while maintaining high purity.

Effect of Reaction Temperature: The influence of reaction temperature was investigated over the range of 140–170 °C while maintaining a constant residence time of 40 min. As summarized in Table 1, product yield increased steadily from 69.9% at 140 °C to 80.7% at 150 °C, reaching a maximum of 94.6% at 160 °C. A slight decrease in yield to 93.2% was observed at 170 °C, indicating that higher temperatures do not provide additional benefit and may promote minor side reactions or thermal degradation. Throughout the temperature optimization study, product purity remained constant at approximately 99%, demonstrating the excellent selectivity of the continuous-flow process. These results indicate that 160 °C is the optimum reaction temperature, providing an excellent balance between conversion, selectivity, and process efficiency.

Effect of Residence Time: Residence time was subsequently optimized at the selected reaction temperature of 160 °C. Reducing the residence time to 20 min resulted in a lower isolated yield of 72.2%, indicating incomplete conversion of the starting material. Increasing the residence time to 30 min improved the yield to 82.9%, while further extension to 40 min produced 95.0% yield. A marginal increase to 95.5% was obtained at 50 min, suggesting that the reaction approaches completion after approximately 40 min and that longer residence times offer negligible improvement. These findings indicate that a residence time of 40 min is sufficient for efficient conversion while maintaining high productivity in continuous operation.

Product Characterization: The isolated product obtained under optimized conditions exhibited 99% purity. Structural characterization by ^1H NMR, ^{13}C NMR, and mass spectrometry confirmed the successful formation of 4-(2-nitrophenyl) morpholine. The observed molecular ion peak corresponded to the expected molecular mass, while the NMR spectra were consistent with the proposed chemical structure, confirming the identity and high purity of the synthesized compound.

Eventually the results clearly demonstrate the advantages of continuous-flow synthesis over conventional batch processing. Precise control of reaction temperature, efficient heat and mass transfer, and uniform residence time distribution contributed to consistently high product purity and excellent reproducibility. The optimized operating conditions of 160 °C and 40–50 min residence time produced up to 95.5% isolated yield with 99% purity, highlighting the capability of microreactor technology for efficient aromatic nucleophilic substitution reactions. Furthermore, the continuous-flow methodology minimizes reaction volume, improves process safety at elevated temperatures, and offers straightforward scalability by extending operational time rather than increasing reactor size. These advantages make the developed protocol an attractive approach for the sustainable and industrial production of pharmaceutical intermediates and fine chemicals.

CONCLUSION

The present study successfully demonstrated the continuous-flow synthesis of 4-(2-nitrophenyl) morpholine using a coiled tube microreactor. Systematic optimization of reaction parameters revealed that both reaction temperature and residence time significantly influence product yield. Among the conditions investigated, a reaction temperature of 160 °C and a 40–50 min residence time provided the best performance, affording the desired product in up to 95.5% isolated yield with 99% purity. Increasing the temperature beyond 160 °C did not improve the yield, indicating that this temperature represents the optimum balance between conversion and selectivity. The continuous-flow process exhibited excellent reaction control, efficient heat and mass transfer, and consistent product quality, highlighting its advantages over conventional batch synthesis. The ability to safely operate at elevated temperatures in a compact reactor, together with improved reproducibility and scalability, demonstrates the potential of continuous-flow technology for the efficient production of pharmaceutical intermediates and fine chemicals. Overall, this work establishes a robust and practical continuous-flow protocol for aromatic nucleophilic substitution reactions and further supports the adoption of

microreactor-based processing as a sustainable and industrially relevant approach for modern organic synthesis.

REFERENCE

- (a) Darvas, F.; Hessel, V.; Dorman, G. *Flow Chemistry*; De Gruyter: Berlin, 2014. (b) Jensen, K. F.; Reizman, B. J.; Newman, S. G. *Lab Chip* **2014**, 14, 3206. (c) Reschetilowski, W. *Microreactors in Preparative Chemistry*; Wiley-VCH: Weinheim, 2013. (d) Wirth, T. *Microreactors in Organic Synthesis and Catalysis*, 2nd ed.; Wiley-VCH: Weinheim, 2013. (e) Wiles, C.; Watts, P. *Green Chem.* **2012**, 14, 38. (f) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.* **2011**, 47, 4583. (g) Hartman, R. L.; McMullen, J. P.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2011**, 50, 7502. (h) Wiles, C.; Watts, P. *Chem. Commun.* **2011**, 47, 6512. (i) Hessel, V. *Chem. Eng. Technol.* **2009**, 32, 1655.
- For a comprehensive review on the synthesis of natural products in flow, see: Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013**, 42, 8849. For a recent example, see: Newton, S.; Carter, C. F.; Pearson, C. M.; de C Alves, L.; Lange, H.; Thansandote, P.; Ley, S. V. *Angew. Chem., Int. Ed.* **2014**, 53, 4915.
- For a discussion on continuous manufacturing in pharmaceutical industry, see (a) Malet-Sanz, L.; Susanne, F. J. *Med. Chem.* **2012**, 55, 4062. (b) Poechlauer, P.; Colberg, J.; Fisher, E.; Jansen, M.; Johnson, M. D.; Koenig, S. G.; Lawler, M.; Laporte, T.; Manley, J.; Martin, B.; O'Kearney-McMullan, A. *Org. Process Res. Dev.* **2013**, 17, 1472. (c) Jimenez-Gonzalez, C.; Poechlauer, P.; Broxterman, Q. B.; Yang, B.-S.; am Ende, D.; Baird, J.; Bertsch, C.; Hannah, R. E.; Dell'Orco, P.; Noorman, H.; Yee, S.; Reintjens, R.; Wells, A.; Massonneau, V.; Manley, J. *Org. Process Res. Dev.* **2011**, 15, 900. (d) Baxendale, I. R.; Braatz, R. D.; Hodnett, B. K.; Jensen, K. F.; Johnson, M. D.; Sharratt, P.; Sherlock, J.-P.; Florence, A. J. *J. Pharm. Sci.* **2015**, 104, 781.
- (a) Rodrigues, T.; Schneider, P.; Schneider, G. *Angew. Chem., Int. Ed.* **2014**, 53, 5750. (b) Elvira, K. S.; Solvas, X. C.; Wootton, R. C. R.; deMello, A. J. *Nat. Chem.* **2013**, 5, 905.
- (a) Plouffe, P.; Macchi, A. *Org. Process Res. Dev.* **2014**, 18, 1286. (b) Newman, S. G.; Jensen, K. F. *Green Chem.* **2013**, 15, 1456. Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.* **2011**, 47, 4583.
- Baumann, M.; Garcia, A. M. R.; Baxendale, I. R. *Org. Biomol. Chem.* **2015**, 13, 4231–4239. doi:10.1039/C5OB00245A.
- Webb, D.; Jamison, T. F. *Org. Lett.* **2012**, 14, 2465–2467. doi:10.1021/ol300722e
- Shu, W.; Pellegatti, L.; Oberli, M. A.; Buchwald, S. L. *Angew. Chem.* **2011**, 123, 10853–10857. doi:10.1002/ange.201105223
- Noël, T.; Kuhn, S.; Musacchio, A. J.; Jensen, K. F.; Buchwald, S. L. *Angew. Chem.* **2011**, 123, 6065–6068. doi:10.1002/ange.201101480
- Poh, J.-S.; Browne, D. L.; Ley, S. V. *React. Chem. Eng.* **2016**, 1, 101–105. doi:10.1039/C5RE00082C
- Nagaki, A.; Kim, H.; Yoshida, J.-i. *Angew. Chem.* **2009**, 121, 8207–8209. doi:10.1002/ange.200904316
- Tsubogo, T.; Oyamada, H.; Kobayashi, S. *Nature* **2015**, 520, 329–332. doi:10.1038/nature14343
- Cole, K. P.; Groh, J. M.; Johnson, M. D.; Burcham, C. L.; Campbell, B. M.; Diserod, W. D.; Heller, M. R.; Howell, J. R.; Kallman, N. J.; Koenig, T. M.; May, S. A.; Miller, R. D.; Mitchell, D.; Myers, D. P.; Myers, S. S.; Phillips, J. L.; Polster, C. S.; White, T. D.; Cashman, J.; Hurley, D.; Moylan, R.; Sheehan, P.; Spencer, R. D.; Desmond, K.; Desmond, P.; Gowran, O. *Science* **2017**, 356, 1144–1150. doi:10.1126/science.aan0745
- Adamo, A.; Beingessner, R. L.; Behnam, M.; Chen, J.; Jamison, T. F.; Jensen, K. F.; Monbaliu, J.-C. M.; Myerson, A. S.; Revalor, E. M.; Snead, D. R.; Stelzer, T.; Weeranoppanant, N.; Wong, S. Y.; Zhang, P. *Science* **2016**, 352, 61–67. doi:10.1126/science.aaf1337
- Kupracz, L.; Kirschning, A. *Adv. Synth. Catal.* **2013**, 355, 3375–3380. doi:10.1002/adsc.201300614
- Hartwig, J.; Ceylan, S.; Kupracz, L.; Coutable, L.; Kirschning, A. *Angew. Chem., Int. Ed.* **2013**, 52, 9813–9817. doi:10.1002/anie.201302239
- Murray, P. R. D.; Browne, D. L.; Pastre, J. C.; Butters, C.; Guthrie, D.; Ley, S. V. *Org. Process Res. Dev.* **2013**, 17, 1192–1208. doi:10.1021/op4001548
- Hartman, R. L.; Naber, J. R.; Buchwald, S. L.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2010**, 49, 899–903. doi:10.1002/anie.200904634

- 19 Deadman, B. J.; Collins, S. G.; Maguire, A. R. *Chem. – Eur. J.* **2015**, 21, 2298–2308. doi:10.1002/chem.201404348
- 20 Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K. E. T.; Battilocchio, C.; Ley, S. V.; Stevens, C. V. *Chem. Soc. Rev.* **2016**, 45, 4892–4928. doi:10.1039/C5CS00902B
- 21 Mascia, S.; Heider, P. L.; Zhang, H.; Lakerveld, R.; Benyahia, B.; Barton, P. I.; Braatz, R. D.; Cooney, C. L.; Evans, J. M. B.; Jamison, T. F.; Jensen, K. F.; Myerson, A. S.; Trout, B. L. *Angew. Chem., Int. Ed.* **2013**, 52, 12359–12363. doi:10.1002/anie.201305429
- 22 McQuade, D. T.; Seeberger, P. H. *J. Org. Chem.* **2013**, 78, 6384–6389. doi:10.1021/jo400583m
- 23 Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013**, 42, 8849–8869. doi:10.1039/c3cs60246j
- 24 Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, 1, 675–680. doi:10.1039/c0sc00381f
- 25 Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.* **2012**, 354, 17–57. doi:10.1002/adsc.201100584