



Flow electrosynthesis for efficient *O*-trifluoromethylation of electron-deficient phenols

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ABSTRACT

A sustainable strategy for *O*-trifluoromethylation of electron-deficient phenols by combining electrochemical synthesis with flow technology is presented. The reaction is optimized by screening experiments to establish a fast and efficient flow protocol. Simultaneous anodic oxidation of Langlois reagent and the phenols in a micro flow cell leads to direct preparation of trifluoromethyl ethers in yields up to 90%. This one-step protocol is tolerant of several functional groups, shows good regioselectivity and works without any chemical oxidants and catalysts by using electrical current as an inexpensive and sustainable reagent.

1. Introduction

The introduction of trifluoromethyl groups offers the opportunity to adjust the physical and biological properties of organic molecules, particularly regarding their polarity, lipophilicity and metabolic stability [1]. For this reason, molecules containing CF₃ groups have drawn considerable attention in the design and development of new compounds in research fields ranging from materials to life sciences [2–5]. During recent decades, significant progress has been made in the introduction of CF₃ moieties into aromatic hydrocarbons [6–9]. This emerging interest in trifluoromethylation has contributed to the development of methods for CF₃ substitution at heteroatoms, particularly the trifluoromethylation at chalcogen atoms (O, S, Se) [9]. The trifluoromethoxy group (OCF₃), in particular, has attracted the interest of fluorine chemists in recent years due to various desirable characteristics, such as its specific electronic [10] and conformational properties [11] as well as its outstanding lipophilicity [12]. Despite the emerging interest in OCF₃ groups and particularly aryl trifluoromethyl ethers, their preparation remains a major challenge. One direct strategy for preparation of aryl trifluoromethyl ethers is the *O*-trifluoromethylation of phenols. This approach has been investigated for decades, but has not yet produced satisfactory yields. Several examples of *O*-trifluoromethylation have been reported, but in these cases harsh reaction conditions, sophisticated reagents, metal catalysts or multiple step reactions are necessary [8,13,14]. Furthermore, the choice of starting material is largely limited to electron-rich phenols. The first approach to *O*-trifluoromethylation of electron-poor pentafluorophenol was made by

Buxton et al. in 1973 (Scheme 1(a)) [15]. This method requires high temperatures and pressures, a large excess of toxic reagents, generates huge amounts of reagent waste and produces only low yields of the desired octafluoroanisole. Therefore, *O*-trifluoromethylation of electron-deficient phenols is still an under-explored and challenging research field. Further development is necessary with a special focus on a more sustainable and efficient synthesis strategy.

In the past two decades, electrochemical synthesis has emerged as an increasingly powerful and versatile strategy for the sustainable and (atom)-economic synthesis of organic compounds. Conventional chemical oxidizing and reducing agents, as well as metal catalysts, can be replaced by using an electrical current as a green, cheap, and inherently safe reagent. The electron transfer usually occurs under ambient conditions and exhibits excellent reaction efficiency without generating large amounts of reagent waste. Thus, electrochemical methods have gained great popularity in organic chemistry, in both academic research and industrial applications [16–18].

Most laboratory-scale electrochemical reactions are performed in batch reactors. This allows a relatively simple reaction setup, but batch electrolysis cells are often limited in their efficacy. A more powerful electrochemical operating mode can be achieved by the introduction of flow technology. Electrochemical flow cells typically consist of two parallel plate electrodes separated by a small distance (usually 1 mm or less). If necessary, a membrane can be inserted between them to separate anode and cathode and prevent unwanted mass transport. The electrolyte is pumped through the electrode gap, where the electrochemical reaction takes place. This setup has several advantages: electrochemical

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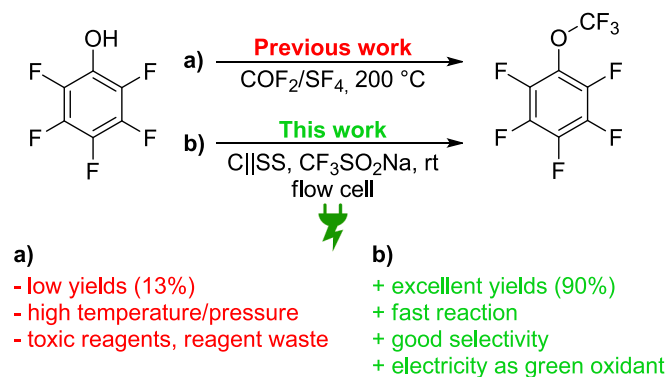
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Scheme 1. Comparison of different synthesis strategies for the preparation of octafluoroanisole from pentafluorophenol: (a) previous work; (b) this work. C||SS: graphite anode || stainless steel cathode.

flow reactors provide a considerably larger ratio of electrode surface to reactor volume than batch cells, and also allow control over the residence time of reagents at the electrodes. This leads to shorter reaction times and can also prevent unwanted side reactions [19–21]. Furthermore, flow electrolyzers allow continuous production and are more scalable than batch cells. Therefore, flow electrolysis is the superior electrolysis mode and is generally preferred in the chemical industry [22,23].

Considering these advantages, we wished to improve the recently developed electrochemical *O*-trifluoromethylation of electron-poor phenols, which results in very interesting synthons, e.g. for molecular electronics. However, the reported electrochemical batch process suffered from some of the typical drawbacks of batch electrolysis, namely, limited yields, slow conversion of starting materials, and unsatisfactory regioselectivity [24]. In this paper, we present a faster and more efficient protocol for electrochemical *O*-trifluoromethylation of electron-deficient phenols by application of flow electrochemistry (Scheme 1 (b)). This is the first time that the combination of electrochemistry and flow technology for *O*-trifluoromethylation has been reported. The electrolysis was conducted in a micro flow cell setup under constant current conditions. To optimize the reaction conditions, screening experiments were performed using pentafluorophenol as a model substrate. The optimized reaction conditions were then applied to the *O*-trifluoromethylation of other electron-deficient phenols.

2. Materials and methods

2.1. General Information

All commercially acquired reagents were of analytical grade and used without further purification. Acetonitrile was of HPLC grade. 1,3,4,5,6,7,8-Heptafluoro-naphthalen-2-ol **1b** was synthesized as described in the Supporting Information. GC-MS data were recorded using a combination of a ThermoScientific Trace GC Ultra and a ITQ900 mass spectrometer. A Macherey Nagel OPTIMA 210 fused-silica capillary column (0.32 mm diameter, 0.5 μ m coating, 30 m length) was used for all measurements. ^1H , ^{13}C and ^{19}F NMR spectra were recorded on a 400 MHz (AV400 HD) and 500 MHz (AV500 HD) Bruker NMR spectrometer at room temperature. The ^1H NMR shifts were determined relative to CDCl_3 (7.26 ppm), the ^{13}C NMR shifts relative to CDCl_3 (77.16 ppm) and the ^{19}F NMR shifts relative to internal standard CCl_3F (0.00 ppm). All electrochemical flow reactions were performed with the commercially available modular flow cell system “ElectraSyn flow” by IKA (Staufen, Germany). A Masterflex Ismatec peristaltic pump was used to pump the electrolyte through the flow cell. Constant current conditions were maintained via a Keysight E36104B DC power supply.

2.2. General procedure

The chosen phenol (0.05 M), sodium trifluoromethanesulfinate (0.2 M), and sodium perchlorate monohydrate (0.2 M) were dissolved in acetonitrile/water 4:1. The flow cell was assembled with the corresponding electrode half cells (electrode surface: $2 \times 6 \text{ cm}^2$) at a defined electrode distance with the matching gasket (0.5 mm gasket: 0.6 ml cell volume, 1.0 mm gasket: 1.2 ml cell volume). The cell was mounted vertically and the electrolyte was pumped into the cell from below towards the top to enable a constant flow rate and to allow gaseous byproducts to escape easily. After conditioning of the flow cell and peristaltic tubes with an acetonitrile/water 4:1 mixture, the reactant solution was pumped through the cell at a defined flow rate. After 2 ml had been pumped, the electrolysis was started with a defined constant current for a specific amount of time. The first 3 ml of the electrolyzed solution were discarded to ensure consistent conditions. At the end of the procedure, 25 ml of product solution were collected. The yields of the desired trifluoromethyl ethers were determined by ^{19}F NMR spectroscopy using fluorobenzene as internal standard, since highly fluorinated small molecules exhibit a high volatility and are therefore difficult to isolate. The NMR sample was prepared by adding a defined amount of fluorobenzene and an aliquot of the product solution to the NMR tube. Afterwards, the reaction solution was diluted with H_2O and extracted with dichloromethane ($4 \times 20 \text{ ml}$). The combined organic phases were washed with aqueous Na_2CO_3 solution (1 mol/L, $3 \times 30 \text{ ml}$) and dried over Na_2SO_4 . The solvents were evaporated under reduced pressure. Experimental details and characterization data for the trifluoromethyl ethers **3a-e** can be found in the Supporting Information.

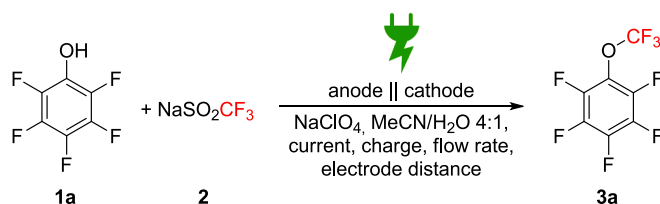
3. Results and discussion

3.1. Optimization of reaction conditions

To optimize the reaction conditions for *O*-trifluoromethylation in the flow cell, screening experiments were performed with pentafluorophenol **1a** as a model substrate (see Scheme 2). Conditions derived from a previously reported method [24] were used as starting parameters (Table 1). For each experiment, only one parameter was altered, the remaining conditions being kept constant. The flow rate was not considered as an isolated parameter, but was adjusted according to the applied current and required reaction time, depending on the amount of charge. The composition of the electrolyte (sodium perchlorate in acetonitrile/water mixture) was not further optimized, since this is already an inexpensive, stable, and well-performing system [24].

Current density was taken as the first screening parameter, and was investigated in the range 2.5–15 mA/cm^2 . As can be seen from Table 2, the best yield of **3a** under these conditions is obtained with a value of 5 mA/cm^2 (31%), with only a slight improvement compared to 2.5 and 10 mA/cm^2 . Experiments with higher currents (15 mA/cm^2 and above) were not possible due to the formation of precipitates in the flow cell, which inhibited the electrolyte flow. Consequently, 5 mA/cm^2 was selected as the preferred current density and therefore all subsequent experiments were conducted with this setting.

Next, the optimal amount of charge applied to the system was explored in a range from 1 to 8 *F*/mol with respect to pentafluorophenol



Scheme 2. Screening reaction to optimize the reaction conditions for electrochemical *O*-trifluoromethylation of pentafluorophenol under flow conditions.

Table 1
Starting parameters for the screening experiments with pentafluorophenol.

Parameter	Value
Solvent	MeCN/H ₂ O 4:1
Supporting electrolyte	0.2 mol/l NaClO ₄
Current density	10 mA/cm ²
Charge amount	2.0 F/mol (with respect to 1a)
Electrode configuration	Graphite graphite (1.0 mm distance)
Concentration of 1a	0.05 mol/l
Flow mode	Single cell pass

Table 2
Results of the screening experiments to determine the best current density for the electrochemical *O*-trifluoromethylation of pentafluorophenol **1a**. The experimental details can be found in Table S1 in the Supporting Information.

Current density (mA/cm ²)	Flow rate (ml/min)	Reaction time (min)	Yield (%)
2.5	0.187	134	26
5	0.373	67	31
10	0.746	34	26
15	1.119	22	–

1a (Fig. 1(a), Table S2). When 1 F/mol was consumed, only 12% octafluoroanisole could be obtained. Increasing the amount of charge stepwise up to 6 F/mol led to successive increases in the yield, up to 57%. Applying 8 F/mol resulted in a rapid decrease in yield, down to 40%, which was an unexpected result since 8 F/mol was found to be the ideal amount of charge in the batch cell process. One reason for this could be that the low flow rate (only 0.093 ml/min) prevented the complete removal of gaseous byproducts, particularly the SO₂ formed at the anode and H₂ at the cathode, thereby inhibiting the desired electrolysis [25]. In general, when gas production occurs in a flow process, higher flow rates are preferred to remove the gas more quickly [26]. Since most parameters in the flow electrolysis are interlinked, simply increasing the flow rate at a fixed current would result in a decrease in the amount of charge. One effective way of keeping the amount of charge constant while increasing the flow rate is to carry out the electrolysis in the form of multiple cell passes, pumping the reaction mixture through the flow cell several times. For example, in an electrolysis with two cell passes, the flow rate is doubled compared to a single pass experiment. Thus, the amount of charge per step is divided by two and consequently, the electrolyte must be pumped through the same cell twice to keep the applied charge constant.

Based on this idea, we checked if the reaction could be improved by passing the reaction mixture through the cell several times. This was

studied for total charges of 6 and 8 F/mol (Fig. 1(b), Table S3). Beginning with 6 F/mol, we performed single, double, and triple cell pass experiments. For all three experiments, the yield of octafluoroanisole remained nearly constant at about 60%. In contrast, when the total amount of charge was 8 F/mol, the yield depended strongly on the number of cell passes. While a single-step experiment led to a yield of only 40%, a two-step electrolysis gave 75% octafluoroanisole, almost doubling the yield. Conducting a three-step electrolysis led to a decrease in yield to 57%. It can be concluded that the application of 8 F/mol in a two-step process leads to the best result by far and this procedure was therefore used in all further reactions.

Smaller interelectrode distances usually reduce the ohmic drop in the cell, leading to improved energy transfer and higher current efficiencies. Therefore, we varied the distance between anode and cathode by assembling the flow cell with gaskets of different thicknesses. With a 1 mm spacer, octafluoroanisole **3a** was synthesized with a yield of 75%. Halving the electrode distance to 0.5 mm increased the yield to 90% at the same flow rate (Table S4).

Using the 0.5 mm electrode spacer, the concentration of supporting electrolyte NaClO₄ was then optimized (Fig. 1(c), Table S5). A maximum yield of 90% was obtained with an electrolyte loading of 0.2 mol/l. Increasing the concentration to 0.3 mol/l led to a slight decrease in yield to 83%. Lowering the concentration of supporting electrolyte resulted in a larger drop of octafluoroanisole yield to 67% at 0.1 mol/l and 68% at 0.05 mol/l. Remarkably, the electrolysis still yielded 58% **3a** without any supporting electrolyte, while maintaining a low terminal voltage of approximately 3 V. Hence, the ionic Langlois reagent in MeCN/H₂O already provides excellent electrical conductivity. However, since the drop in yield was too large in the absence of supporting electrolyte, all further experiments were conducted with 0.2 mol/l sodium perchlorate.

To further optimize the space–time yield, we tried to find out if doubling the concentration of starting materials **1a** and **2** would improve the efficiency of the reaction (Table S6). When 0.1 mol/l phenol was applied, a decrease in yield from 90% (0.05 mol/l) to 77% was observed. Since doubling the concentration of starting material requires twice the reaction time at a constant current density, the yield per hour is superior with a lower concentration (0.05 mol/l) of reactant and therefore more efficient.

Finally, we investigated the influence of the electrode material on the electrolysis (Table 3). When the graphite cathode was substituted by stainless steel (1.4404), the yield of octafluoroanisole remained unchanged (90%), emphasizing that the cathode reaction is not relevant for the outcome of the *O*-trifluoromethylation. Stainless steel is less expensive than graphite, so all further experiments were conducted with stainless steel cathodes. When the flow cell was assembled with a glassy carbon anode and a stainless steel cathode, the amount of

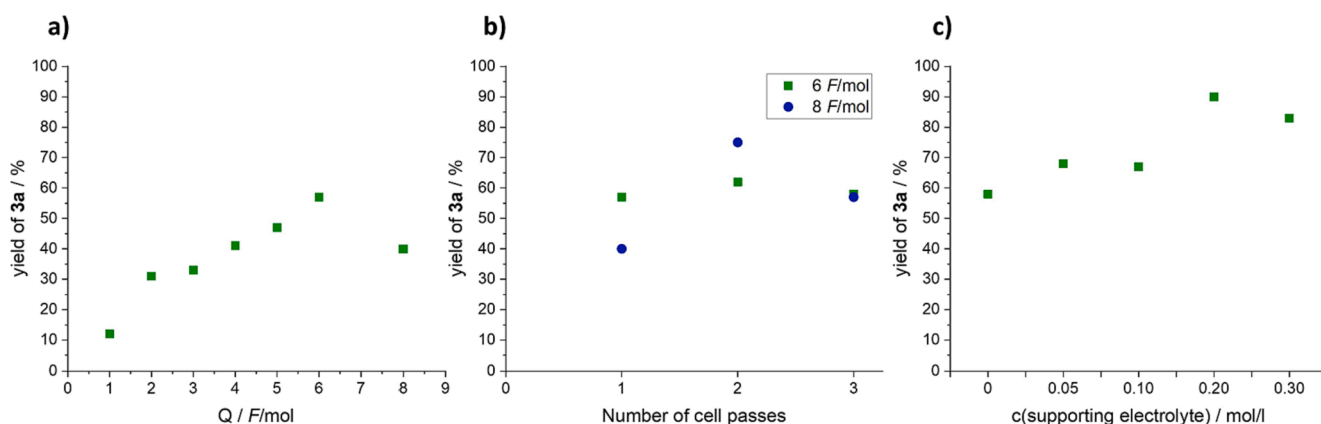


Fig. 1. Results of experiments to determine the optimal values of: (a) amount of charge; (b) number of cell passes for total charges of 6 and 8 F/mol; and (c) concentration of supporting electrolyte for the electrochemical trifluoromethylation of pentafluorophenol **1a**. The experimental details can be found in Tables S2, S3 and S5 in the Supporting Information.

Table 3

Determination of optimal electrode materials for the electrochemical *O*-trifluoromethylation of pentafluorophenol **1a**. All electrode configurations are listed as: anode || cathode. The experimental details can be found in Table S7 in the Supporting Information.

Electrodes	Yield (%)
Graphite graphite	90
Graphite stainless steel	90
Glassy carbon stainless steel	85
BDD stainless steel	–

octafluoroanisole obtained decreased slightly to 85%. When the anode material was changed from glassy carbon to boron-doped diamond (BDD), the experiment had to be stopped after a few minutes, as the formation of a solid compound in the cell prevented a constant electrolyte flow. Thus it is not possible to state a yield for the BDD anodes.

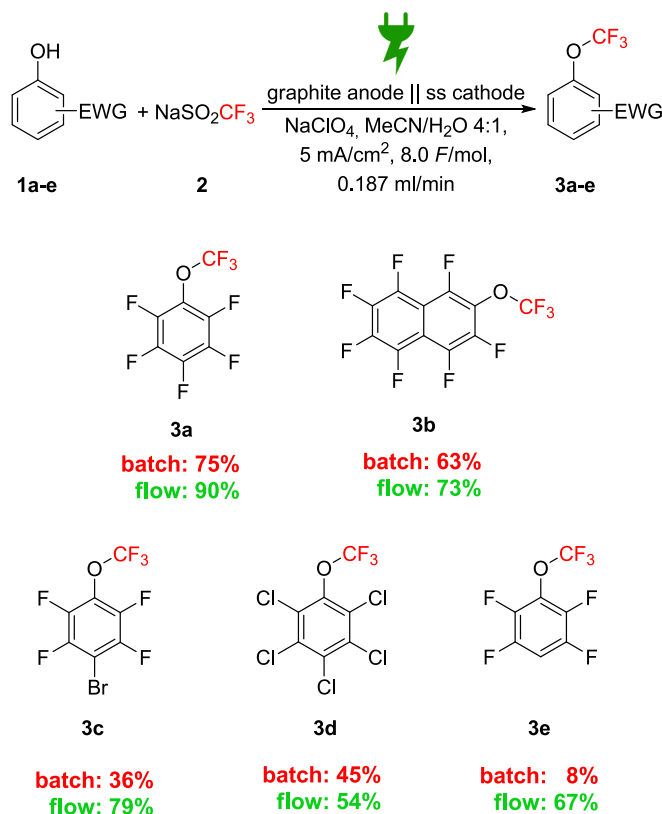
3.2. Investigation of the scope

Using the previously optimized parameters, we investigated the scope of the *O*-trifluoromethylation by choosing selected, electron-withdrawing phenols that had also been investigated in the batch cell process reported earlier, to enable a comparison between batch and flow processes (Scheme 3). Based on previous results, the oxidation potentials of the phenols used must be similar to the oxidation potential of the Langlois reagent for an efficient reaction (see Fig. S1 in the Supporting Information for cyclic voltammetry studies and a proposed mechanism).

The *O*-trifluoromethylation of the model substrate pentafluorophenol **1a** in the batch cell gave 75% octafluoroanisole **3a**, while in the optimized flow process a major increase in yield up to 90% was possible. Use of heptafluoronaphthol **1b** as the starting material in the flow electrolysis resulted in 73% yield of the corresponding trifluoromethyl ether **3b**, which also represents an improvement compared to the batch reactor (63%). Electrolysis starting from brominated tetrafluorophenol **1c** was also performed. Changing the electrolysis mode from batch to flow led to a doubling of the yield of **3c** from 36% to 79%. As well as these reactions with fluorinated phenol derivatives, chlorine-substituted systems such as pentachlorophenol **1d** also resulted in improved yields with the flow protocol. Using the batch reactor, a 45% yield of the corresponding trifluoromethyl ether **3d** was obtained. Choosing the flow cell leads to an improved yield of 54%. Finally, 2,3,5,6-tetrafluorophenol **1e** was used as the starting material. The batch process showed selectivity issues, since this not-fully-fluorinated phenol was prone to side reactions, namely the trifluoromethylation of the aromatic ring by a direct C–H substitution, which was the preferred reaction. For this reason a yield of only 8% of the desired *O*-trifluoromethylated compound **3e** could be obtained. In contrast, the flow cell process led to a remarkable increase in yield to 67%. The unwanted side reaction still occurred, but only in minor amounts of less than 10%. Hence, the flow electrolysis process offers superior reaction efficiency compared to the batch cell.

4. Conclusion

In summary, we have developed an efficient protocol for simple and sustainable *O*-trifluoromethylation of electron-poor phenols by combining the advantages of electrochemical synthesis and flow technology. The reaction was optimized for flow conditions by performing optimization experiments with pentafluorophenol. In all experiments conducted under optimized conditions, the flow cell gave superior yields of up to 90%, depending on the starting material, compared to the batch process (up to 75%). In addition, the flow process only requires a current density of 5 mA/cm² for maximum performance, which is half of the optimal current density needed for the batch process. Furthermore, the



Scheme 3. Scope of the electrochemical *O*-trifluoromethylation of electron-poor phenols with a comparison of the yields obtained in batch and flow cells.

flow electrolysis process takes only about 4 h, while for the same amount of starting material in the same volume of electrolyte (0.05 mol/l phenol in 25 ml electrolyte), a reaction time of more than 19 h is required, emphasizing the superior reaction efficiency of flow electrolysis. The regioselectivity was also considerably improved. When the electrolysis is conducted in batch mode there is no possibility of controlling the selectivity of the trifluoromethylation, leading to unwanted, dominating side reactions when substrates containing C–H bonds are used. The flow cell, in contrast, always yielded the desired compound as the main product with only minor amounts of side products. Thus, the major challenges of the batch cell process (slow conversion of starting materials, moderate yields and limited regioselectivity) could all be overcome by our advanced synthesis strategy. It should be noted that this process still performs well without any additional supporting electrolyte and requires only inexpensive electrode materials. Our optimized protocol provides easy and rapid access to an otherwise difficult to access class of molecules by application of electrical current as a green reagent.

CRediT authorship contribution statement

Johannes Bernd: Methodology, Conceptualization, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Andreas Terfort:** Supervision, Project administration, Conceptualization, Resources, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.elecom.2023.107545>. This file contains the synthesis of phenols which were not commercially available, experimental and characterization data for the trifluoromethyl ethers as well as experimental details for the screening reactions. A reaction mechanism is also proposed.

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