Received: 22 January 2020 | Revised: 4 March 2020 | Accepted: 15 March 2020

DOI: 10.1002/jhet.3983

WILEY

ARTICLE

Improved method for the total synthesis of thiofentanyl

M. J. Taghizadeh | **S. J. Hosseini** | **S. M. Moosavi** | **H. Parsa**

Department of Chemistry, Faculty of Science, University of Imam Hossein, Tehran, Iran

Correspondence
M. J. Taghizadeh, Department of Chemistry, Faculty of Science, University of Imam Hossein, Tehran, Iran.
Email: mohammadjavadtaghizadeh31@yahoo.com

Abstract

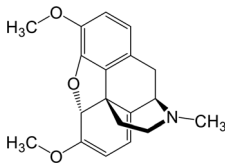
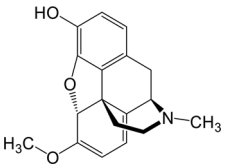
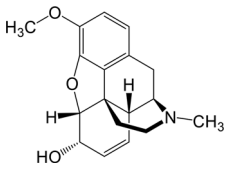
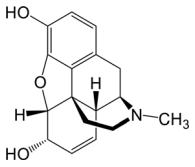
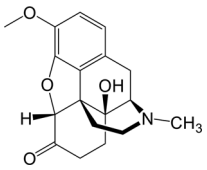
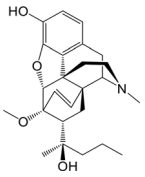
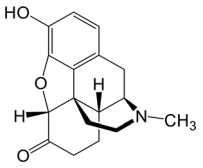
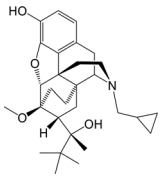
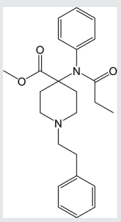
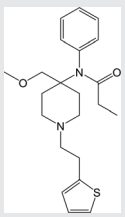
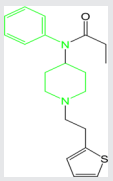
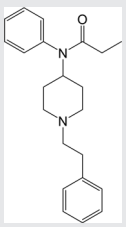
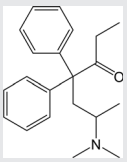
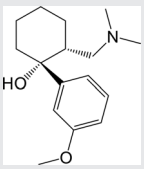
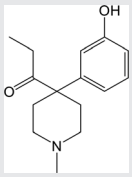
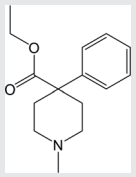
Thiofentanyl is a potent analgesic and anesthetic drug that belongs to the micro-receptor agonist group and is mainly used in animal's anesthesia. We present an optimized synthesis route for synthesis of thiofentanyl using nanocatalysts such as MCM-41-SO_3H and SBA-15-Ph-PrSO_3H as green, heterogeneous and recyclable catalysts according to the strategy. The intermediate 2-(thiophen-2-yl) ethyl methanesulfonate (**1**) easily obtained after conversion of the alcohol functional group into the mesylate leaving group using methanesulfonyl chloride (97% yield). The alkylation of commercially available 4-piperidone monohydrate hydrochloride with 2-(thiophen-2-yl) ethyl methanesulfonate in the presence of phase transfer catalyst was then carried out giving N-[2-(2-thienyl) ethyl]-4-piperidone (**2**) with 90% yield. *N*-[2-(2-thienyl)ethyl]-4-piperidone was then reacted with aniline in the presence of MCM-41-SO_3H catalyst giving the imine derivative which reduced with sodium triacetoxyborohydride to *N*-phenyl-1-(2-(thiophen-2-yl)ethyl) piperidine-4-amine (ANTP) (**4**) with 80% yield. ANTP was finally acylated using propionyl chloride to achieve thiofentanyl (**5**) with 90% yield. High yields, mild reaction conditions, decreased reaction times, and convenient workup were the advantages of this method compared to the previous work.

1 | INTRODUCTION

Natural medicines are directly derived from plant or animal extraction, but semisynthetic drugs are the result of a change in the structure of natural drugs, and full-synthesized drugs are the result of a process of laboratory synthesis without the simulation of natural drugs. The natural drugs which developed by pharmacists are consequences of research under the medicine that our ancestors used in the whole world, on the other hand, the improvement of full-synthesized drugs requiring research and development of chemical reactions in the field of organic chemistry. The process of synthesis of full-synthesized drugs can be controlled and modified by chemists. Accordingly, the effect of synthetic drugs sometimes becomes so much stronger than natural compounds.[1] Opioid analgesics are a collection of natural and chemical compounds that are also reputed to quasi-morphine or opioid drugs.[2,3] Various examples of opioid analgesics are shown in Table 1.[4]

Among various types of analgesic compounds, anilidopiperidines including Fentanyl(50-100 × Morphine), Carfentanil (7000-8000× Morphine), Lofentanil (5000-6000 × Morphine), and others,[5] which belong to the synthetic opioids class, provide the most potential as analgesics. Anilidopiperidines, due to the fast onset and short duration of action, act in the central nervous system to decrease pain and are extensively used in surgical anesthesia as the citrate salt at doses ranging from 2 to 50 μg/kg. Features including, low-molecular weight, high potency, and lipid solubility of fentanyles make them suitable for delivery via transdermal therapeutic system.[6] Fentanyl and its derivatives are used in various medical conditions such as observant patients, managing postoperative pains, in obstetrics and also in various orthopedic interventions. Fentanyl transdermal patches are useful in controlling chronic cancer pain,[7] due to the slow and controlled release of the drug over several days, Many fentanyl analogues have been synthesized[5,8–14] as

TABLE 1 Various examples of opioid analgesics

Opium alkaloids and derivatives			
Thebaine	Oripavine	Codeine	Morphine
			
Semisynthetic derivatives of opium alkaloids			
Oxycodone	Etorphine	Hydromorphone	Buprenorphine
			
Synthetic opioids			
Anilidopiperidines			
Carfentanyl	Sufentanil	Thiofentanyl	Fentanyl
			
Other common opioids		Phenylpiperidines	
Methadone	Tramadol	Ketobemidone	Pethidine
			

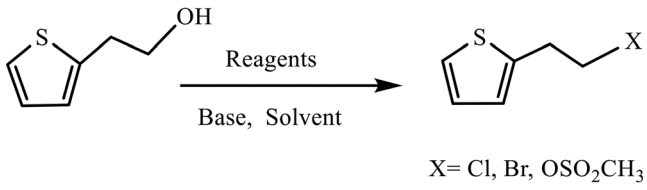
potential candidates for novel drugs, to establish the structure-activity relationship and to investigate the opioid receptors. Lots of works have been performed on the synthesis of fentanyl and its derivatives.[15,16] However, limited works have been accomplished on the synthesis of thiofentanyl. The effect of the thiofentanyl drug is almost similar to carfentanil, and has been used in various formulations such as thiofentanyl-xylazine, thiofentanyl-medetomidine, and formulations containing muscle relaxants for relaxation and disability of animals.[17,18] Synthetic route for producing thiofentanyl is similar to that of fentanyl, but in first step, 2-(thiophen-2-yl) ethyl methanesulfonate is substituted instead of phenethyl bromide. In this research, the alternative and optimized synthesis of thiofentanyl is described. The five-step strategy produced thiofentanyl through a convenient

and efficient method using reusable and highly efficient heterogeneous catalysts in excellent yields (75%-80%).

2 | RESULTS AND DISCUSSION

Synthesis of the target, thiofentanyl, started with the preparation of 2-(thiophen-2-yl) ethyl methanesulfonate from the 2-thiophen ethanol (Scheme 1).[19] The reaction of 2-(Thiofene-2-yl) ethanol and methanesulfonyl chloride in presence of triethylamine and dry dichloromethane solvent under a nitrogen atmosphere, gave this product with excellent yield (97%). This reaction was carried out initially at zero temperature and continued at ambient temperature. High cost and low availability to 2-(thiophen-2yl) ethyl methanesulfonate and use of this substance as starting material in preparation of thiofentanyl caused 2-(thiophen-2yl) ethyl methanesulfonate (**1**) to be synthesized. Of course, synthesis of 2-thiofen ethyl bromide and 2-thiofen ethyl chloride was also studied but the desired yields were not achieved. Therefore, 2-(thiophen-2yl) ethyl methanesulfonate was used as the primary substance in the N-alkylation step.

In the next step, the alkylation of commercially available 4-piperidone monohydrate hydrochloride with 2-(thiophen-2-yl)ethyl methanesulfonate carried out in presence or absence of phase transfer catalyst (PTC) catalyst to synthesize *N*-[2-(2-thienyl)ethyl]-4-piperidone (NTP) (**2**) with 55% to 90% yield (Table 2, entry 1-6). This method is very simple and efficient and the reaction performed under mild conditions and at room temperature. N-alkylation step was not performed in absence of PTC (entry 7, 8). The use of the PTC benzyltriethyl ammonium chloride (TEBA) resulted in the synthesis of NTP (entry 1-6). Although, the Cs_2CO_3 has been reported as the base in recent work,[17] no meaningful difference was observed using K_2CO_3 as the base and the product was obtained with 90% yield (entry 1).



Reagents: MsCl, $SOCl_2$, CBr_4

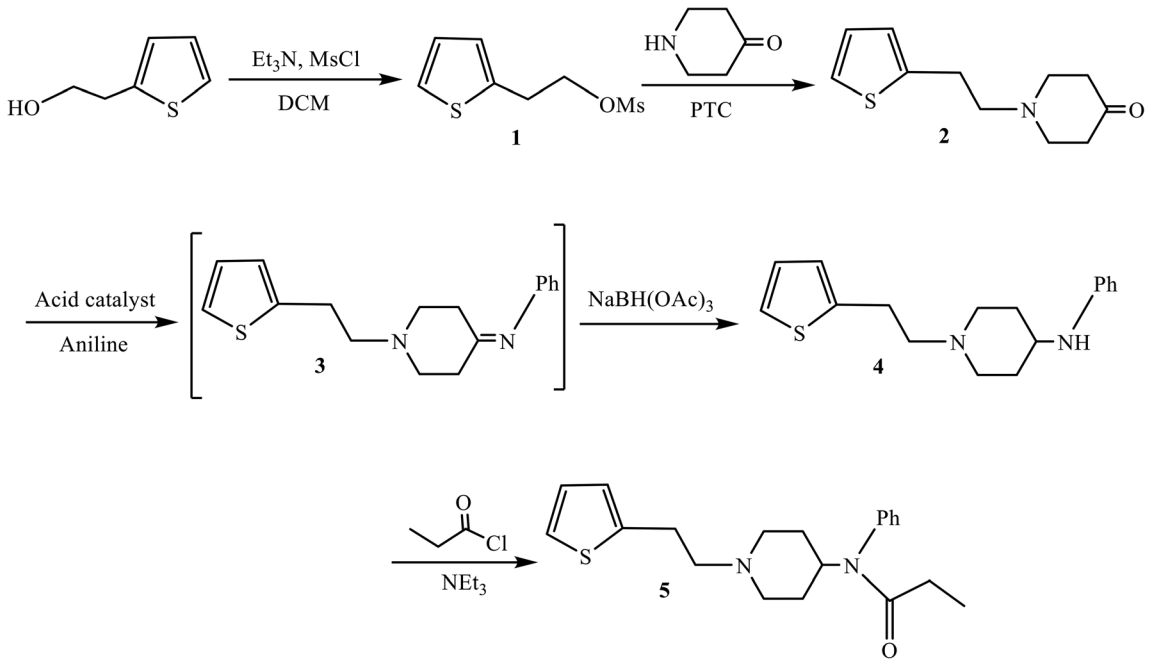
SCHEME 1 Synthesis of 2-(thiophen-2yl) ethyl methanesulfonate

The reaction of ketone **2** with aniline in the presence of acid catalysts at different conditions provided imine **3** with about 60% to 90% yield (Scheme 2). The carbonyl group of compound **2** is coordinated with proton of acid catalyst which activates it toward nucleophilic attack of aniline. The imine was slowly hydrolyzed on silica gel, so the column chromatography was not used for workup and purification. Therefore, the imine reacted with the reductive agents in situ. The investigation of various solvents was shown in Table 3 and DCM was found to be the best choice. Acid catalysts were next investigated, in the condensation of aniline with ketone. Acid catalysts such as MCM-41-SO_3H, SBA-15-Ph-PrSO_3H, acetic acid, and and so on have been used. And nanocatalyst MCM-41-SO_3H (entry 6) gave a better yield. The reaction occurs inside the pores on the surface of which sulfonic acid groups were supported that are capable of hydrogen bonding with the carbonyl oxygen of the NTP. Interaction between oxygen of carbonyl group and sulfonic acid groups results in higher susceptibility to nucleophilic attack on carbonyl groups for imine formation[20–21] (Scheme 3). Finally, the acetylation reaction of the amine group with propionyl chloride was performed in the presence of different bases. Between the used bases, due to the similarity in yields and availability and safety, triethylamine was the best choice. This reaction was carried out within 2 hours at 90% yield (Table 4).

TABLE 2 Optimization of catalyst for *N*-alkylation step

Entry	Catalyst		Time (h)	Yield (%)[a]
1	20 mol% TEBA	2 mmol K_2CO_3	24	90
2	20 mol% TEBA	2 mmol Cs_2CO_3	24	90
3	10 mol% TEBA	2 mmol Cs_2CO_3	24	60
4	30 mol% TEBA	2 mmol Cs_2co_3	24	70
5	20 mol% TEBA	1 mmol K_2CO_3	24	55
6	20 mol% TEBA	1 mmol Cs_2CO_3	24	60
7	Polyethylene glycol-300	2 mmol K_2CO_3	24	No product
8	20 mol% TEBA	—	24	No product
9	—	2 mmol K_2CO_3	24	No product
10	—	2 mmol Cs_2CO_3	24	No product

[a]Isolated yield.



SCHEME 2 Synthesis of thiofentanyl

TABLE 3 Optimized conditions for synthesis of ANTP

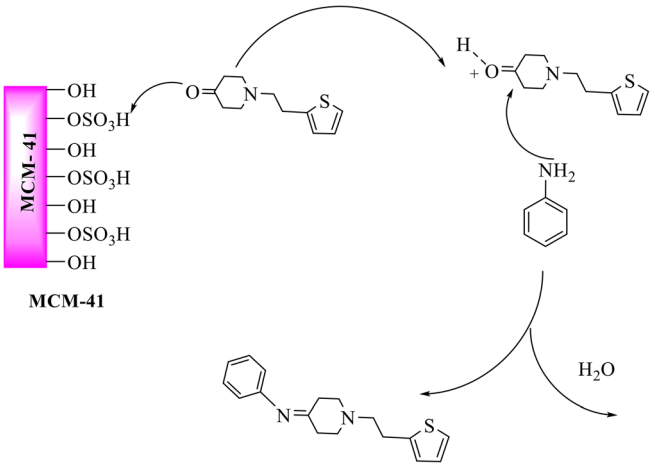
Entry		Catalyst	Solvent	Temperature	Time (h)	Yield (%)[a]
1	Imination	PTSA	Toluene	Reflux	24	40
	Reduction	$NaBH_4$	THF	RT	24	
2	Imination	PTSA	Toluene	Reflux	24	45
	Reduction	$LiAlH_4$	THF	RT	24	
3	Imination	Acetic acid	DCM	RT	10	50
	Reduction	$LiAlH_4$			10	
4	Imination	Acetic acid	DCM	RT	8	65
	Reduction	$NaBH(OAc)_3$			8	
5	Imination	MCM-41-SO_3H	DCM	RT	5	55
	Reduction	$LiAlH_4$			10	
6	Imination	MCM-41-SO_3H	DCM	RT	5	80
	Reduction	$NaBH(OAc)_3$			5	
7	Imination	MCM-41-SO_3H	Toluene	Reflux	12	50
	Reduction	$NaBH(OAc)_3$			12	
8	Imination	SBA-15-Ph $PrSO_3H$	DCM	RT	5	75
	Reduction	$NaBH(OAc)_3$			5	

Abbreviation: ANTP, *N*-phenyl-1-(2-(thiophen-2-yl)ethyl) piperidine-4-amine.
[a]Isolated yield.

3 | EXPERIMENTAL

3.1 | General

All chemicals were purchased from Merck, Fluka, and Sigma-Aldrich companies and were used without further purification. All the organic solvents were purchased from commercial suppliers and were purified according to standard procedures. Analytical thin layer chromatography (TLC) for monitoring reactions was performed using Merck 0.2 mm silica gel 60F-254 Al-plates using ethyl acetate and *n*-hexane as eluents.



SCHEME 3 Proposed mechanisms for formation of *N*-phenyl-1-(2-(thiophen-2-yl)ethyl) piperidine-4-amine

TABLE 4 Optimized conditions for synthesis of thiofentanyl

Entry	Catalyst	Solvent	Time (h)	Yield (%)[a]
1	Et_3N	DCM	2	90
2	Et_3N	CH_3CN	2	75
3	DIPEA	DCM	2	90
4	Pyridine	DCM	2	90
5	DIPEA	CH_3CN	2	70
6	Pyridine	CH_3CN	2	75

[a]Isolated yield.

Column chromatography was accomplished using Merck Silica gel 60 (0.063-0.200 mm). Infrared spectra were obtained using a Perkin-Elmer Spectrom-100 FT-IR spectrometer. ^{1}H NMR (250 500 MHz) and ^{13}C NMR (60 120 MHz) spectra were recorded with $CDCl_3$ as solvent at ambient temperature and tetramethylsilane as internal standard. Mass spectra were recorded on an Agilent Technologies, Model: 5975C VL MSD by EI mass spectrometry on a Q-TOF instrument. All yields refer to the isolated products.

3.2 | Characterization of nano catalyst MCM-41-SO_3H

In this work, MCM-41 was synthesized according to the explained procedure in literature[22] MCM-41 was sulfonated by covalently bonded sulfonic acid on the inside surface of pores to provide the silica-supported nanomaterial with Bronsted acid properties. Then was reacted with chlorosulfonic acid to give a white powder that was named MCM-41-SO_3H.[23]

3.3 | Characterization of Nano catalyst SBA-15-Ph-PrSO_3H

In this work, SBA-15-Ph-PrSO_3H was synthesized according to the explained procedure in literature.[24]

3.4 | Synthesis

3.4.1 | 2-(Thiophen-2-yl) ethyl methanesulfonate (1)

A mixture of triethylamine (1.50 mmol), 2-(Thiofene-2-yl)ethanol (1 mmol) and anhydrous dichloromethane (dry; 15 mL) was stirred at the room temperature under a nitrogen atmosphere for 1 hour. It was cooled to 0°C to 5°C with ice-salt bath and then methanesulfonyl chloride (1.50 mmol) was added dropwise in 10 minutes. The mixture was warmed to ambient temperature under a nitrogen atmospheric pressure and stirred for 2 hours. After completion of the reaction (TLC, 2 hours), the mixture transfered to a separatory funnel and partitioned (CH_2Cl_2/H_2O) and the organic layer was separated. The organic phase was washed with saturated $NaHCO_3$ solution and brine ($NaCl/H_2O$). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 2-(thiophen-2-yl) ethyl methanesulfonate as light brown oil (0.20 g, 97%), Rf = 0.54 (3:7 EtOAc/hexane); ^{1}HNMR (250 MHz, $CDCl_3$) δ = 7.91 (dd, J = 4.8 Hz, 0.6 Hz, 1H), 6.95 (dd, J = 5.4 Hz, 3.6 Hz, 1H), 6.91 to 6.90 (m, 1H), 4.42 (t, J = 6.6 Hz, 2H), 3.27 (t, J = 6.6 Hz, 2H), 2.92 (s, 3H); ^{13}C NMR (60.2 MHz, $CDCl_3$) d 138.1, 127.1, 126.2, 124.5, 69.7, 37.4, 29.8. Anal. calcd (%) for $C_7H_{10}O_3S_2$: C, 40.76; H, 4.89; O, 23.27; S, 31.08. Found: C, 40.56; H, 4.99; O, 23.32; S, 31.13.

3.4.2 | N-[2-(2-Thienyl) ethyl]-4-piperidone (2)

20 mol% TEBA and K_2CO_3 (10 mmol) was dissolved in dry acetonitrile (25 mL) in a round-bottom flask equipped with a stir bar and a condenser. The mixture was stirred 15 minutes at 60°C, and then was added 4-piperidone monohydrate hydrochloride (10 mmol) in little portions. The mixture was stirred for 1 hour at 60°C and then 2-(thiophen-2-yl) ethyl methanesulfonate (5 mmol) was added dropwise. The resulting suspension was vigorously stirred and refluxed at 80°C for 24 hours. After completion of the reaction (TLC, 24 hours), the mixture was filtrated and transferred to a separator

funnel and partitioned (CH_2Cl_2//H_2O). The organic phase was washed with saturated $NaHCO_3$ solution and brine (NaCl/H_2O). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford *N*-[2-(2-thienyl) ethyl]-4-piperidone as a light yellow oil (0.941 g,90%), Rf = 0.25 (40:60 EtOAc/hexane), IR (KBr) (ν_{max}, cm^{-1}): 3100, 2951, 2823, 2793, 1714, 1353, 1224, 1123, 851 710; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.14 (dd, J = 5.4 Hz, 1.2 Hz, 1H), 6.92 (dd, J = 5.4 Hz, 3.6 Hz, 1H), 6.84 (dq, J = 3.6 Hz, 1.2 Hz, 1H), 3.04 (t, J = 7.2 Hz, 2H), 2.82 (t, J = 6.0 Hz, 4H), 2.77 (t, J = 7.2 Hz, 2H), 2.48 (t, J = 6.0 Hz, 4H); ^{13}C NMR (60 MHz, $CDCl_3$) d 209.0, 142.4, 126.6, 124.7, 123.7, 60.4, 53.0, 41.3, 28.3. Anal. calcd (%) for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69; O, 7.64; S, 15.32. Found: C, 63.15; H, 7.32; N, 6.59; O, 7.61; S, 15.32.

3.4.3 | *N*-Phenyl-1-(2-(thiophen-2-yl) ethyl) piperidine-4-amine (4)

Aniline (1 mmol), *N*-[2-(2-thienyl) ethyl]-4-piperidone (1 mmol) and MCM-41-SO_3H (0.02 g) was taken up in methylene chloride (25 mL) in a round-bottom flask equipped with a stir bar. The light brown solution was stirred at ambient temperature for 5 hours. Then, slow addition of sodium triacetoxyborohydride (2 mmol) was applied in small portions. The reaction mixture was stirred at ambient temperature for 5 hours. After completion of the reaction, the mixture was filtrated and transferred to a separator funnel. The mixture was partitioned (CH_2Cl_2/H_2O). The organic phase was washed with saturated $NaHCO_3$ solution and brine (NaCl/H_2O). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuum to give light brown oil. The oily mixture was purified by Column chromatography (6:4 EtOAc/hexane) to give **4** as light yellow solid (0.982 g,80%), Rf = 0.31 (60:40 EtOAc/hexane), IR (KBr; ν_{max}, cm^{-1}): 3423, 3285, 2933, 2804, 2763, 1601, 1526, 1496, 1317, 1269, 746, 705, 693; ^{1}H NMR (150 MHz, $CDCl_3$) δ = 7.18 to 7.15 (m, 2H), 7.13 (dd, J = 5.4 Hz, 1.2 Hz, 1H), 6.92 (dd, J = 5.4 Hz, 3.6 Hz, 1H), 6.84 to 6.82 (m, 1H), 6.69 (tt, J = 7.2 Hz, 0.6 Hz, 1H), 6.62 to 6.58 (m, 1H), 1.52 (S, 1H), 2.24-3.31 (m, 1H), 3.33 (t, J = 6.6 Hz, 2H), 2.95 to 2.93 (m, 2H), 2.68 (t, J = 6.6 Hz, 2H), 2.22 (td, J = 13.2 Hz, 2.4 Hz, 2H), 2.10 to 2.07 (m, 2H), 1.54-1.51 (m, 2H); ^{13}C NMR (62 MHz, $CDCl_3$) d 147.1, 142.9, 129.3, 126.6, 124.6, 123.5, 117.2, 113.3, 60.0, 52.4, 49.9, 32.6, 28.0; Mass spectrum (EI, 70 eV), m/z (Irel, %): $[M]^+$ 300 (3), 189 (98), 132 (84), 146 (100), 118 (83), 97 (99). Anal. Calcd for $C_{17}H_{22}N_2S$: C, 71.29; H, 7.74; N, 9.78; S, 11.19. Found: C, 71.35; H, 7.71; N, 9.80; S, 11.18.

3.4.4 | Thiofentanyl (5)

N-phenyl-1-(2-(thiophen-2-yl) ethyl) piperidine-4-amine (1 mmol) and triethylamine (2 mol) was dissolved in methylene chloride (25 mL) in a round bottom flask equipped with a stir bar. It was stirred at ambient temperature for 1 hour. The solution was cooled to 0°C to 5°C with ice-salt bath and then propionyl chloride (2 mmol) was added dropwise in 10 minutes. The resulting mixture was stirred for 1 hour at ambient temperature. After completion of the reaction, the mixture transferred to a separator funnel. The mixture was partitioned (CH_2Cl_2/H_2O). The organic phase was washed with saturated $NaHCO_3$ solution and brine (NaCl/H_2O). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuum to give light brown oil. The oily mixture was purified by column chromatography (4:6 EtOAc/hexane) to give **5** as light yellow solid (0.308 g, 90%), Rf = 0.21 (50:50 EtOAc/hexane), IR (KBr; ν_{max}, cm^{-1}): 2932, 2805, 1640, 1595, 1496, 1391, 1269, 1055, 707; ^{1}HNMR (500 MHz, $CDCl_3$) δ = 7.38 to 7.33 (m, 3H), 7.09 to 7.06 (m, 2H), 6.88 (dd, J = 4.8 Hz, 3.0 Hz, 1H), 6.77 to 6.75 (m, 1H), 4.67 (tt, J = 12.0 Hz, 4.2 Hz, 1H), 2.97 to 2.92 (m, 4H), 2.61 to 2.58 (m, 2H), 2.17 (td, J = 12.0 Hz, 1.8 Hz, 2H), 1.91 (q, J = 7.8 Hz, 2H), 1.81 to 1.78 (br s, 1H), 1.40 (qd, J = 11.4 Hz, 3.6 Hz, 2H), 1.00 (t, J = 7.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) d 173.5, 142.6, 138.8, 130.4, 129.3, 128.3, 126.6, 124.5, 123.4, 60.0, 53.0, 52.1, 30.5, 28.5, 27.8, 9.6; Mass spectrum (EI, 70 eV), m/z (Irel, %): $[M + 1]^+$ 343 (3), 189 (70), 245 (96), 146 (100), 97 (75), 57 (62). Anal. Calcd for $C_{20}H_{26}N_2OS$: C, 70.14; H, 7.65; N, 8.18; O, 4.67; S, 9.36. Found: C, 70.34; H, 7.55; N, 8.23, O, 4.69; S, 9.39.

4 | CONCLUSIONS

In this work, we have illustrated preferable and improved method for the synthesis of thiofentanyl. The mesylated thiophene ethanol obtained after reaction of thiophene ethanol with mesyl chloride. Then, the alkylation of 4-piperidone monohydrate hydrochloride with 2-(thiophen-2-yl) ethyl methanesulfonate in the presence of catalyst was carried out with 90% yield. NTP was then reacted with aniline in the presence of MCM-41-SO_3H catalyst giving the imine derivative which reduced with sodium triacetoxyborohydride to *N*-phenyl-1-(2-(thiophen-2-yl) ethyl)piperidine-4-amine with 80% yield. Finally, acylation of *N*-phenyl-1-(2-(thiophen-2-yl) ethyl) piperidine-4-amine carry out by using propionyl chloride to achieve thiofentanyl with high yield. The total synthesis of thiofentanyl with this condition was accomplished in four steps with 90% yield. The mentioned synthesis method,

proposes several advantages of short reaction times, high yields, mild condition, simplicity, and easy workup compared to the other conventional methods of synthesis.

ORCID

M. J. Taghizadeh https://orcid.org/0000-0003-2661-0870

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Taghizadeh MJ, Hosseini SJ, Moosavi SM, Parsa H. Improved method for the total synthesis of thiofentanyl. *J Heterocyclic Chem*. 2020;1–7. https://doi.org/10.1002/jhet.3983