

## One-Pot Synthesis of 2,4,5-Triphenyl Imidazoles from 1,2-Diols as Key Reagents

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A simple one-pot procedure for the preparation of 2,4,5-triphenyl imidazole derivatives is presented. The procedure involves the lead tetraacetate oxidation of 1,2-diols to give aldehydes *in situ*, which then undergo a three-component reaction with benzil and ammonium acetate to yield the imidazole derivatives.

**Keywords:** Imidazoles; Lead tetraacetate; Multicomponent reaction; 1,2-Diols; Benzil; Ammonium acetate.

### INTRODUCTION

Multicomponent reactions (MCRs) have emerged as a powerful tool for industrial and academic research groups because of their shorter reaction times as well as the avoidance of the isolation of intermediates, their purification, and characterization.<sup>1–3</sup> Imidazoles have a privileged structure as they occur as fragments in drugs displaying a wide spectrum of pharmacological activities.<sup>4–9</sup> A large number of compounds bearing substituted imidazole derivatives have entered preclinical and clinical trials over the last few years. These derivatives represent an important structural motif in commercial drugs<sup>10</sup> such as the anti-gastroesophageal reflux drug Omeprazole, platelet aggregation inhibitor Trifénagrel, angiotensin II receptor blocker Olmesartan, and the anti-high-blood-pressure drugs Eprosartan and Losartan (Figure 1).

Imidazole derivatives have received significant importance because of their diverse biological properties such as anti-inflammatory,<sup>11</sup> antimicrobial,<sup>12</sup> anticancer,<sup>13</sup> antitubercular,<sup>14</sup> antifungal,<sup>15</sup> antibacterial,<sup>16</sup> antiviral,<sup>17</sup> antioxidant,<sup>18</sup> and amebicidal activities.<sup>19</sup> The great potential of substituted imidazole derivatives in the pharmaceuticals field has therefore triggered growing interest in their synthetic study.

These applications have stimulated widespread interest in the synthesis of imidazole derivatives. The typical syntheses of imidazole derivatives have been well documented in the literature.<sup>20–22</sup> The most important of these are (1) one-pot cyclocondensation of

aldehydes with benzoin or benzil and ammonium acetate,<sup>23</sup> (2) one-pot cyclocondensation of aldehydes with benzil, aromatic amine, and ammonium acetate,<sup>24</sup> and (3) one-pot cyclocondensation of aromatic nitriles.<sup>25</sup> This has led to the development of new, improved methodologies involving the use of a number of catalysts such as Yb(OPf)<sub>3</sub>,<sup>26</sup> Cu(NO<sub>3</sub>)<sub>2</sub>/zeolite,<sup>27</sup> potassium dihydrogen phosphate,<sup>28</sup> ZrOCl<sub>2</sub>·8H<sub>2</sub>O,<sup>29</sup> Zr(acac)<sub>4</sub>,<sup>30</sup> NiCl<sub>2</sub>·6H<sub>2</sub>O,<sup>31</sup> *p*-toluenesulfonic acid (PTSA),<sup>32</sup> TiCl<sub>4</sub>·SiO<sub>2</sub>,<sup>33</sup> MCM-41,<sup>34</sup> ZrCl<sub>4</sub>,<sup>35</sup> sodium bisulfite,<sup>36</sup> polymer-supported zinc chloride,<sup>37</sup> alum,<sup>38</sup> zinc oxide,<sup>39</sup> trichloroisocyanuric acid,<sup>40</sup> tetrabutyl ammonium bromide,<sup>41</sup> ceric ammonium nitrate,<sup>42</sup> nano copper/cobalt ferrites,<sup>43</sup> microwave,<sup>44</sup> amberlyst,<sup>45</sup> novel polymers,<sup>46</sup> antimony trichloride/stannous chloride dihydrate,<sup>47</sup> SbCl<sub>3</sub>/SiO<sub>2</sub>,<sup>48</sup> sulfamic acid/Fe<sub>3</sub>O<sub>4</sub>,<sup>49</sup> and nano aluminum nitride.<sup>50</sup> Although several methodologies have been documented, most of them have their own drawbacks such as poor yields, the use of toxic catalysts, and tedious work-up. Aldehydes are ubiquitous substrates in many powerful MCRs. However, they are in general unstable, especially because of aerial oxidation to acids, and are prone to polymerization or hydrolysis. Thus, in many cases aldehydes must be purified just before their use because the presence of other products not only affects the concentration of the active aldehyde but also interferes with the chemical reactions.<sup>51</sup> Hence, there is a need to develop a rapid and efficient synthetic protocol for the one-pot synthesis of substituted imidazole scaffolds.

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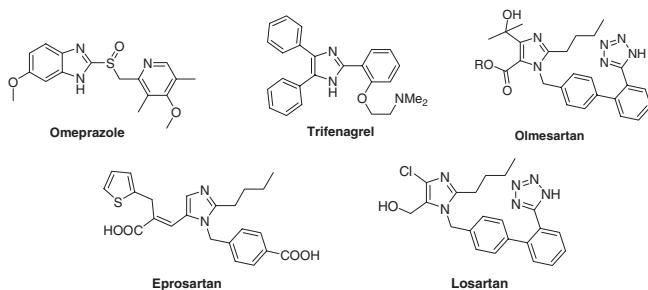


Fig. 1. Typical imidazole drugs.

In continuation of our work on the synthesis of heterocycles and development of useful synthetic methodologies,<sup>2,52–57</sup> in this study we report the use of lead tetraacetate as an oxidizing agent for the synthesis of 2,4,5-triphenyl imidazole derivatives under mild conditions. Lead tetraacetate is an inexpensive, commercially available, and easy-to-handle reagent.

## RESULTS AND DISCUSSION

In our preliminary studies, 1 equiv of 1,2-diphenyl-1,2-ethanediol **1a**, 2 equiv of benzil **2**, 4 equiv of ammonium acetate **3**, and 1 equiv of lead tetraacetate in dioxane were chosen for the model reaction (Scheme 1). Initially, when the model reaction was carried without lead tetraacetate from room temperature to 101°C, no desirable product was observed even after prolonged reaction time. This indicated that an oxidizing agent was absolutely necessary for the reaction. Interestingly, in the presence of lead tetraacetate, when the same set of substrates were tested under reflux condition in dioxane, they provided **4a** in 71% yield in 4.5 h. The compound **4a** was confirmed by IR and <sup>1</sup>H NMR. From this encouraging result, we were prompted to check whether the yield could be further improved by changing the solvent. Other solvents such as DCM, acetonitrile, ethanol, acetone, THF, methanol, DMF, and DMSO were screened (Table 1) under reflux condition for the

Table 1. Optimization of solvents for the synthesis (**4a**)

Entry	Solvents	Time (h)	Yield (%)
1	DCM	5.5	48
2	Dioxane	4.5	71
3	Acetonitrile	3	90
<b>4</b>	<b>Ethanol</b>	<b>3</b>	<b>96</b>
5	Acetone	4.5	74
6	THF	4	76
7	Methanol	3.5	84
8	DMF	5.5	45
9	DMSO	5.5	52

same reaction. Among the solvents, ethanol was found to be the best one for this reaction in terms of yield and reaction time.

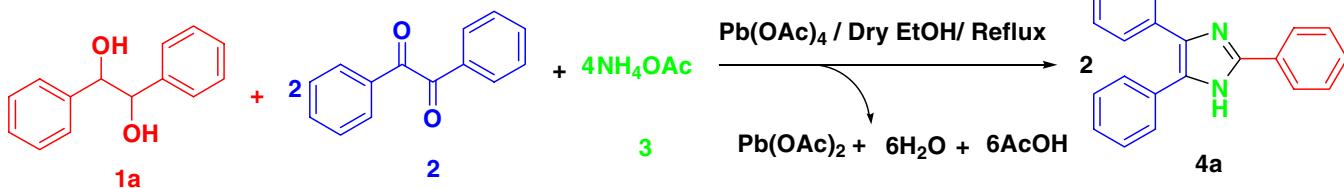
The scope and limitations of this three-component reaction under optimized reaction conditions were studied using a variety of 1,2-diols, benzil, and ammonium acetate. The reaction worked well in case of 1,2-diols tethered with OH, Cl, Br, F, and OCH<sub>3</sub> groups. Moderate yield was obtained for the reaction involving 1,2-diol tethered with NO<sub>2</sub> group. In all cases, the reaction proceeded smoothly to afford the desired products with good to excellent yields (Table 2).

Mechanistically,<sup>60,61</sup> lead tetraacetate oxidizes 1,2-diol to benzaldehyde giving acetic acid, which facilitates the formation of the imine between benzaldehyde and ammonium acetate. The imine then reacts with the intermediate that is formed by the reaction of benzil with ammonium acetate to give the corresponding imidazole via cyclization and dehydration (Figure 2).

## EXPERIMENTAL

### General information

Melting points were determined on an electric melting point apparatus and were uncorrected. Fourier transform infrared (FT-IR) spectra were recorded on an Agilent Cary 630 instrument. <sup>1</sup>H NMR (400 MHz)



Scheme 1 Synthesis of 2,4,5-triphenyl imidazole derivatives using lead tetraacetate as a reagent.

Table 2. Synthesis of 2,4,5-triphenyl imidazole derivatives (**4a–o**)

Entry	1,2-Diols	Products	Time (h)	Yield (%)	Obs. Mp (°C)	Lit. Mp (°C) <sup>ref</sup>
1			3	96	276–278	275–277 <sup>43</sup>
2			2.5	89	233–235	234–236 <sup>39</sup>
3			2.5	90	244–246	245–247 <sup>38</sup>
4			3	91	218–220	218–220 <sup>58</sup>
5			3.5	92	231–233	
6			4.5	82	242–244	240–242 <sup>23</sup>
7			4	89	255–257	
8			3	92	232–234	233–235 <sup>39</sup>
9			3.5	91	246–248	248–250 <sup>39</sup>

Table 2. Continued

Entry	1,2-Diols	Products	Time (h)	Yield (%)	Obs. Mp (°C)	Lit. Mp (°C) <sup>ref</sup>
10			3	90	238–240	239–241 <sup>23</sup>
11			4	89	257–259	
12			2.5	95	255–257	256–258 <sup>54</sup>
13			4	88	263–265	265–267 <sup>59</sup>
14			2	96	219–221	218–220 <sup>36</sup>
15			4	89	263–265	

and  $^{13}\text{C}$  NMR (100 MHz) spectra were recorded in  $\text{CDCl}_3$  and  $\text{DMSO}-d_6$  with TMS as internal standard using a Bruker spectrometer. Chemical shifts are expressed in  $\delta$  ppm. Elemental analyses were carried out using an Elemental Vario Micro Cube Rapid Analyzer. Lead tetraacetate is a solid compound, and its purity is  $\geq 99.99\%$ .

#### Typical experimental procedure for the synthesis of 2,4,5-triphenyl-1*H*-imidazole (4a)

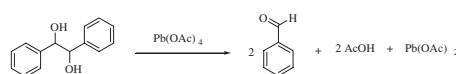
Lead tetraacetate (0.44 g, 1 mmol) was added to a solution of 1,2-diphenylethane-1,2-diol (0.21 g, 1 mmol) in dry ethanol (10 mL). The reaction mixture was stirred at

room temperature for 5 min. Then, benzil (0.42 g, 2 mmol) and ammonium acetate (0.32 g, 4.2 mmol) were added to a round-bottom flask fitted with a reflux condenser and a guard tube. Then reaction mixture was heated at 70°C in an oil bath for 3 h. The reaction was allowed to cool to room temperature, and 10 mL of water was added. The resulting precipitate was collected by filtration and washed with cold ethanol to afford the product. The crude product was purified by recrystallization from ethanol.

#### CONCLUSION

In conclusion, we have developed an efficient and facile method for the synthesis of 2,4,5-triphenyl

## Step 1.



## Step 2.

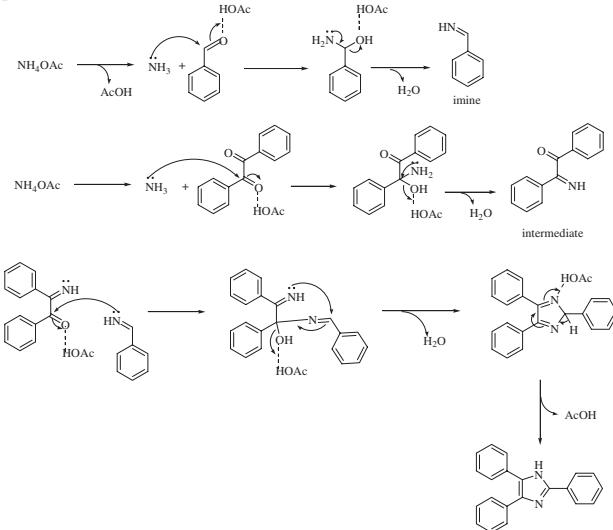


Fig. 2 Plausible mechanism for the formation of imidazole derivatives.

imidazole derivatives via a one-pot, three-component condensation reaction between 1,2-diols, benzil, and ammonium acetate. The current strategy can be used to decrease the number of steps in a multistep synthesis.

## Spectral data of imidazole compounds

**2,4,5-Triphenyl-1*H*-imidazole (4a).** A pale brown solid, 284 mg (96% yield). IR (ATR,  $\text{cm}^{-1}$ ): 3325 (NH); mp 275–277°C.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  9.22 (s, 1H, NH), 8.05–6.73 (m, 15H, Ar-H) ppm. Anal. Calcd for  $\text{C}_{21}\text{H}_{16}\text{N}_2$ : C, 85.11; H, 5.44; N, 9.45; found: C, 85.09; H, 5.43; N, 9.42%.

**2-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (4b).** A white solid, 293 mg (89% yield). IR (ATR,  $\text{cm}^{-1}$ ): 3328 (NH); mp 234–236°C.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  12.79 (s, 1H, NH), 8.15–7.21 (m, 14H, Ar-H) ppm. Anal. Calcd for  $\text{C}_{21}\text{H}_{15}\text{N}_2\text{Cl}$ : C, 76.24; H, 4.57; N, 8.47; found: C, 76.22; H, 4.56; N, 8.44%.

**2-(3-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (4c).** A white solid, 297 mg (90% yield). IR (ATR,  $\text{cm}^{-1}$ ): 3315 (NH); mp 245–247°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  11.25 (s, 1H, NH), 8.40–7.24 (m, 14H, Ar-H) ppm. Anal. Calcd for  $\text{C}_{21}\text{H}_{15}\text{N}_2\text{Cl}$ : C, 76.24; H, 4.57; N, 8.47; found: C, 76.22; H, 4.56; N, 8.44%.

**2-(4-Ethoxyphenyl)-4,5-diphenyl-1*H*-imidazole (4d).**

A pale brown solid, 309 mg (91% yield). IR (ATR,  $\text{cm}^{-1}$ ): 3330 (NH); mp 218–220°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  10.03 (s, 1H, NH), 8.41–6.84 (m, 13H, Ar-H), 3.98 (m, 2H,  $\text{CH}_2$ ), 1.39 (m, 3H,  $\text{CH}_3$ ) ppm. Anal. Calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}$ : C, 81.15; H, 5.92; N, 8.23; found: C, 81.12; H, 5.90; N, 8.21%.

**2-(3-Bromo-4-methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (4e).**

A pale brown solid, 372 mg (92% yield). IR (ATR,  $\text{cm}^{-1}$ ): 3320 (NH); mp 231–233°C.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  12.59 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable), 8.30–7.19 (m, 13H, Ar-H), 3.90 (s, 3H,  $\text{OCH}_3$ ) ppm.  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 100 MHz):  $\delta$  155.3, 144.0, 136.9, 135.0, 130.9, 129.4, 128.5, 128.2, 128.1, 128.0, 127.6, 127.0, 126.4, 125.8, 124.4, 112.8, 110.8, 56.3 ppm. Anal. Calcd for  $\text{C}_{22}\text{H}_{17}\text{N}_2\text{OBr}$ : C, 65.20; H, 4.23; N, 6.91; found: C, 65.18; H, 4.20; N, 6.88%.

**2-(4-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (4f).**

A brown solid, 279 mg (82% yield). IR (ATR,  $\text{cm}^{-1}$ ): 3320 (NH); mp 240–242°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  10.02 (s, 1H, NH), 8.26–7.26 (m, 14H, Ar-H) ppm. Anal. Calcd for  $\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}_2$ : C, 73.89; H, 4.43; N, 12.31; found: C, 73.88; H, 4.41; N, 12.28%.

**2-(3-Bromo-4-chlorophenyl)-4,5-diphenyl-1*H*-imidazole (4g).**

A white solid, 364 mg (89% yield). IR (ATR,  $\text{cm}^{-1}$ ): 3335 (NH); mp 255–257°C.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  12.77 (s, 1H, NH), 8.41–7.21 (m, 13H, Ar-H) ppm.  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 100 MHz):  $\delta$  159.2, 156.8, 143.1, 137.3, 134.8, 130.7, 129.7, 128.6, 128.4 (2C), 128.2, 128.1, 127.8, 127.0, 126.6, 126.4, 126.3, 117.2, 117.0, 108.5, 108.2 ppm. Anal. Calcd for  $\text{C}_{21}\text{H}_{14}\text{N}_2\text{BrCl}$ : C, 61.56; H, 3.44; N, 6.84; found: C, 61.54; H, 3.43; N, 6.82%.

**4,5-Diphenyl-2-*p*-tolyl-1*H*-imidazole (4h).** A white solid, 285 mg (92% yield). IR (ATR,  $\text{cm}^{-1}$ ): 3312 (NH); mp 233–235°C.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  12.56 (s, 1H, NH), 7.98–7.19 (m, 14H, Ar-H), 2.35 (s, 3H,  $\text{CH}_3$ ) ppm. Anal. Calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_2$ : C, 85.13; H, 5.85; N, 9.03; found: C, 85.11; H, 5.82; N, 9.02%.

**2-(4-Bromophenyl)-4,5-diphenyl-1*H*-imidazole (4i).**

A white solid, 341 mg (91% yield). IR (ATR,  $\text{cm}^{-1}$ ): 3320 (NH); mp 248–250°C.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  12.61 (s, 1H, NH), 7.79–7.22 (m, 14H, Ar-H) ppm. Anal. Calcd for  $\text{C}_{21}\text{H}_{15}\text{N}_2\text{Br}$ : C, 67.21; H, 4.03; N, 7.47; found: C, 67.18; H, 4.02; N, 7.45%.

**2-(4-Fluorophenyl)-4,5-diphenyl-1*H*-imidazole (4j).**

A pale brown solid, 282 mg (90% yield). IR (ATR,  $\text{cm}^{-1}$ ): 3322 (NH); mp 239–241°C.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  12.80 (s, 1H, NH), 7.60–7.23 (m, 12H, Ar-H) ppm. Anal. Calcd for  $\text{C}_{21}\text{H}_{15}\text{N}_2\text{F}$ : C, 80.24; H, 4.81; N, 8.91; found: C, 80.22; H, 4.78; N, 8.90%.

**2-(4-Bromo-3-chlorophenyl)-4,5-diphenyl-1*H*-imidazole (4k).**

A white solid, 364 mg (89% yield). IR (ATR,  $\text{cm}^{-1}$ ): 3315 (NH); mp 257–259°C.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  12.76 (s, 1H, NH), 8.27–7.22 (m, 13H, Ar-H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 100 MHz):  $\delta$  158.2, 155.7, 143.2, 137.3, 134.8, 130.7, 128.6, 128.2, 128.1 (2C), 127.8, 127.0, 126.8, 126.6, 125.7 (2C), 120.0, 119.8, 117.4, 117.2 ppm. Anal. Calcd for  $\text{C}_{21}\text{H}_{14}\text{N}_2\text{ClBr}$ : C, 61.56; H, 3.44; N, 6.84; found: C, 61.53; H, 3.42; N, 6.83%.

**4-(4,5-Diphenyl-1*H*-imidazol-2-yl)phenol (4l).** A white solid, 296 mg (95% yield). IR (ATR,  $\text{cm}^{-1}$ ): 3324 (NH); mp 256–258°C.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  12.58 (s, 1H, NH), 9.51 (s, 1H, OH), 7.54–6.76 (m, 14H, Ar-H) ppm. Anal. Calcd for  $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}$ : C, 80.75; H, 5.16; N, 8.97; found: C, 80.72; H, 5.14; N, 8.96%.

**2-(2,6-Dichlorophenyl)-4,5-diphenyl-1*H*-imidazole (4m).**

A white solid, 321 mg (88% yield). IR (ATR,  $\text{cm}^{-1}$ ): 3310 (NH); mp 265–267°C.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  12.72 (s, 1H, NH), 7.65–7.20 (m, 13H, Ar-H) ppm. Anal. Calcd for  $\text{C}_{21}\text{H}_{14}\text{N}_2\text{Cl}_2$ : C, 69.05; H, 3.86; N, 7.67; found: C, 69.03; H, 3.83; N, 7.66%.

**2-(3,4-Dimethoxyphenyl)-4,5-diphenyl-1*H*-imidazole (4n).**

A white solid, 341 mg (96% yield). IR (ATR,  $\text{cm}^{-1}$ ): 3332 (NH); mp 218–220°C.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  12.01 (s, 1H, NH), 7.55–7.10 (m, 13H, Ar-H), 3.87 (s, 3H,  $\text{OCH}_3$ ), 3.82 (s, 3H,  $\text{OCH}_3$ ) ppm. Anal. Calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_2$ : C, 77.51; H, 5.66; N, 7.86; found: C, 77.50; H, 5.64; N, 7.83%.

**2-(2-Chloro-6-fluorophenyl)-4,5-diphenyl-1*H*-imidazole (4o).**

A pale brown solid, 309 mg (89% yield). IR (ATR,  $\text{cm}^{-1}$ ): 3325 (NH); mp 263–265°C.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  12.81 (s, 1H, NH), 7.61–7.24 (m, 13H, Ar-H) ppm.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 100 MHz):  $\delta$  136.9, 134.9, 134.6, 134.5, 131.8, 131.7, 130.7, 129.7, 129.6, 129.2, 129.0, 128.7, 128.4, 128.1, 128.0, 127.8 (2C), 127.7, 127.1, 126.5, 125.7 ppm. ESI-MS: [M + H] 349.3. Anal. Calcd for  $\text{C}_{21}\text{H}_{14}\text{N}_2\text{ClF}$ : C, 72.31; H, 4.05; N, 8.03; found: C, 72.30; H, 4.03; N, 8.02%.

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## Supporting information

Additional supporting information is available in the online version of this article.

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