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Research article

Highly productive and scalable approach to synthesize ticlopidine: A potent thienopyridine anti-platelet aggregation drug

Muhammad Faisal [a,*], Quret ul Aein [a], Aamer Saeed [a,**], Amara Mumtaz [b], Fayaz Ali Larik [a]

[a] Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan
[b] Department of Pharmacy, COMSATS Institute of Information Technology, 22060 Abbottabad, Pakistan

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ABSTRACT

Ticlopidine (trade name Ticlid), an acidic thienopyridine derivative, is an effective, well-known and long-acting inhibitor of platelet aggregation. Because of its potent inhibitory activity for treating a variety of diseases, the development of efficient approaches for accessing ticlopidine represents an important endeavour. Therefore, in this research work, we developed a promising novel five-step synthetic approach for synthesizing ticlopidine. This method provides ticlopidine in 60% overall yield from readily available starting material *viz.* thiophene. In this methodology, all steps afforded excellent yields and are operationally simple and environmentally acceptable. This approach also offers various attractive advantages, for example, it's applicable for large-scale synthesis, has simple work-up procedures and short reaction times, and uses inexpensive and readily available reagents. Furthermore, 4,5,6,7-tetrahydrothieno[3,2-c]pyridine is a key precursor for the synthesis of numerous bioactive compounds such as prasugrel and clopidogrel. This protocol provides 4,5,6,7-tetrahydrothieno[3,2-c]pyridine in 62% overall yield *via* a 4-step synthetic approach.

1. Introduction

Ticlopidine (**1,** trade name Ticlid) is an anti-platelet drug in the thienopyridine class, which is an adenosine diphosphate (ADP) receptor inhibitors. A stroke is a serious health condition that occures when the supply of blood to a part of the brain is reduced or interrupted. Within minutes, brain cells begin to die. Ticlopidine is considered a second-line option for the prevention of thrombotic strokes among patients who have previously had a TIA (transient ischaemic attack) or stroke [1]. A literature review reveals that ticlopidine **1** is superior to aspirin **2** for the prevention of future strokes or death. Ticlopidine also has more serious side effects compared to those of aspirin; therefore, it is recommended for those patients who cannot take aspirin (Figure 1) [2–4]. Ticlopidine is FDA (Food and Drug Administration) approved for stroke prevention and, when mixed with aspirin, it is approved for preventing closure in patients with a new coronary. Investigations in humans and animals have proven that ticlopidine is a powerful inhibitor of platelet aggregation induced by ADP and variably inhibits aggregation caused by collagen, thrombin, arachidonic acid, adrenalin and plate activating factor. The inhibition of platelet aggregation is dependent on both time- and dose- and its onset of potency is 1–2 days. Its greatest potency is observed after 2–5 days and its potency remains 75 h after the final dose. There are also numerous off-label applications of ticlopidine, including the prevention of heart attack, peripheral vascular disease, diabetic eye disease, and sickle-cell disorder as well as the acute treatment of unstable angina and myocardial infarction [2, 4, 5, 6].

Ticlopidine **1** belongs to the P2Y12 inhibitor family of drugs [6]. Other drugs in this family include prasugrel (Effient **3**), ticagrelor (Brilinta **4**), and clopidogrel (Plavix **5**). Ticlopidine works by preventing platelets from aggregating and stopping them from forming harmful clots (Figure 1). It helps maintain smooth blood flow in humans and stops blood clots by binding to the P2Y12 receptor on platelets, preventing ADP from activating the platelets. It acts as an antagonist of adenosine diphosphate receptors and is used clinically in the management of conditions such as thromboembolic strokes and to prevent thrombus formation secondary to cardiovascular surgical procedures [7]. Also, it has been reported to be a suicide inhibitor of CYP2C19, acting as a substrate of the enzyme, and undergoing biotransformation into a metabolite that subsequently causes mechanism-based inhibition [3]. Ticlopidine and related thienopyridines such as clopidogrel **5** have similarly been reported to inhibit the metabolism of fluorogenic probe substrates by CYP2C19 [8]. It is also a potent inhibitor of CYP2B6-mediated bupropion

* Corresponding author.
** Corresponding author.
E-mail addresses: mfaisal4646@gmail.com (M. Faisal), aamersaeed@yahoo.com (A. Saeed).

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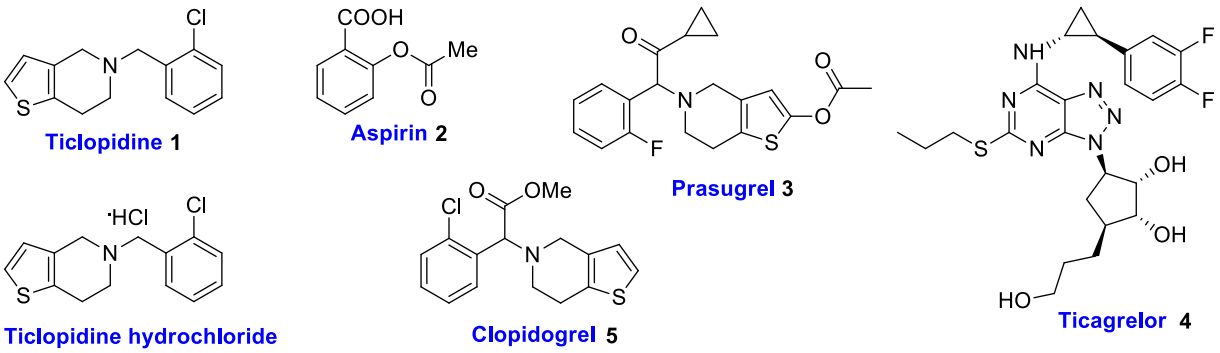


Figure 1. Structure of aspirin and P2Y12 inhibitors.

hydroxylation *in vivo* [9]. In addition to its potent inhibitory activity against these two isoforms, *in vitro* studies have also revealed its low selectivity and potential inhibition of other CYP450s [10]. However, Walsky and Obach reported that ticlopidine was markedly more selective for CYP2B6 when pre-incubated with hepatic microsomes prior to addition of probe substrates for other CYP450 isoforms [11].

Chemically, ticlopidine HCl is 5-[(2-chlorophenyl)methyl]-4,5,6,7-tetrahydrothieno [3,2-c] pyridine hydrochloride. It is a colourless crystalline solid with a molecular mass of 264 g/mol. It is highly soluble in H_2O and self-buffers to a pH of 3.7. It is also highly soluble in MeOH, is sparingly soluble in DCM and EtOH, somewhat soluble in propanone and insoluble in a pH 6.3 buffer solution [12, 13, 14]. Ticlopidine pills for oral administration are marketed as blue-imprinted, film-coated, oval, white tablets containing 250 mg of ticlopidine HCl. Each pill also contains starch, povidone, microcrystalline cellulose (MCC), magnesium stearate, citric acid and stearic acid as inactive constituents. The thick white film-coating contains titanium dioxide, polyoxyethylene and hydroxypropylmethyl cellulose [15, 16].

The above factors highlight the importance of ticlopidine as is a useful, and superlative drug, and therefore, developing methods for preparing this drug on a large scale in a practical and less expensive manner of great interest. To accomplish this goal, convenient, atom- and step-economical, low-cost and environmentally benign synthetic routes are desired. A careful survey of the literature revealed few reports dealing with the synthesis of ticlopidine. However, unfortunately, the synthetic processes in these reports involve superstoichiometric quantities of transition metal promoters, harsh reaction conditions, large number of steps, low overall yields, expensive or highly toxic reagents and operational complexity that lead to poor process throughput [17, 18, 19, 20, 21, 22, 23, 24]. The synthetic route that is employed commercially to generate ticlopidine **1** should meet many standards in terms of safety, control, throughput, legality and environmental impact. Additionally, an appropriate route for the preparation of a variety of ticlopidine derivatives would facilitate the production of targets that are currently objects of intense interest as new and more potent anti-platelet drugs. To achieve these synthetic goals, herein, we report a highly efficient and convenient, five-step synthetic approach for preparing ticlopidine **1** in 60% overall yield. This environmentally acceptable approach is highly valuable for the large-scale production of ticlopidine. The main chemicals and reagents used in this approach are thiophene **6**, paraformaldehyde, sulfuric acid, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), ferric chloride, piperidine, LAH, 1,3-dioxolane **9**, trifluoroacetic acid (TFA), 2-bromochlorobenzene **13** and cobalt bromide [18, 21]. The synthetic procedures in this protocol are very simple and provide excellent yield in short reaction times. Furthermore, 4,5,6,7-tetrahydrothieno[3,2-c]pyridine **11** is a key precursor in the synthesis of numerous bioactive compounds such as prasugrel and clopidogrel. This protocol provides **11** in 62% overall yield *via* a 4-step synthetic approach [25, 26]. This effort will be very beneficial for the scientific community and pharmaceutical industry.

2. Results and discussion

In this five-step synthetic procedure, ticlopidine **1** was obtained in 48% overall yield *via* route A and in 60% overall yield *via* route B. The five-step synthetic approach is illustrated in Figure 2.

The synthetic sequence leading to ticlopidine started with the formylation of thiophene **6**. The reaction of thiophene **6** with paraformaldehyde in the presence of sulfuric acid, DDQ and CH_3CN at reflux (80 °C) for 5 h afforded 2-thiophenecarboxaldehyde **7** in 94% yield. This quite effective technique proceeds *via* an acid catalysed hydroxy methylation of **6** to afford 2-thiophenemethanol **17** by paraformaldehyde with concomitant selective oxidation of the intermediate aromatic carbinol **17** by DDQ to give aldehyde product 2-thiophenecarboxaldehyde **7** (Figure 2) [26]. Notably, in this reaction, 2,3-dichloro-5,6-dicyanohydroquinone (DDHQ) was formed during the oxidation, which was re-oxidized to DDQ *via* washing with HNO_3. Hence, the recovery DDQ was investigated to be possible in this approach [27]. This high yielding and unique oxidative hydroxymethylation technique would be a beneficial alternative to conventional approaches [28].

In the next step, the obtained 2-thiophenecarboxaldehyde **7** was subjected to Henry reaction conditions to construct 2-(2-nitrovinyl) thiophene **8a**. To accomplish the Henry reaction, various conditions were tested (Table 1) [29,30]. The investigation revealed that the microwave-assisted Henry protocol and ferric chloride/piperidine-mediated Henry approach were the most efficient methodologies to yield nitro **8a**. In the microwave-assisted Henry reaction, aldehyde **7** in the presence of nitromethane and a catalytic amount of NH_4OAc was irradiated at 250 W for 1 h at 90 °C, furnishing nitro **8a** in 90% yield (Table 1, Entry 7) [29]. Microwave irradiation offered a unique one-pot method of preparing nitro **8a** in excellent yield without using any solvent (Figure 2). The time required for the formation of nitro **8a** using microwave irradiation was much less than that required for conventional conditions [31, 32], and side products; for instance, nitro alcohol **8b**, dinitro compounds or dimers of nitrostyrenes were not formed. Hence, this protocol is environmentally acceptable, rapid and operationally simple. However, in the ferric chloride/piperidine-mediated Henry reaction, aldehyde **7** was reacted with nitromethane in the presence of $FeCl_3$ (Lewis acid), piperidine (base) in a refluxing toluene for 2 h to give nitro **8a** in 95% yield (Table 1, Entry 3) [30]. This technique has numerous benefits: (i) it is appropriate for large-scale synthesis, (ii) it uses simple work-up and separation procedures, and (iii) it uses inexpensive catalysts.

The next task was to reduce the nitroolefin of 2-(2-nitrovinyl)thiophene **8a**. For this purpose, various approaches were examined [33, 34, 35, 36, 37], and these approaches are listed in Table 2. Among all the protocols, the BH_3-THF/$NaBH_4$-mediated methodology (Table 2, Entry 2) and the LAH/THF-based approach (Table 2, Entry 1) were the most suitable. In the BH_3-THF/$NaBH_4$-mediated methodology, nitro **8a** was reduced to thiophene-2-ethylamine (**9**, 75%) *via* treatment with *in situ*-generated BH_3-THF and a catalytic amount of $NaBH_4$ [37].

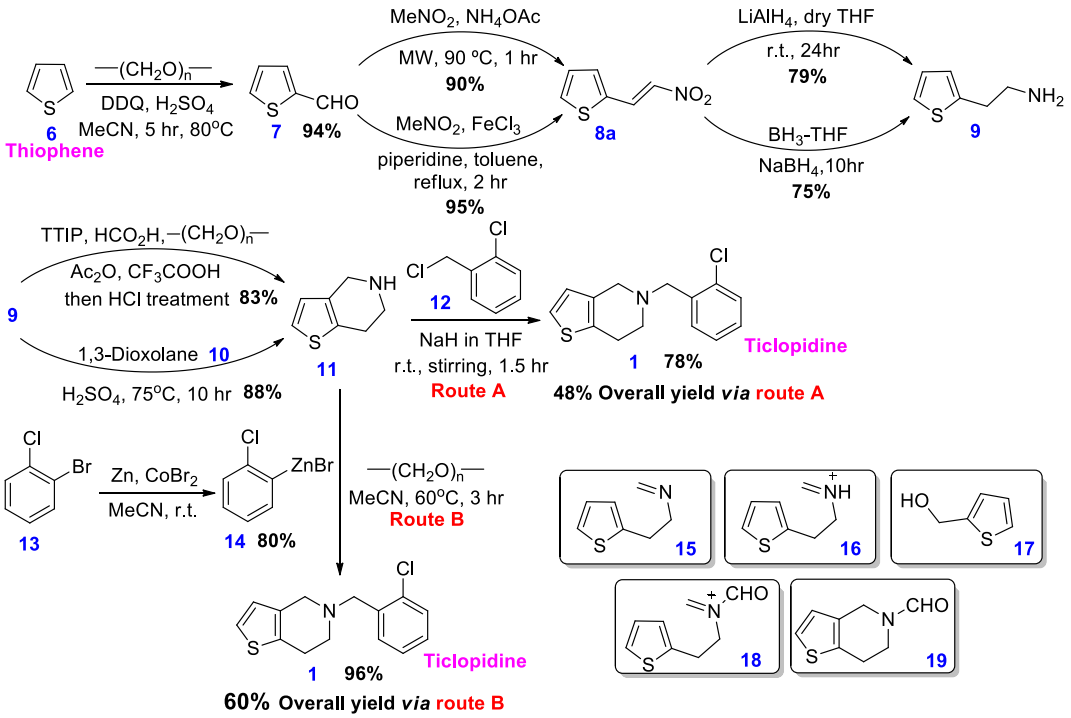
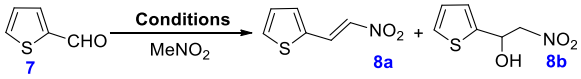


Figure 2. Total synthesis of ticlopidine.

Table 1. Henry reaction at various conditions.

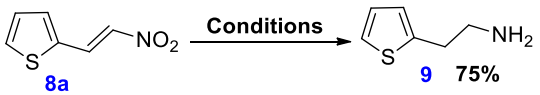


Entry	Conditions	8a (Yield %)	8b (Yield %)
1	$AlCl_3$, piperidine, toluene, reflux, 4 h	80	12
2	$ZnCl_2$, piperidine, toluene, reflux, 3 h	72	16
3	$FeCl_3$, piperidine, toluene, reflux, 2 h	95	Trace
4	$FeCl_3$, Et_3N, toluene, reflux, 4 h	82	11
5	$FeCl_3$, K_2CO_3, toluene, reflux, 6 h	75	12
6	NaOH, methanol, stirring at 0 °C, 1 h	71	20
7	NH_4OAc, MW, 90 °C, 1 h	90	0
8	NH_4OAc, vigorous stirring, 24 h	74	0
9	TBAF, MW, 90 °C, 1 h	82	0
10	TBAF, vigorous stirring, 24 h	71	0

Alternatively, in the LAH/THF-based approach, nitro **8a** is treated with LAH in the presence of dry THF at r.t. for 12 h to deliver amine **9** in 79% yield (Figure 2) [36]. LAH is a very strong reducing agent, and in this reaction, it reduces the nitroolefin. The simple work-up, ready commercial availability of the reducing agent, short reaction times and high yield make this process a promising alternative to the current procedures for the preparation of amine **9** [33–35,38,39].

With amine **9** in hand, the next step was cyclization. To do this, two protocols were employed, namely a titanium isopropoxide-based method and a 1,3-dioxolane-mediated approach [40]. In the titanium

Table 2. Investigated protocols to reduce nitroolefin of 2-(2-nitrovinyl)thiophene.



Entry	Conditions	9 (Yield %)
1	$LiAlH_4$, dry THF, r.t., 1 2hr	79%
2	*in situ* generated BH_3-THF//$NaBH_4$(cat.), 10 h	75%
3	SmI_2/H_2O/isopropylamine, r.t., 10 h	64%
4	LiTEBH/BH_3, 60 °C, 5 h	67%
5	$SnCl_2/Et_2OH$, reflux for 24 h	32%
6	Pd/C moderate conditions (5 bar H_2, 30–90 °C)	59%

isopropoxide-based method, a one-pot Pictet-Spengler reaction was performed as follows: amine **9** and paraformaldehyde were condensed at 80 °C in titanium (IV) tetraisopropoxide (TTIP) for 3 h, and *in situ*-formed imine **15** was treated with acetic-formic anhydride at 70 °C for 2 h to produce formyliminium ion **18**. Noteworthy, cyclization of the imine to a formyl iminium ion readily occurred in trifluoroacetic acid (TFA). To this solution, a large excess of TFA was added at 0 °C and then the solution was heated at 70 °C for an appropriate time, producing intermediate **19**. The hydrolysis of **19** with HCl afforded 4,5,6,7-tetrahydrothieno[3,2-c]pyridine **11** in 83% yield (Figure 2) [40]. On the other hand, in the 1,3-dioxolane-mediated approach, amine **9** was treated with 1,3-dioxolane **10** in the presence of sulfuric acid at 75 °C for 10 h yielding amine **11** (88%) *via* the formation of intermediate **16** [41]. 1,3-Dioxolane **10** in H_2SO_4 provides a higher yield than paraformaldehyde, formaldehyde, 1,3,5-trioxane and 1,3-dioxolane in conc. aqueous HCl. This interesting cyclization involved the initial construction of corresponding Schiff base **16**, which then underwent a Pictet-Spengler reaction to furnish ring-closed amine **11**. Notably, expected intermolecular aminomethylation did not occur. H_2SO_4 was observed to be more effective than HCl, which is presumably because H_2SO_4 is diprotic. 1,3-Dioxolane has several advantages over formaldehyde, *i.e.*, (i) its low boiling point facilitates higher throughput and faster drying, and (ii) it has a pleasant, non-irritating odour and, therefore, does not create special ventilation problems. Thus, although 1,3-dioxolane is more expensive than the currently available commercial forms of formaldehyde, it is valuable in applications in which these forms cannot be readily employed or are less efficient. Notably, the amine **11** is also a key precursor for the synthesis of prasugrel (Effient **3**) and clopidogrel (Plavix **5**) [25]. The overall yield of amine **11** was 62% *via* this four-step approach. The end game of the synthesis of ticlopidine **1** commenced with the attachment of a 1-chloro-2-methylbenzene fragment to amine **11**. For this purpose, two different routes (A and B) were employed. From route A, ticlopidine **1** was obtained in 78% yield *via* the S_N2 displacement reaction of 1-chloro-2-(chloromethyl) benzene **12** with 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine **11** in the presence of NaH in THF at room temperature for 1.5 h. From route B, ticlopidine **1** was obtained in 96% by a three-component reaction between amine **11**, paraformaldehyde and 2-chlorophenylzinc bromide **14** at 60 °C (Figure 2). In this reaction, organozinc **14** (>3 equiv.) was allowed to react with amine **11** and paraformaldehyde (1.9 equivalents, depolymerized prior to use by heating for 2 h at 60 °C) in acetonitrile for 1 h at 60 °C. Route B utilized **14**, which is a highly suitable nucleophile for the multi-component synthesis of the benzylamine nucleus of ticlopidine **1** [41]. Organozinc reagent **14** was prepared in 80% yield by a one-pot reaction of 2-bromochlorobenzene **13** with Zn dust in the presence of cobalt bromide and acetonitrile at room temperature. The overall yield of ticlopidine **1** was 48% *via* route A and 60% *via* route B. Route B provides a higher yield and hence can be regarded as more robust route for accessing ticlopidine **1**.

3. Conclusion

In a five-step synthetic procedure, ticlopidine was obtained in 48% overall yield *via* route A and in 60% overall yield *via* route B. The satisfactory yield of ticlopidine *via* route B suggests that this methodology is more suitable and convenient for preparing ticlopidine. Facile work-up procedures, short reaction times, excellent yields and low occurrence of side products make this technique reliable and attractive alternative to the existing approaches for the preparation of ticlopidine. All the chemicals and reagents used herein are commercially available and are very inexpensive. The synthetic procedures in this protocol are operationally simple and provide excellent yields with short reaction times. Furthermore, this is a convenient, low-cost, atom- and step-economical strategy that is also applicable for the construction of derivatives of ticlopidine. Moreover, this approach is highly valuable for the large-scale production of ticlopidine. This research will help clarify recent synthesis techniques for the preparation of drugs, identify the most appropriate synthetic approach, develop further new transformational methodologies and improve current transformational approaches. This work provides a strong platform from which to conduct further research in this field and investigates additional hypotheses. We hope that the results of our work will inspire further research and benefits the scientific community and pharmaceutical industry.

4. Experimental

4.1. Materials and general methods

Chemicals, reagents and solvents were obtained from Spectrochem, SRL, Merck, Aldrich and Process Chemicals. Routine reaction monitoring was carried out with pre-coated silica gel-60 TCL plates (Aldrich, Silica gel H TLC Grade), which were visualised with I_2 vapour. Chromatographic purifications were performed with silica gel (Wakogel® C-100E). Melting points were measured with a capillary apparatus. ^{1}H NMR spectra were acquired on a Varian Gem2300 300 MHz spectrometer (chemical shifts are w.r.t residual solvent peaks; Tetramethylsilane = δ 0 ppm). All coupling constants are expressed in Hz and are reported absolute values.

4.2. Synthetic procedure for 2-thiophenecarboxaldehyde (7)

To synthesize desired product **7**, thiophene (**6** 1.6 g, 20 mmol), sulfuric acid (0.5 mg, 0.005 mmol), paraformaldehyde (6 g, 200 mmol), DDQ (9.08 g, 40 mmol) and acetonitrile (20 mL) were placed in a two-neck round-bottom flask. The reaction mixture was stirred for 5 h at 80 °C. The progress of the reaction was observed by TLC (10% ethyl acetate in *n*-hexane as the solvent system). After the reaction, the reaction flask mixture was allowed to cool to room temperature. The formed precipitates were collected by filtration and washed with EtOAc. Further purification of the crude product was performed by silica gel-based chromatography with EtOAc in *n*-hexanes (1:2) as the solvent system. 2-Thiophenecarboxaldehyde (**7**) was obtained as a colourless liquid in 90% yield after purification.

4.2.1. Synthetic procedure for 2-(2-nitrovinyl)thiophene (6a) via a microwave-assisted Henry reaction

A 4 mL glass microwave tube, was charged with a mixture of nitromethane (3 mL) and 2-thiophenecarboxaldehyde **7** (112 mg, 1 mmol). Then, ammonium acetate (0.02 g, 0.3 mmol) was added to this tube. Next, the reaction, was performed in a microwave system (CEM-Discover) at 250 W and 90 °C for 60 min. Then, the reaction mixture was cooled, and the crude product was obtained by evaporation of solvent (nitromethane) using a Büchi micro-distillation apparatus. The crude product, containing nitrostyrenes, was then purified by silica gel-based chromatographic purification using EtOAc in hexanes (1:2) as the eluent to obtain the desired product (8a) as a yellow solid in 90% yield.

4.2.2. Synthetic procedure for 2-(2-nitrovinyl)thiophene (8a) via a ferric chloride/piperidine-mediated Henry reaction

Toluene (2 mL) and 2-thiophenecarboxaldehyde (**7**, 224 mg, 2 mmol) were stirred for 15 min in a round-bottom flask, and then, CH_3NO_2 (12 mmol) and piperidine (17 mg, 0.2 mmol) were added. Next, the reaction mixture was refluxed gently for 2 h. After the reaction was completed, as observed by TLC (using a solvent system of 10% ethyl acetate in *n*-hexane), the reaction mixture was cooled to r.t. Then, the solvent was evaporated under reduced pressure, and the residue was further purified by silica gel-based column chromatography using 5% EtOAc in PET ether as the eluent. The desired product (2-2-nitrovinyl)thiophene, **8a**) was obtained as a light-yellow solid in 95% yield.

4.2.3. Synthetic procedure for thiophene-2-ethylamine (9) via a LAH/THF-based approach

To a round-bottom flask, containing a solution of LAH (8.9 mL, 1 M/Et_2O) in anhydrous THF (25 mL) in an ice bath was added 2-(2-nitrovinyl)thiophene (**8a**, 0.68 g, 4.4 mM) in anhydrous THF (10 mL) with the assistance of a double-ended needle. After the addition of **8a** in THF, the ice bath was removed and the mixture was vigorously stirred at r.t. for one day. The progress of the reaction was monitored by TLC using 10% EtOAc in hexane. After completion of the reaction, the mixture was quenched by the addition of H_2O (2 mL) and washed with 10% sodium hydroxide (10 mL) solution. Celite was added to the mixture, which contained a precipitate, and the solids were removed by filtration and thoroughly rinsed with Et_2O. The filtrate was dried ($MgSO_4$) and filtered, and the solvents were removed to yield thiophene-2-ethylamine (**9**, 79%; yellow oil).

4.2.4. Synthetic procedure for thiophene-2-ethylamine (9) via BH_3-THF/$NaBH_4$-mediated methodology

To achieve a very high dry reaction environment, a 100mL flask was flame dried prior to the reaction, flushed with nitrogen and equipped with a magnetic stirrer, a septum inlet and a reflux condenser. The flask was transferred into anice bath to cool the flask to 0 °C, and sodium borohydride (19.00 mmol, 0.72 g) was added to the flask. Then, THF (30 mL) and BF_3–Et_2O (24 mmol, 3 mL) were sequentially added to the flask. After the addition of the reagents was complete, the ice bath was removed and further the reaction was carried out at r.t. for approximately 15 min. A solution of **8a** (2-(2-nitrovinyl)thiophene) in THF (4 mmol in 10 mL of tetrahydrofuran) was added dropwise to the flask by means of a syringe. The reaction mixture was allowed to reflux in an oil bath for 10 h. TLC in a solvent system of 10% ethyl acetate in *n*-hexane was employed to monitor the reaction progress. The reaction mixture was cooled to r.t, and H_2O (50 mL) was cautiously add to quench the reaction. Then, 50 mL of 1 M hydrochloric acid was added to acidify the solution. The reaction was heated at 80–85 °C for almost 2 h. Then, the reaction mixture was cooled to r.t, and the acidic layer subsequently washed with ether (4 × 50 mL). Aqueous NaOH was added to the acidic layer, which liberated thiophene-2-ethylamine (**9**). Solid NaOH was added, and the product was extracted with ether (4 × 50 mL). The ether layer was dried over anhydrous Epsom salt, and the product was obtained by removal of the solvent under reduced pressure. Thiophene-2-ethylamine (**9**) was obtained as the desired product in as a yellow oil in 75% yield.

4.2.5. Synthetic procedure for 4,5,6,7-tetrahydrothieno[3,2-c]pyridine (11) via a 1,3-dioxolane-mediated approach

Thiophene-2-ethylamine (**9**, 1.8 g, 14.6 mmol) was transferred to 500mL single-neck round-bottom flask, which was fitted with a long condenser. Concentrated H_2SO_4 (20 mL) was poured into the flask, and the reaction mixture was stirred. Stirring was continued for 1 h and 1,2-dioxolane (5.4 g, 73.4 mmol) was then poured into the reaction mixture with continuous stirring. After that, a temperature of approximately 75 °C was maintained for 10 h and the reaction progress was monitored by TLC with a solvent system of 10% ethyl acetate in *n*-hexane. After completion of the reaction, the reaction mixture was allowed to cool to r.t. The reaction mixture was washed with toluene, and the toluene layer was further washed with 100 mL of water and concentrated. Chromatographic purification on silica gel was performed to purify the crude product. Methanol: chloroform (9:1) was used as the solvent system to elute **11** as a highly pure yellow oil in 88% yield.

4.2.6. Synthetic procedure for 4,5,6,7-tetrahydrothieno[3,2-c]pyridine (11) via a titanium isopropoxide-based method

A round-bottom flask was equipped with a long condenser and a magnetic stirrer. Under an argon atmosphere, a mixture of paraformaldehyde (15.72 mmol), thiophene-2-ethylamine (**9**, 2.00 g, 15.72 mmol) and Ti(O-*i*Pr)$_4$ (5.68 g, 18.86 mmol) was transferred to the flask, and the system was heated at 80 °C for 2 h. Then, the reaction flask was transferred to an ice bath to cool the reaction mixture to 0 °C and an acetic-formic anhydride solution (prepared from formic acid (18.1 g, 393 mmol) and acetic anhydride (40.2 g, 393 mmol)) was added to the reaction mixture at this low temperature. Then, the reaction mixture was heated at 70 °C for 30 min CF_3CO_2H (44.82 g, 393 mmol) was poured into the mixture, and heating was maintained at the same temperature for an additional 90 min. Methanol (200 mL) was added to dilute the reaction mixture. The titania (TiO_2) was removed by a column chromatography *via* a small silica column using a $CHCl_3$–MeOH solvent system as the eluent. The eluate was concentrated under low pressure to *ca.* 70 mL, and the obtained residue was extracted with chloroform. The extraction solvent was evaporated under reduced pressure and *c*-HCl (12 mL or 24 mL) and EtOH (28 mL) were then added. The resulting mixture was then refluxed under an argon atmosphere for approximately 4–18 h. After that, water was added to dilute the mixture, and 10% NaOH was added to make the solution alkaline. The mixture was then extracted with chloroform. The crude product was purified by column chromatography over silica gel with MeOH–$CHCl_3$ (9:1) to afford **11** as a yellow oil in 83% yield.

4.2.7. Synthetic procedure for ticlopidine (1) via route A

Sodium hydride (0.82 g, 17.2 mmol) was transferred to a round-bottom flask containing THF (10.0 mL). To this suspension was added a solution of **11** (2.0 g, 14.4 mmol). The mixture was stirred at r.t. under a N_2 atmosphere for half an hour, and then *o*-chlorobenzyl chloride (**12**, 3.48 g, 21.6 mmol) was added to the mixture. After 90 min of stirring at r.t., 30 mL of toluene was added. Then, the mixture was refluxed for 15–20 h. The consumption of the reactants over time was monitored by TLC in with a solvent system of 10% EtOAc in *n*-hexane. After completion of the reaction, the mixture was cooled, and 80mL of 1 M HCl was used to acidify the reaction mixture. Two layers were formed, and they were separated. A dilute solution of sodium hydroxide in water was added into the separated aqueous layer to make the solution basic (pH 13–14). Further extraction was performed by using methylene chloride. The methylene chloride layer was then washed with H_2O (1 × 50 mL) and a salt solution (1 × 50 mL), dehydrated using anhydrous $MgSO_4$ and concentrated in *vacuo*. Silica gel chromatography (solvent system: pentane/CH_2Cl_2/NEt_3 in a 93/5/2 ratio) was used for purification to afford ticlopidine (**1**, 78 % yield) as pale-yellow oil.

4.2.8. Synthetic procedure for ticlopidine (1) via route B

Acetonitrile (14 mL) was transferred to a round-bottom flask and flushed with argon. Zinc dust (2.4 g, 36 mmol), dodecane (0.08 mL), 1,2-dibromoethane (0.2 mL) and trifluoroacetic acid (0.08 mL) were added to the flask, and the reaction mixture was heated under vigorous stirring until the production of gas was observed. The heating of the solution ceased, and the solution was cooled for 20 min. Cobalt bromide (0.26 g, 1.2 mmol) and bromochlorobenzene (**13**, 1.4 mL, 12 mmol) were added to the mixture, and the mixture was stirred at the appropriate temperature for 35 min, which provided the desired product (2-cholorophenyl zinc bromide, **14**, yield = 75%).

A round-bottom flask was flushed with Ar gas. Then, paraformaldehyde (0.34 g, 8 mmol) and acetonitrile (6 mL) were added. The mixture was then heated at 60 °C for 2 h. Next, **11** (0.62 g, 4.4 mmol) and a solution of organozinc **14** (20 mL) were added sequentially to the reaction flask. The reaction mixture was further stirred for 60 min at 60 °C. The progress of the reaction was monitored over time using TLC with a solvent system of 10% EtOAc in hexane. After completion of the reaction, a saturated solution of NH_4Cl (120 mL) was added, and the reaction mixture was washed with excess dichloromethane (CH_2Cl_2). The dichloromethane layer was further extracted with water (200 mL), and the organic layer was dried using anhydrous sodium sulfate and concentrated. The crude oil was purified by passage through a short silica gel column (solvent system: pentane/CH_2Cl_2/NEt_3 in a 93/5/2 ratio) to obtain ticlopidine (**1**) as a pale-yellow oil. The reaction yield was 95% and purity was >99.5% (GC).

4.3. Spectral data

4.3.1. 2-Thiophenecarboxaldehyde (7)

Appearance: colorless liquid; $\mathbf{R_f}$: 0.56 (*n*-Hexane: EtOAc (1:9)); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 7.32–7.35 (m, 1H), 8.06–8.08, m, 1H), 8.15 (d, 1H, $J = 4.8$ Hz), 9.95 (s, 1H); **^{13}C NMR** (75 MHz, DMSO): δ_c 129.4, 136.5, 138.4, 143.9, 184.7; **Anal. Calcd for C_5H_4OS**: C, 53.55; H, 3.59; O, 14.27; S, 28.59. Found: C, 53.66; H, 3.65; O, 14.26; S, 28.55.

4.3.2. 2-(2-Nitrovinyl)thiophene 8a

Appearance: yellow solid; $\mathbf{R_f}$: 0.32 (*n*-Hexane: EtOAc (1:9)); **M.P**: 81 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 8.14 (d, $J = 14.3$ Hz, 2 H), 7.55 (d, $J =$ 6 Hz, 1 H), 7.50 (s, 1 H), 7.45 (d, $J = 3$ Hz, 1 H), 7.14 (dd, $J = 1.33$ Hz, 5.6 Hz, 1 H); **^{13}C NMR** (75 MHz, DMSO): δ_c 135.3, 134.6, 133.7, 132.1, 131.6, 128.9; **Anal. Calcd for $C_6H_5NO_2S$**: C, 46.44; H, 3.25; N, 9.03; O, 20.62; S, 20.66. Found: C, 46.54; H, 3.44; N, 9.66; O, 20.77; S, 20.56.

4.3.3. Thiophene-2-ethylamine 9

Appearance: yellow oil; $\mathbf{R_f}$: 0.70 (*n*-Hexane: EtOAc (1:9)); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 7.16 (m, 1H); 6.95 (m, 1H), 6.85 (m, 1H), 2.98 (m, 4H, $J = 9$), 1.42 (bs, 2H); **^{13}C NMR** (75 MHz, DMSO): δ_c 136.6, 128.5, 128.3, 126.8, 40.4, 33.2; **Anal. Calcd for C_6H_9NS**: C, 56.65; H, 7.13; N, 11.01; S, 25.21. Found: C, 56.34; H, 7.45; N, 11.51; S, 25.45.

4.3.4. 4,5,6,7-Tetrahydrothieno[3,2-c]pyridine 11

Appearance: yellow oil; $\mathbf{R_f}$: 0.40 (*n*-Hexane: EtOAc (1:9)); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 7.07 (d, $J = 5$ Hz, 1H), 6.74 (d, $J = 5$ Hz, 1H), 3.92 (t, $J = 2$ Hz, 2H), 3.15 (t, $J = 6$ Hz, 2H), 2.80 (t, $J = 6$ Hz, 2H), 1.74 (brs, 1H); **^{13}C NMR** (75 MHz, DMSO): δ_c; 134.4, 133.7, 125.0, 121.9, 45.7, 43.8, 25.9; **Anal. Calcd for C_7H_9NS**: C, 60.39; H, 6.52; N, 10.06; S, 23.03. Found: C, 60.55; H, 6.54; N, 10.55; S, 23.43.

4.3.5. Ticlopidine 4

Appearance: pale yellow oil; $\mathbf{R_f}$: 0.60 (*n*-Hexane: EtOAc (1:9)); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 2.89–2.94 (m, 4H), 3.68 (s, 2H), 3.86 (s, 2H), 6.72 (d, $J = 6.2$ Hz, 1H), 7.10 (d, J = 7.3 Hz, 1H), 7.40–7.25 (m, 2H), 7.38 (dd, $J = 7.5$, 1.5 Hz, 1H), δ 7.54 (dd, $J = 7.5$, 2 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO): δ_c 25.4, 50.7, 53.0, 58.3, 122.7, 125.3, 126.8, 128.3, 129.5, 130.7, 133.4, 133.7, 134.3, 135.9; **Anal. Calcd for $C_{14}H_{14}ClNS$**: C, 63.74; H, 5.35; Cl, 13.44; N, 5.31; S, 12.16. Found: C, 63.75; H, 5.34; Cl, 13.55; N, 5.66; S, 12.11.

Declarations

Author contribution statement

Muhammad Faisal: Conceived and designed the experiments; Wrote the paper.

Aamer Saeed: Conceived and designed the experiments.

Quret ul Aeina: Performed the experiments.

Hesham R. El-Seedi: Analyzed and interpreted the data.

Fayaz Ali Larik: Analyzed and interpreted the data; Wrote the paper.

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The authors declare no conflict of interest.

Additional information

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