Regioselective, One-Pot Syntheses of Symmetrically and Unsymmetrically Halogenated 2',6'-Bispyrazolylpyridines

Supratim Basak, Pramiti Hui, Rajadurai Chandrasekar

School of Chemistry, University of Hyderabad, Central University Post, Gachi Bowli, Hyderabad 500046, India
Fax +91(40)23134824; E-mail: rscsc@uohyd.ernet.in; E-mail: chandrasekar100@yahoo.com

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Abstract: A series of regio-selectively 3', 4-, 4', 4''-, and 5'-halogenated heterocyclic 2',6'-bispyrazolylpyridine derivatives was prepared by a direct halogenation reaction in a simple, one-pot synthesis in good to excellent yield (in gram scale). This methodology yielded several symmetrically and asymmetrically substituted mono-, di-, tri-, and tetra-halo (bromo and iodo) substituted 2',6'-bispyrazolylpyridine cores, which may serve as potential intermediates for several metal-catalyzed coupling reactions.

Key words: heterocycles, halogenation, halogenated 2,6-bis(pyrazol-1-yl)pyridine, N-ligands, pyridines

In the area of heterocyclic chemistry, the 2',6'-bispyrazolylpyridine (bpp)1–3 unit is an important structural alternative to the 2,2',6',2''-terpyridine (terpy)4–12 system due to its three readily available nitrogen-chelating sites (Figure 1). These tridentate heterocyclic ligand derivatives have been attracting considerable attention as synthetic building blocks in supramolecular chemistry,12 photochemistry,12–14 biology,15 spin cross-over compounds,16–20 and polymers.21–23 Since the first synthesis of the bpp core by Goldsby et al., this further functionalization of its pyridine and pyrazole carbons remains a huge challenge due to the lack of availability of diverse halogroups in the entire unit. Interestingly, the last 15 years have witnessed a remarkable development in functional group transformation reactions through aryl–halide C–X (X = halo) bond activation e.g., Suzuki,24 Sonogashira,25 Stille26 and Buchwald27 coupling methods. Unfortunately, due to the lack of diverse X atoms in the bpp unit, its chemistry has been severely limited and has not developed as much as its counterpart ligand terpy.23 Hence, there is an apparent demand for different regioselective halogenated bpp cores due to their importance as potential synthetic intermediates in many transition-metal catalyzed cross-coupling reactions.24–27

To our surprise, with the exception of two articles, we were unable to find reports describing the synthesis of halogenated (on pyridine and pyrazole carbons) bpp-derivatives. The first literature report describes the pyrazole-centered dihalogenation reaction performed on a naked bpp core.28 Secondly, Chandrasekar and Ruben et al. have reported the synthesis of a 4'-iodo-substituted bpp moiety in a six-step reaction from commercially available citraconic acid.16

The 4'-iodo-substitution on the bpp core, paved the way for further synthetic modification of the bpp unit by employing Suzuki and Sonogashira reaction conditions, which resulted in the generation of a series of 4'-functionalized bpp derivatives.16–18 Motivated by this result, in order to extend the utility of the bpp unit, we have conducted several pyrazole, pyridine and pyrazole/pyridine centered halogen exchange reactions on the bpp core. The diverse halogenated products1–14 thus obtained are potential intermediates with which to engineer several tailor-made bpp ligands (e.g., using transition-metal catalyzed reactions) (Scheme 1).

In this article, we present a direct and efficient synthetic strategy through which to achieve regioselective bromination and iodination reactions on the bpp in (i) a single pyrazole ring, (ii) two pyrazole rings, (iii) a single pyrazole and pyridine unit, and (iv) two pyrazole and pyridine units under optimum reaction conditions. Using the ap-
proach mentioned above, many site-selective halogenation approach at the 3′-, 4′-, 4″-, and 5′-positions of the bpp core were effectively carried out under controlled reaction conditions, which resulted in quantitative preparation (in grams) of a series of mono-, di-, tri- and tetra-halogenated (brominated and iodinated) bpp-derivatives 1–14 (Scheme 1).

Our regioselective halogenation approach began with 4′-substituted 2′,6′-bispyrazolylpyridines 17–20. To build these cores, we started our synthesis from the commercially available citrazinic acid as per our previously reported procedure.16 We used compounds 17–20 to synthesize several brominated and iodinated products by the direct exchange of pyridine-H and/or pyrazole-H by halogen (Br or I) atoms in a regioselective manner in a controlled single-pot quantitative preparation (Scheme 2).

The pyrazole and pyrazole/pyridine centered regioselective halogenation is presented in Scheme 2. Generally, Br₂ in acetic acid (BR) was used for bromination, whereas, an I₂/HIO₃ (IR) system was used for iodination; both types of reaction were performed in the presence of catalytic amounts of sulfuric acid. At first, we studied the selectivity of reacting the NH₂-substituted bpp core of 18 with an excess of bromination and iodination reagents in order to generate a tetra-halogenated compound. We anticipated that the two carbons ortho to the NH₂-substituted bpp core of 18 with an excess of bromination and iodination reagents in order to generate a tetra-halogenated compound. We anticipated that the two carbons ortho to the NH₂-substituted bpp core of 18 with an excess of bromination and iodination reagents in order to generate a tetra-halogenated compound. We anticipated that the two carbons ortho to the NH₂-substituted bpp core of 18 with an excess of bromination and iodination reagents in order to generate a tetra-halogenated compound. We anticipated that the two carbons ortho to the NH₂-substituted bpp core of 18 with an excess of bromination and iodination reagents in order to generate a tetra-halogenated compound. We anticipated that the two carbons ortho to the NH₂-substituted bpp core of 18 with an excess of bromination and iodination reagents in order to generate a tetra-halogenated compound. We anticipated that the two carbons ortho to the NH₂-substituted bpp core of 18 with an excess of bromination and iodination reagents in order to generate a tetra-halogenated compound. We anticipated that the two carbons ortho to the NH₂-substituted bpp core of 18 with an excess of bromination and iodination reagents in order to generate a tetra-halogenated compound. We anticipated that the two carbons ortho to the NH₂-substituted bpp core of 18 with an excess of bromination and iodination reagents in order to generate a tetra-halogenated compound.

In order to prepare the symmetrically and asymmetrically halo-substituted bpp core, 19 was used as a starting material since, in this case, an iodo group is already available at the 4′-position. Here, although the iodo-group is an ortho and para-director, it was observed that (i) the C-4 and C-4″ pyrazole carbons are more reactive towards bromination than iodination (iodination requires elevated temperatures) (ii) the deactivating nature of the 4′-ido

**Scheme 2**

\[ \text{ IR } = \text{ I}_2, \text{ HIO}_3, \text{ H}^+ \\
\text{ BR } = \text{ Br}_2, \text{ MeCOOH}, \text{ H}^+ \]

**Yields**

- 1: 99%
- 2: 80%
- 3: 99%
- 4: 85%
- 5: 65%
- 6: >99%
- 7: 55%
- 8: 50%
- 9: >99%
- 10: 75%
- 11: 65%
- 12: 60%
- 13: 60%
- 14: 55%

**Reagents and Conditions**

- 1: NaNO₂, concentrated H₂SO₄, under reflux, to obtain NMR-pure compound with an estimated yield of 99%. Extraction with chloroform gave NMR-pure compound 1 in an excellent gram scale yield (>99%) without any chromatographic purification.
- Bromination at the pyrazole C-4 and C-4″ positions are evident from the absence of a multiplet peak at \( \delta = 6.48 \) ppm in the \( ^1H \) NMR spectrum (which is the characteristic region for these two protons). Our attempts to restrict the halogenation to only the pyridine or pyrazole gave mixture of products, as evidenced by LCMS analysis, where the crude reaction mixture showed the presence of di-brominated \( (m/z = 384) \) and tri-brominated \( (m/z = 462) \) compounds, along with the tetra-brominated product 1 \( (m/z = 542) \), making their separation difficult. Similarly, tetra-iodinated product 3 was also prepared quantitatively on a gram scale (99% yield) by using an excess (6 equiv) of iodinating agent. Furthermore, in order to facilitate the reaction with sterically less crowded meta-di-halo groups, deamination was performed by diazotization of compound 1 and 3 using NaNO₂, in the presence of a few drops of concentrated H₂SO₄, under reflux, to obtain 2 and 4 in 80–85% yield. The appearance of new resonance peaks at \( \delta = 8.49 \) and 8.99 ppm (4′C-H) for compounds 2 and 4, respectively, in the \( ^1H \) NMR spectra confirmed the structure of the deaminated products.
group directs the halo-substitution only to the active pyrazole units and not to the pyridine. For example, the treatment of 19 with two equivalents of Br₂ gave only a pyrazole centered (4- and 4¢-positions) mixed bromo- and iodo-substituted, symmetric bpp unit 5 as a white solid in a decent 65% yield (Scheme 2). Formation of 5 was unambiguously confirmed by LCMS (m/z = 494.75) and ¹H NMR spectroscopy (3 singlets). Furthermore, a symmetric 4-,4¢,4¢¢-triodo-substituted bpp core 6 was also prepared from 19 by using an excess (4 equiv) of iodinating reagent at 130 °C. Regular workup afforded compound 6, in a quantitative >99% yield as colorless crystalline needles (Scheme 2). Surprisingly, in neither case (5 and 6), was halogenation of the pyridine ring 3¢- and 5¢-positions observed.

Motivated by the pyrazole selective iodination reaction of 19, by controlling the amount of iodinating reagent and lowering the temperature, a limited monoiiodination of a single pyrazole ring was attempted. This was performed by controlled slow addition (2 drops/15 min) of slightly less than one equivalent of the iodinating mixture and by keeping the reaction mixture at 70 °C. The reaction was carefully followed by thin layer chromatography (after neutralizing the reaction mixture), to stop the reaction before the formation of diiodinated side-product. After four hours, regular work-up of the crude mixture gave the unsymmetrically C-4 substituted diiido-2,6¢-bispyrazolyl pyridine 7 in 55% yield (Scheme 2). Likewise, compound 8 was synthesized by a restricted mono-bromination (0.5 equiv) of 19 under ice-cold conditions in a quantitative yield (50% from 19) as colorless needles. Taking advantage of the available vacant pyrazole C-4 position in 8, via the iodination reaction, an attractive mixed 4-bromo-4¢,4¢¢-diiodo-substituted asymmetric bpp core 9 was synthesized quantitatively (99%).

In order to circumvent the tetra-halogenation reaction observed in 18, we synthesized ester derivatives of bpp 20 from 17 (Scheme 3). Further crystallization of 20 in chloroform by slow evaporation technique gave colorless needle-like crystals in a quantitative yield (>99%). We anticipated that compound 20 will direct the halogenation only to the pyrazole ring and will facilitate the generation of symmetric and asymmetric mono- and di-halo-substituted bpp. As per our expectation, by optimizing the temperature, amount of halogen and addition rate, a series of 4-bromo (10), 4¢,4¢¢-dibromo (11), 4-iodo (12), 4¢,4¢¢-diiodo (13) and a mixed asymmetric 4-iodo-4¢-bromo (14) substituted ester derivative of bpp were successfully synthesized from 20 in a regiospecific manner. Compound 10 was obtained selectively in an acceptable 25% yield using one equivalent of brominating agent under ice-cold conditions. Here, 11% of 11 was also obtained as a side-product. While increasing the reaction temperature to room temperature and using two equivalents of Br₂ gave 12% of 10 and 88% of 11. Further increase in the temperature up to 100 °C with the use of two equivalents of Br₂ afforded the white compound 11 in a quantitative yield (>99%). A mono-iodinated bpp derivative 12 was successfully synthesized in a modest yield of 42% (as colorless needles) at 70 °C using one equivalent of iodinating reagent. At 130 °C, increasing the amount of iodinating reagent up to two equivalents gave compound 13 in quantitative yield (>99%). Analogous to the synthesis of 9, by treating 12 with an excess of Br₂ at 80 °C, an asymmetrically substituted mixed bromo and iodo-substituted bpp core 14 was synthesized effectively in a quantitative yield (>99%).

It is essential to mention here that in all our halogenation reactions the selective formation of mono and dihalo bpp was achieved by carefully monitoring the reaction by thin layer chromatography (after neutralizing the reaction mixture). The mono-halo compounds always exhibit higher Rf values than the starting material and the dihalo-compounds show the highest Rf values. Most of the iodo-compounds could be readily crystallized in chloroform.

In summary, we have developed, for the first time, a straightforward route to the facile synthesis of a series of bromo and iodo-substituted tridentate bpp derivatives 1–14 in a regioselective manner. The regioselectivity was effected either on a pyrazole unit alone or on both pyrazole and pyridine units together. In the pyridine unit, selective

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Scheme 3
halogenation reactions at the 3¢, 5¢- or 4¢-positions were performed by varying substituents at the 4¢-position. The two pyrazole units were also activated at the 4- and/or 4¢-positions selectively, which resulted in the generation of mono or dihalo-substituted bpp cores. For example, two novel tetrabromo- and tetraiodo-substituted bpp units (2 and 4) were synthesized. A mixed dibromo- and iodo-bearing bpp (5) and a symmetrically substituted triodo-bispyrazolylpyridine 6 were also fruitfully synthesized. Compound 5 may facilitate selective metal-catalyzed functional group transformation at either the 4¢-iodo position or the 4,4¢-dibromo positions due to their different reactivities. Interestingly, we were able to prepare an unsymmetrically substituted diiodinated product 7, where the pyridine and pyrazole units each bear an iodo-functionality. Synthetically challenging mixed bromo- and iodo-substituted bpp cores 9 and 14 were also prepared. Compounds 1–14 are promising intermediates for many site-selective organic functional group transformations via transition-metal-catalyzed cross-coupling reactions. We hope that these diverse C–X bonds appended to the bpp may broadly open up the chemistry of the 2¢,6¢-bispyrazolylpyridine unit. Further functional group transformations of 1–14 are in progress.

1H and 13C NMR spectroscopic data were recorded on a Bruker DPX 400 spectrometer with solvent proton or carbon as internal standards [CDCl3; δ = 7.26 (1H) and 77.0 (13C) ppm; DMSO-d6; δ = 2.50 (1H) and 40.0 (13C) ppm]. Deuterated solvents CDCl3 and DMSO-d6 were obtained from Aldrich and Merck respectively. Column chromatography was performed using Merck silica gel (particle size 100–200 mesh). LC mass spectrometry was performed on Shimadzu LCMS-2010A mass spectrometer. IR spectra were recorded on a JASCO FT/IR-5300 instrument. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light. Pyrazole, citrazinic acid, and HIO3 were obtained from Aldrich. Potassium metals, TFA, Br2, and diglyme were purchased from spectrochem Pvt. LTD, Mumbai. EtOH and H2SO4 were obtained from Merck. Ac2O and NaNO2 were obtained from Qualigens Fine Chemicals, Mumbai. AcOH, Na2S2O3, benzene, CH2Cl2, hexane, petroleum ether, CHCl3, and MeOH were obtained from Finar Chemicals Limited, Ahmedabad, India. All solvent were distilled prior to use. Oxaly chloride (C2O2Cl2), I2, LiOH, TMACl, POCl3, anhydrous MgSO4, K2CO3, and KI were obtained from Avra Synthesis, Hyderabad, India.

Compounds 18–21 were synthesized as described in a previously reported procedure.16

2¢,6¢-Bis(4¢,4¢-bromopyrazolyl-1,1¢-yl)-4¢-amino-3¢,5¢-dibromopyridine (1); Typical Bromination Procedure 4¢-Amino-2¢,6¢-bispyrazolyl pyridine (18; 500 mg, 2.21 mmol) was charged in a round-bottomed flask with AcOH (5 mL) andaq H2SO4 (10%, 1.5 mL). The reaction flask was heated at 70 ºC. Separately, a solution of Br2 (density = 3.11 g/mL, 0.68 mL, 13.26 mmol) dissolved in AcOH (10 mL) was slowly added into the flask dropwise. When half of this solution (5 mL) was added, a dense orange-yellowish solution was formed. Then the Br2 solution was added quicker and the temperature rose to 80 ºC. The mixture was allowed to stir for 2 h. After cooling to r.t. the mixture was quenched withaq NaHCO3 and then Na2CO3 solutions until pH ~8 was reached. Just enough Na2SO3 was then added to destroy any excess bromine. The white precipitate was extracted with CHCl3 (3 × 100 mL) and the organic extract was washed with brine (100 mL) and dried over anhydrous MgSO4. The solvent was evaporated under reduced pressure to obtain product 1 without any chromatographic purification.

Yield: 1.2 g (99%); white solid.

IR (KBr): 3466, 3366, 3111, 1744, 1605, 1561, 1539, 1470, 1387, 1348, 1167, 1061, 951, 783, 743, 631, 594 cm–1.

1H NMR (400 MHz, CDCl3); δ = 8.07 (s, 2 H, pyrazole), 7.73 (s, 2 H, pyrazole), 5.85 (s, 2 H, NH2).

13C NMR (100 MHz, CDCl3); δ = 153.5, 146.2, 142.1, 130.5, 96.5, 96.1.

LCMS: m/z: calculated 541.83; found: 541.82.

Anal. Calcd for C11H5Br4N5: C, 25.08; H, 0.96; N, 13.29. Found: C, 24.48; H, 1.18; N, 15.65.

2¢,6¢-Bis(4¢,4¢-bromopyrazolyl-1,1¢-yl)-3¢,5¢-dibromopyridine (2) To a solution of 1 (100 mg, 0.1845 mmol) in EtOH (5 mL), benzene (1 mL), and concd H2SO4 (0.5 mL), was added NaNO2 (0.5 g) and the mixture was heated under reflux for 4 h. After cooling to r.t., the reaction mixture was quenched withaq NaHCO3 and Na2CO3 solutions until pH ~8 was reached. The white precipitate that formed was extracted with CHCl3 (3 × 100 mL) and the organic extract was dried over MgSO4 and concentrated under reduced pressure. Compound 2 was separated from 1 (Rf = 0.61) by column chromatography (silica gel; CH2Cl2; Rf = 0.90).

Yield: 0.72g (80%); white solid.

IR (KBr): 3414, 3353, 3245, 1740, 1663, 1624, 1576, 1520, 1485, 1404, 1383, 1306, 1231, 1016, 1111, 1049, 963, 920, 829, 764, 633, 421 cm–1.

1H NMR (400 MHz, CDCl3); δ = 8.49 (s, 1 H, pyridine), 8.18 (s, 2 H, pyrazole), 7.78 (s, 2 H, pyrazole).

13C NMR (100 MHz, CDCl3); δ = 151.5, 145.6, 142.9, 130.3, 109.9, 96.9.

LCMS: m/z: calculated 526.81; found: 526.8.

Anal. Calcd for C12H4Br4N5O: C, 25.08; H, 0.96; N, 13.29. Found: C, 25.18; H, 1.06; N, 13.45.

2¢,6¢-Bis(4¢,4¢-iodopyrazolyl-1,1¢-yl)-4¢-amino-3¢,5¢-diiodopyridine (3); Typical Iodination Procedure 4¢-Amino-2¢,6¢-bispyrazolyl pyridine (18; 100 mg, 0.44 mmol) was charged in a round-bottomed flask containing AcOH (5 mL) andaq H2SO4 (30%, 1.0 mL). The flask was heated at 70 ºC. A deep-violet aqueous solution (10 mL) containing HIO3 (0.3 g, 1.77 mmol), I2 (0.91 g, 3.54 mmol) and two drops of concentrated H2SO4 was prepared. This solution was added dropwise to the solution of 18 (during the addition the temperature of the mixture rose to 130 ºC). The reaction mixture was stirred 1 d under an argon atmosphere. After cooling to r.t., just enoughaq Na2SO3 was added to destroy any excess iodine. The mixture was quenched withaq sat. NaHCO3, and then with aqueous Na2CO3 solution until pH ~8 was reached. The white precipitate that formed was extracted with CHCl3 (3 × 50mL), dried over MgSO4, and evaporated under reduced pressure. The crude solid mixture was washed with cold CHCl3 to remove yellow colored impurities and to afford product 3 in pure form.

Yield: 0.32 g (>99%); white powder.


1H NMR (400 MHz, CDCl3); δ = 8.02 (s, 2 H, pyrazole), 7.76 (s, 2 H, pyrazole), 6.03 (s, 2 H, NH2).

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Anal. Calcd for C$_{11}$H$_6$Br$_2$IN$_5$: C, 26.70; H, 1.22; N, 14.15. Found: C, 18.05; H, 0.88; N, 11.68.

LCMS: $m/z$ calcld: 729.82; found: 729.0.

Anal. Calcd for C$_{11}$H$_7$I$_2$N$_5$: C, 28.53; H, 1.52; N, 15.13. Found: C, 28.65; H, 1.48; N, 15.31.

LCMS: $m/z$ calcld: 462.45; found: 462.45.

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Regioselective Halogenation of 2',6'-Bispyrazolylpyridines

**2'-4-(Bromopyrazol-1-yl)-6'-4-iodopyrazol-1'-yl)-4'-iodopyridine (9)**

Prepared according to the general iodination protocol using 8 (35 mg, 0.084 mmol), AcOH (5 mL) and aq H₂SO₄ (30%, 1.0 mL). Separately, a deep-violet aqueous solution (10 mL) containing HIO₃ (0.155 g, 0.015 mmol), I₂ (0.043 g, 0.168 mmol) and two drops of concd H₂SO₄, was slowly added into the solution of 8 (280 mg) in aq H₂SO₄ (10 mL) at 70 °C until the spot of 8 disappeared in TLC (Rf = 0.27 (CH₂Cl₂–hexane, 3:2)). The CHCl₃ extract was evaporated under reduced pressure to isolate compound 9.

Yield: 45 mg (>99%); white solid.

**Ethyl 2',6'-Bis(pyrazol-1-yl)-isonicotinate (20)**

2',6'-Dipyrrollylsicinonic acid (17; 150 mg, 0.59 mmol) was dissolved in EtOH (100 mL) and concd H₂SO₄ (2 mL). The mixture was heated to reflux for 4 h, then the excess EtOH was removed under vacuum to give an oily liquid. To this, H₂O (100 mL) was added (to remove H₂SO₄) and the solution was extracted with CHCl₃ (3 × 50 mL). The organic fraction was washed with brine, dried over MgSO₄ and concentrated under reduced pressure to yield a colorless oil that hardened upon standing.

Yield: 0.15 g (95%); white solid.

**Ethyl 2',6'-Bis(4,4'-bromopyrazol-1,1'-yl)isonicotinate (11)**

Prepared according to the general bromination protocol using 20 (150 mg, 0.53 mmol), AcOH (5 mL) and aq H₂SO₄ (10%, 1.0 mL), and a deep-violet aqueous solution (10 mL) containing HIO₃ (0.04 g, 0.21 mmol), I₂ (0.11 g, 0.42 mmol) and two drops of concentrated H₂SO₄. The crude compound was isolated by column chromatography on silica gel (EtOAc–PE, 1:4; Rf = 0.43) to give 11.  As a side product, 4,4'-diiodinated compound 13 was obtained by collecting the first fraction (Rf = 0.58; 79 mg, 28% yield). Both compounds were readily crystallized in CHCl₃.

Yield: 90 mg (42%); colorless needles.

**Ethyl 2',6'-Bis(4,4'-iodopyrazol-1-yl)-6'-pyrazol-1'-yl)isonicotinate (12)**

Prepared according to the general iodination protocol using 20 (150 mg, 0.53 mmol), AcOH (5 mL) and aq H₂SO₄ (30%, 1.0 mL), and a deep-violet aqueous solution (10 mL) containing HIO₃ (0.04 g, 0.21 mmol), I₂ (0.11 g, 0.42 mmol) and two drops of concentrated H₂SO₄. The crude compound was isolated by column chromatography on silica gel (EtOAc–PE, 1:4; Rf = 0.43) to give 12. As a side product, 4,4'-diiodinated compound 13 was obtained by collecting the first fraction (Rf = 0.58; 79 mg, 28% yield). Both compounds were readily crystallized in CHCl₃.

Yield: 280 mg (>99%); colorless needles.

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1H NMR (400 MHz, CDCl3): δ = 8.58 (s, 2 H), 8.34 (s, 2 H), 7.77 (s, 2 H), 4.43–4.49 (q, J = 7.2 Hz, 2 H, CH2), 1.42–1.46 (t, 3 H, J = 7.2 Hz, 3 H).

13C NMR (100 MHz, CDCl3): δ = 163.6, 149.8, 147.6, 145.0, 144.0, 131.7, 127.3, 109.3, 62.4, 60.9, 14.3.

LCMS: m/z calcd 537.90; found: 537.00.


Ethyl 2’-(4-Bromopyrazol-1-yl)-6’-(4’-iodopyrazol-1’-yl)isonicotinate (14)
Prepared according to the general bromination protocol using 12 (100 mg, 0.24 mmol), AcOH (5 mL) and aq H2SO4 (10%, 1.0 mL), and a solution of Br2 (density = 3.11 g/mL, 0.058 mL, 1.12 mmol) dissolved in AcOH (10 mL). The obtained white solid product 14 was readily crystallized from CHCl3.

Yield: 0.1 g (99%); transparent needles.

IR (KBr): 3098, 2917, 1771, 1734, 1618, 1574, 1456, 1379, 1238, 1179, 1044, 965, 768, 646, 596 cm–1.

LCMS: m/z calcd 488.08; found: 488.00.


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References
(9) Fahlahpour, R.-A. Synthesis 2003, 155.