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ORIGINAL PAPER

A facile synthetic route for antineoplastic drug GDC-0449

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In the current study a facile synthetic route for preparing antineoplastic drug GDC-0449 is investigated. Starting with pyridine-1-oxide and 1-iodo-3-nitrobenzene, the intermediate product 2-(2-chloro-5-nitrophenyl) pyridine was prepared by cross-coupling, deoxidation and halogenation. The final compound was then synthesised by reduction of the nitro group followed by amidation. This synthetic route avoids the use of unstable organometallic or organic boride compounds; it employs relatively inexpensive and bench-stable reagents, involves readily controllable reaction conditions, and achieves a relatively high yield.

Keywords: GDC-0449, pyridine 1-oxide, cross-coupling, halogenation, synthesis

Introduction

The hedgehog (Hh) signalling pathway plays a vital role in cell differentiation, organ development and body patterning during embryogenesis (Varjosalo & Taipale, 2008). Disordered Hh signalling is involved in several human neoplasms including basal cell carcinoma, medulloblastoma, small cell lung cancer and gastrointestinal carcinoma (Berman et al., 2003; Epstein, 2008; Taipale & Beachy, 2001; Watkins et al., 2003). GDC-0449 (*I*) (also HhAntag691) is a small molecular compound that can efficiently suppress over-activation of the Hh signalling pathway (Robarge et al., 2009). In January 2012, the U.S. Food and Drug Administration approved GDC-0449 as the first anti-Hh drug for the treatment of advanced basal cell carcinoma) in adults (US Food and Drug Administration, 2012).

Compound *I* consists of a (pyridin-2-yl)-aryl structure, which can be synthesised from a pyridine-2-yl derivative with an aromatic compound through a cross-coupling reaction. However, due to the special reactive feature of pyridine-2-halides, the formation of the C—C bond in this reaction conventionally requires the use of zinc or a boronation step. A well-established preparatory method for compound *I* involves the Negishi reaction (Gunzner et al., 2011), in which 2-bromopyridine (*II*) is treated with butyllithium (BuLi) followed by the addition of zinc chloride to form pyridin-2-ylzinc bromide. The resulting intermediate is then subjected to a palladium-mediated coupling with intermediate 2-chloro-*N*-(4-chloro-3-iodophenyl)-4-(methylsulfonyl)benzamide (*III*). This step requires an ultra-low temperature (–78 °C) to metallise pyridin-2-yl before the coupling reaction takes place. In addition, it requires the gradual addition of each reactant, a procedure which will represent difficulties if carried out on a large scale. Other approaches to preparing the pyridyl-2-metallised reagent are available, for example, the Grignard reaction of

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2-bromopyridine followed by the addition of other reactants (Matondo et al., 2003; Su et al., 2012). However, in preliminary attempts, this method failed to achieve much reaction efficiency over the BuLi method, probably because Grignard reactions often start slowly and require initiation following an induction period. In the meantime, the intermediate pyridine-2-magnesium can be chemically instable for handling at ambient temperature (Gavryushin et al., 2005; Wang et al., 2009).

An alternative way for preparing *I* is the Suzuki coupling reaction (Knapp et al., 2009; Miyaura & Suzuki, 1979), which shares starting materials with the Negishi reaction but involves different intermediates. It also requires the transformation of compound *II* into an unstable intermediate pyridin-2-ylboronic acid or 6-methyl-2-(pyridin-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione prior to cross-coupling with *III* catalysed using palladium. This procedure includes complicated metallisation reactions and purification processes; it also requires proper storage of all the reactants and intermediates (Dick et al., 2010; Matondo et al., 2003), which also restricts large-scale synthesis of *I*. Hence, it is both clinically and economically desirable to develop a new route to synthesise *I* by utilising simpler, safer but more stable materials. To achieve this, a novel method of preparing compound *I* was designed.

Pyridine-1-oxide (*IV*), rather than pyridine-2-halides, is a good starting material for preparing (pyridin-2-yl)aryl derivatives avoiding the use of harsh reaction conditions (Abramovitch et al., 1976, 1971; Zhao et al., 2009). In direct arylation reactions, *N*-oxides have been proved applicable in the formation of biaryl molecules as substitutions other than those problematic organometallics (Campeau et al., 2005; Leclerc & Fagnou, 2006). In addition, diazine *N*-oxide substrates are suited for use in site-selective arylation reactions; this reactivity can be performed both divergently and sequentially (Campeau et al., 2008a). A recent study also revealed that the *N*-oxide group changes the reactivity profile of the weak azole bias for arylation and, meanwhile, resulting in a dramatic increase in reactivity in direct arylation at all positions of the azole ring (Campeau et al., 2008b).

In the present procedure, the arylation product from the *IV* cross-coupling reaction needs reduction to afford the pyridinyl group. The literature confirms that the *N*-oxides can be readily reduced by phosphorous trichloride (Wenkert & Woodward, 1983). Along with the catalysed pyridine *N*-oxide arylation method, the reduction technique can also assist in developing a facile route for preparing GDC-0449.

In addition, direct carbon–hydrogen functionalisation reactions catalysed by palladium can be an efficient way of preparing carbon–oxygen, carbon–halogen, carbon–nitrogen, carbon–sulphur and carbon–carbon bonds (Dick et al., 2004; Kalyani et al.,

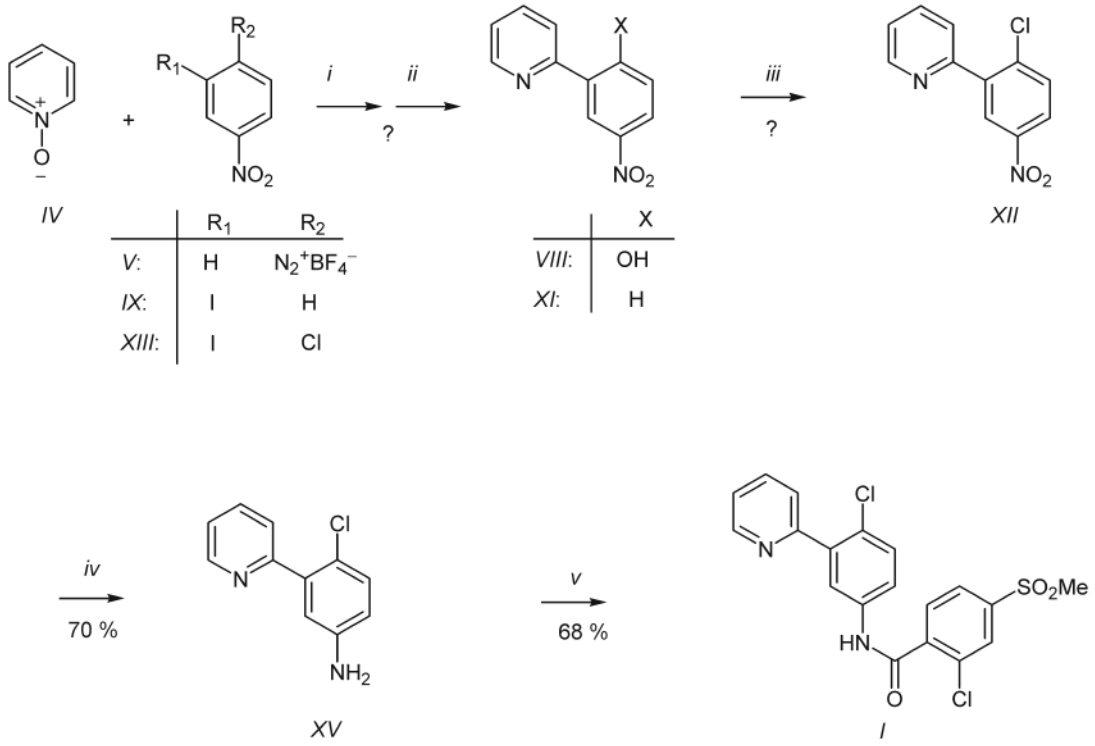

Fig. 1. Proposed new route for synthesis of *I* using *IV* as starting material; *iv*) Fe, acetic acid (100 %), 80 °C, 30 min; *v*) 2-chloro-4-(methylsulphonyl)benzoyl chloride, THF, 0 °C → a.t., 4 h.

2005; Lyons & Sanford, 2010). In particular, a selective and convenient procedure for halogenation on the pyridine-coupled aromatic ring is feasible, as revealed in the work for successfully developing the chelate-directed chlorination, bromination and iodination of arenes using *N*-halosuccinimides as terminal oxidants mediated by palladium catalysis (Hull et al., 2006; Kalyani et al., 2006a, 2006b).

Hence, rather than a pyridine-2-yl derivative, *IV* may serve as a better starting material for the synthesis of compound *I*. On this assumption, a facile synthetic route was designed as illustrated in Fig. 1.

Experimental

General

Detailed procedures are described subsequently. All the reagents including analytical-grade solvents were purchased from commercial sources (Sigma–Aldrich, USA; Aladdin, China or Sinopharm Chemical Reagent, China) and used without further purification. Melting points are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker (Germany) ACF-300/500 MHz spectrometer. Chemical shifts are reported relative to tetramethylsilane (TMS) and are given in δ. Mass spectra (MS) were obtained from Finnigan (USA) MAT-95 Spectrometry Services. The synthesised compounds were obtained as detailed below. Silica gel in the size of 48–75 μm that used for flash chromatography was purchased from Branch of Qingdao Haiyang Chemical (China)

1-(4-nitrophenoxy)pyridinium fluoroborate (VI)

4-nitrobenzenediazonium tetrafluoroborate (*V*; 4.74 g, 0.02 mol) was added drop-wise to 80 mL of acetonitrile solution of *IV* (2.85 g, 0.03 mol) at 0–5 ℃ for 1 h under vigorous stirring, which was maintained at ambient temperature for 24 h. The solvent was evaporated under a reduced pressure to obtain a crude product, which was then recrystallised from methanol to afford *VI* (4.24 g, 70 %).

4-nitro-2-(pyridin-2-yl)phenol (VIII)

VI (5.00 g, 0.016 mol) and potassium phenoxide (2.64 g, 0.020 mol) in 50 mL of acetonitrile solution was heated to reflux for 1.5 h. After cooling to ambient temperature, the solvent was evaporated under reduced pressure. The residue was treated with 50 mL of 2 N HCl followed by extraction three times with 100 mL of ethyl acetate. The organic phase was dried using magnesium sulphate for 12 h then evaporated to afford *VIII* (2.23 g, 65 %).

2-(3-nitrophenyl)pyridine 1-oxide (X)

IV (3.0 g, 0.032 mol) and 1-iodo-3-nitrobenzene (*IX*; 2.0 g, 0.008 mol) were mixed with potassium carbonate (2.2 g, 0.016 mol), palladium acetate (0.090 g, 0.0004 mol) and tri-*tert*-butylphosphine tetrafluoroborate (0.35 g, 0.001 mol) in 40 mL of toluene solution and heated to reflux under nitrogen protection for 48 h. After cooling to ambient temperature, the solution was poured into 100 mL of ethyl acetate and the precipitate was filtered. The filtrate was evaporated under reduced pressure and the crude product was purified by silica gel flash chromatography to afford *X* as a yellow solid (0.73 g, 43 %).

2-(3-nitrophenyl)pyridine (XI)

X (0.65 g, 0.003 mol) and phosphorus trichloride (5 mL, 0.057 mol) were added to 30 mL of chloroform. The mixture was heated to reflux for 12 h. After cooling to ambient temperature, the solution was added to 100 mL of water of 0–5 ℃ under vigorous stirring. The aqueous phase was extracted 2 times with 50 mL of chloroform. The combined organic phase was dried using magnesium sulphate for 12 h, and evaporated under reduced pressure to yield *XI* as a white solid (0.52 g, 87 %).

2-(2-chloro-5-nitrophenyl)pyridine (XII)

XI (0.50 g, 0.003 mol), *N*-chlorosuccinimide (NCS; 0.35 g, 0.003 mol) and palladium acetate (0.028 g, 0.13 mmol) were added to 20 mL of acetic acid. The solution was heated to 100 ℃ for 12 h under nitrogen protection. After cooling to ambient temperature, the mixture was added to 80 mL of cold water of 0–5 ℃ under stirring, and extracted 3 times with 40 mL of ethyl acetate followed by evaporation. This produced a crude product which was further purified by silica gel flash chromatography, resulting in *XII* as a white solid (0.42 g, 72 %).

4-chloro-3-(pyridin-2-yl)aniline (XV)

XII (0.3 g, 1.3 mmol) was added to 10 mL of acetic acid. The solution was heated to 80 ℃ under stirring, and ferrous powder (0.6 g, 0.011 mol) was added under a continuous stirring for 0.5 h. After cooling to ambient temperature, the solution was added into 50 mL of water of 0–5 ℃ and subjected to extraction with 40 mL of dichloromethane 3 times and evaporation. This generated a crude product, which was further purified by column chromatography on silica gel, resulting in *XV* (0.18 g, 68 %).

Table 1. Spectral data of prepared compounds

Compound	Spectral data
VI	^{1}H NMR (DMSO-d$_6$, 500 MHz), δ: 9.76 (d, 2H), 9.14 (t, 1H), 8.42 (d, 2H), 8.33 (d, 2H), 7.59 (d, 2H)
VIII	^{1}H NMR (DMSO-d$_6$, 500 MHz), δ: 15.38 (s, 1H), 8.88 (s, 1H), 8.70 (d, J = 3.7 Hz, 1H), 8.40 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 8.8 Hz, 1H), 8.09 (t, 1H), 7.56 (t, 1H), 7.12 (d, J = 9.0 Hz, 1H)
X	^{1}H NMR (DMSO-d$_6$, 500 MHz), δ: 8.79 (s, 1H), 8.40 (m, 1H), 8.32 (m, 1H), 8.25 (m, 1H), 7.79 (m, 2H), 7.48 (m, 2H). MS, m/z: 217.1 $[M + 1]^+$
XI	^{1}H NMR (CDCl$_3$, 300 MHz), δ: 8.87 (s, 1H), 8.76 (d, J = 4.7 Hz, 1H), 8.42 (d, J = 7.7 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 7.86 (m, 2H), 7.67 (t, 1H), 7.37 (q, 1H).
XII	^{1}H NMR (CDCl$_3$, 500 MHz), δ: 8.78 (d, J = 4.2 Hz, 1H), 8.52 (d, J = 2.8 Hz, 1H), 8.20 (q, 1H), 7.86 (m, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.40 (m, 1H)
XV	^{1}H NMR (DMSO-d$_6$, 500 MHz), δ: 8.64 (m, 1H), 8.85 (m, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.37 (m, 1H), 7.14 (d, J = 8.6 Hz, 1H), 6.61 (q, 1H), 5.32 (s, 2H)
I	IR, $\tilde{\nu}$/cm^{-1}: 1317 (O═S), 1566 (C═N), 1607 (Ph), 1691 (C═O), 3304 (NH) ^{1}H NMR (DMSO-d$_6$, 500 MHz), δ: 10.90 (s, 1H), 8.70 (d, J = 4.4 Hz, 1H), 8.12 (d, J = 1.6 Hz, 1H), 8.01 (q, 2H), 7.92 (m, 2H), 7.74 (q, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.45 (m, 1H), 3.34 (s, 3H) MS-TOF, m/z: 419.1 $[M - 1]^+$, 421.1 $[M + 1]^+$

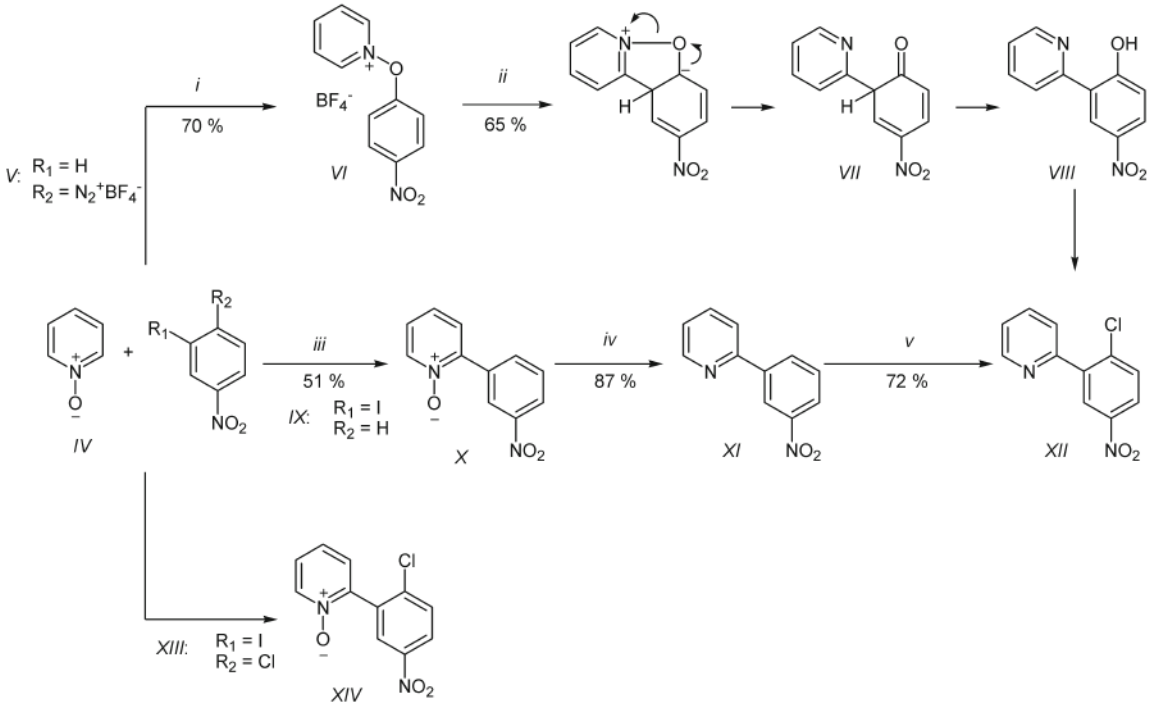

Fig. 2. The determining step in the route was synthesis of intermediate *XII*, *i*) acetonitrile, 0 °C → a.t.; *ii*) PhOK, acetonitrile, 81 °C; *iii*) Pd(AcO)$_2$, P(*t*-Bu)$_3$HBF$_4$, K$_2$CO$_3$, PhMe, 110 °C; *iv*) PCl$_3$, CHCl$_3$, 61 °C; *v*) NCS, Pd(AcO)$_2$, AcOH, 100 °C.

2-chloro-N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulphonyl)benzamide (I)

XV (0.15 g, 0.74 mol) in tetrahydrofuran (THF) was added drop-wise to 2-chloro-4-(methylsulphonyl) benzoyl chloride (0.22 g, 0.85 mol) in THF of 0–5 °C. To this mixture, 0.5 mL of triethylamine was added, stirred at ambient temperature for 4 h and poured into 150 mL of water of 0–5 °C. The crude extract was obtained by extraction with 40 mL of ethyl acetate 3 times and evaporation. After purification by column chromatography on silica gel, the final *I* (0.21 g, 68 %; m.p. = 218 °C) was generated. The spectral data for these compounds are listed in Table 1.

Results and discussion

The data indicate a successful synthesis of *I* using *IV* as the starting material (Fig. 2). The determining step in the route is the procedure for synthesising *XII*,

Table 2. Investigation into synthesis of intermediate *XII*

Compound	R_1	R_2	X	Mole ratio[a]	Yield[b]/%		
					i[c]	*ii*[c]	*iii*[c]
V	H	$N_2^+BF_4^-$	OH	1 : 1	70[d]	65[e]	nr
XIII	I	Cl	Cl	1 : 4	n.r.	–	–
IX	I	H	H	1 : 4	43[f]	87[g]	72[h]

a) Calculated as compound *V*, *XIII* or *IX* compared to compound *IV*; *b*) yield of isolated product; *c*) for synthetic route see Fig. 3; *d*) acetonitrile, 0 °C → a.t., 24 h; *e*) PhOK, acetonitrile, 81 °C, 1 h; *f*) $Pd(AcO)_2$, $P(t\text{-}Bu)_3HBF_4$, K_2CO_3, PhMe, 110 °C, 36 h; *g*) PCl_3, $CHCl_3$, 61 °C, 12 h; *h*) NCS, $Pd(AcO)_2$, AcOH, 100 °C, 12 h; n.r. – no reaction.

an important intermediate.

The route began with the reaction between *IV* and compound *V* being tried first. In the acetonitrile solution, *IV* reacted with *V* to afford compound *VI* (yield of 70 %). After heating in the presence of potassium phenolate, *VI* underwent a rearrangement reaction and was transformed into 4-nitro-6-(pyridin-2-yl)cyclohexa-2,4-dienone (*VII*; yield of 65 %), a tautomer of compound *VIII*. However, further attempts to obtain compound *XII* from *VIII* through reactions with halogenated reagents including phosphorus trichloride, phosphorus pentachloride and thionyl chloride or phosphorus oxychloride were not successful. This was probably due to the negative effect of the tautomerism of *VIII*, or the obstruction of pyridin-2-yl group in the *ortho*-position, on the chlorination of the hydroxyl group.

A synthetic route starting with *IV* and 1-chloro-2-iodo-4-nitrobenzene (*XIII*) was also investigated. Using palladium as the catalyst, however, failed to give rise to 2-(2-chloro-5-nitrophenyl)pyridine 1-oxide (*XIV*), indicating that the cross-coupling ability might have been blocked when chlorine was introduced into the 5-position of *IX*. Accordingly, procedures starting with compound *IV* in combination with *V* or *XIII* were incapable of synthesising the final compound.

In another attempt to synthesise *XII*, the interaction of compound *IX* with *IV* was examined as the starting material and this route finally yielded a favourable result. Intermediate *XII* was successfully synthesised from *IV* by *ortho*-arylation with *IX* to generate *XI* and subsequent reduction by phosphorus trichloride to generate the intermediate *X* of which the nitro-group was further halogenated at the para position (Table 2). Specifically, the cross–coupling reaction between *IV* (4 equivalents) and *IX* (1 equivalent) to produce *X* (yield of 51 %) was catalysed by K_2CO_3 (2 equivalents), $Pd(OAc)_2$ (0.05 equivalents) and $P(t\text{-}Bu)_3HBF_4$ (0.15 equivalents) in a toluene solution at 110 °C for 48 h. The resulting *X* was then treated with phosphorus trichloride in chloroform at 61 °C to generate intermediate *XI* (yield of 87 %). The halogenation procedure entailed the reactants being heated at 100 °C in acetic acid in the presence of NCS (1 equivalent) and $Pd(OAc)_2$ (0.05 equivalents). This generated intermediate *XII* (yield of 72 %) (Fig. 2). Nitro-reduction of *XII* by ferrous powder in acetic acid produced aniline *XV* (yield of 70 %), amidation of which with 2-chloro-4-(methylsulphonyl)benzoyl chloride in THF resulted in final product *I* (yield of 68 %).

Starting material *IV* is bench-stable and readily prepared from pyridine reacting with H_2O_2 in acetic acid at 80 °C; *IX* can be easily prepared via the Sandmeyer reaction with 3-nitryl-aniline. Compounds *IV* and *IX* are commercially available and inexpensive. The cross-coupling reaction between the reactants was carried out in toluene, a common solvent, and generated by conventional heating and stirring operations. Deoxidation, chlorination, nitro group reduction and amidation reaction were also routine readily controllabe processes.

Conclusions

In summary, a facile route for the synthesis of antineoplastic drug GDC-0449 involving starting materials that are commercially available and stable is reported, using reactions that are readily conducted under mild conditions. By contrast, the traditional method of synthesising *I*, in which the Negishi and Suzuki cross–coupling reactions are employed, may encounter a constriction in large-scale production, since the pyridine-2 halide cannot readily react with the bromobenzene unless activated, but activation requires complex reaction conditions as well as delicate handling and renders the intermediate instable. The proposed route has a clear advantage over the Negishi and Suzuki reactions as the cross-coupling in this route can occur directly between *IV* and *IX*, which would keep to the minimum the purification of intermediates, which are difficult to handle and may not be so readily adapted to large-scale production. The proposed method of preparing a halogenated 2-phenylpyridine derivative such as *XII*, which is more easily generated using the present route than by using the zinc or boracic activating reactions, may also be of use in the synthesis of similar pharmacological compounds. In addition, it is worth noting that the other two routes that started with *IV* and *V* or *IV* and *XIII* did not succeed in obtaining *I*. Compound *VIII* is structurally comparable to intermediate *XII* but it is apparently difficult to find a substitute for its pheno-

lic hydroxyl group. Compound *XIII* cannot be coupled with *IV* under the same conditions in which compound *IX* reacted with *IV* suggesting that 5-position- chlorine may curtail the activity of the adjacent iodine position on nitrobenzene. Supplementary studies using improved synthetic techniques may be required to investigate these limitations.

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