Isoxazoles via Cycloaddition of Terminal Alkynes and Nitrile Oxides (from Oximes)

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Abstract: Conditions for the production of isoxazoles in a one-pot process are presented. Nitrile N-oxides are generated by the oxidation (using hypervalent iodine reagents) of oximes that subsequently undergo 1,3-dipolar cycloaddition with terminal alkynes affording the isoxazoles. From a collection of three terminal alkynes and four aldehydic oximes, 11 distinct isoxazoles were prepared. The effectiveness of various oxidants and solvent systems is discussed, as are side reactions.

Keywords: 3,5-diarylisoxazoles, 1,3-dipolar cycloaddition, nitrile N-oxide

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Introduction:

An important feature in many molecules of potential biological significance is the isoxazole ring.[1] These five-membered unsaturated heterocyclic compounds show numerous applications in pharmaceuticals, agrochemistry, and industry. Isoxazoles and their 1,2-dihydro derivates (isoxazolines) have been used as antitumor substances, antibiotics, and prostanoids, among other pharmaceutical applications.[2,3]

As befits an important structural group, there are many approaches to the formation of isoxazole rings. These include, among others, reaction of 1,3-dicarbonyl compounds with hydroxylamine,[4] and cyclization reactions of ynones.[5] Our particular interest was in the 1,3-dipolar cycloaddition reactions of alkynes with nitrile N-oxides, since components seemed readily available, regioselectivity could be established and the reaction was amenable to establishing structural diversity.

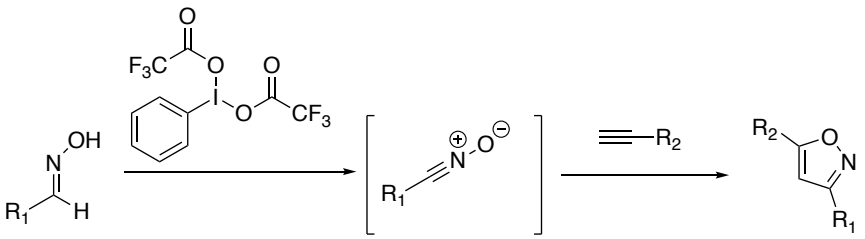
The reaction between oximes and alkynes is direct and has been successfully performed through copper(I)-catalyzed cycloaddition[6], ruthenium(III)-catalyzed cycloaddition[7], and various oxidizing reagents such as [bis(trifluoroacetoxy) iodo]benzene[8] (PIFA) and iodobenzene diacetate (DIB) catalyzed by TFA.[9] Hypervalent iodine reagents in the cycloaddition is an attractive approach because it avoids the use of toxic transition metals as catalysts. Past research

shows that the use of PIFA resulted in much higher isoxazole yields over the method reported using DIB.[8]

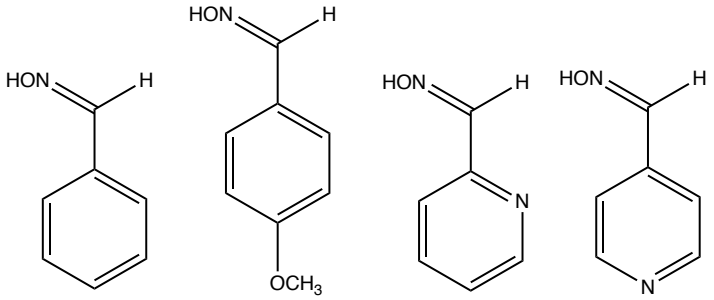
Experimental:

The general scheme for the cycloaddition reactions is shown in Scheme 1.

Scheme 1. Cycloaddition of nitrile oxides to alkynes to form isoxazoles

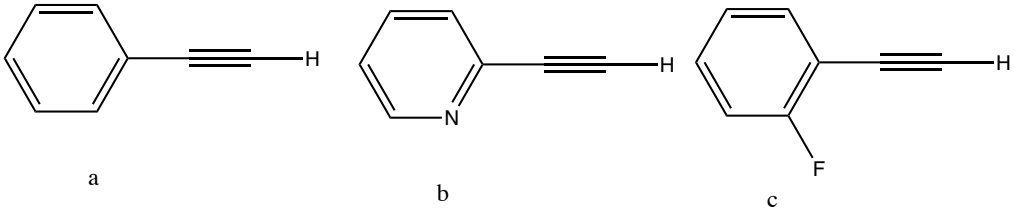


The starting materials for the cycloadditions were the known oximes from benzaldehyde, 4-methoxybenzaldehyde, 2-formylpyridine and 4-formylpyridine numbered 1-4 respectively below.



1 2 3 4

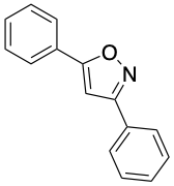
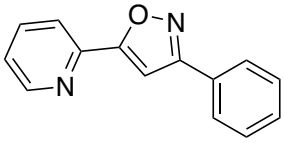
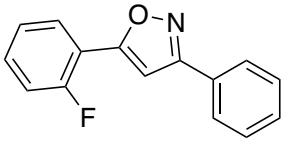
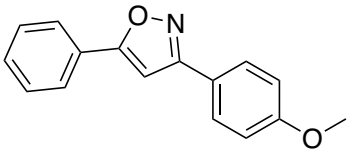
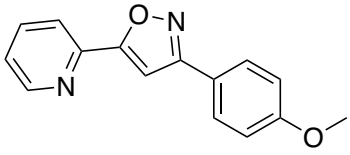
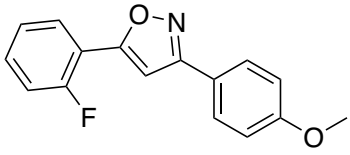
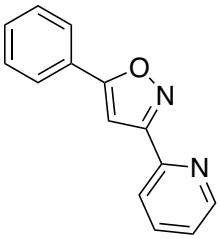
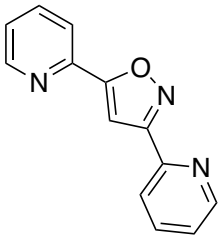
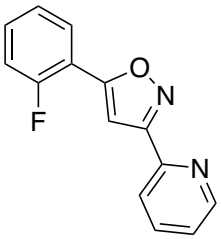
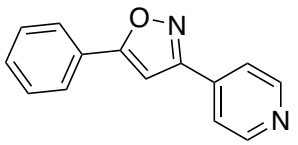
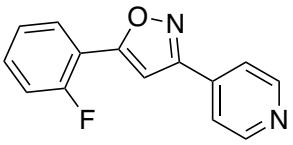
The alkynes used in this study were the commercially available phenylacetylene (a), 2-ethynylpyridine (b) and 2-fluorophenyl acetylene (c).



a b c

The array of compounds prepared are denoted in the following Table 1.

Table 1. Compounds prepared in this study (references for known compounds)

	a	b	c
1	 ref 10	 Ref 8	 Ref 11
2	 Ref 11	 Ref 12	
3	 Ref 13	 Ref 15	
4	 Ref 14	Not Characterized	

Method 1 Procedure for 3,5-Disubstituted Isoxazole Synthesis

To a solution of alkyne (1.2 equiv) and oxime (1 equiv) in 5 mL MeOH/H_2O (5:1), [bis(trifluoroacetoxy)]iodobenzene (1.5 equiv) was added. After being stirred for 2 days at room temperature, 5 mL of 10% sodium thiosulfate solution was added and the mixture was extracted with DCM. The organic layer was dried with $MgSO_4$, filtered, and the solvent evaporated. The products were dissolved in DCM and columned by flash chromatography. Fractions were dried and recrystallized from ether.

Method 2 Procedure for 3,5-Disubstituted Isoxazole Synthesis

To a solution of alkyne (1 equiv) and oxime (1.5 equiv) in 5 mL of MeOH/H_2O (5:1), [bis(trifluoroacetoxy)] iodobenzene (1.5 equiv) was added in three portions (3× 0.5 equiv) every two hours. After stirring for 7 hours at room temperature, 5 mL of 10% sodium thiosulfate solution was added and the mixture was extracted with DCM. The organic layer was dried with

$MgSO_4$, filtered, and the solvent evaporated. The products were dissolved in DCM, columned by flash chromatography, dried, and recrystallized in ether.

Note: HNMR, CNMR and GC/MS on each compound in supplemental information.

3,5-Diphenylisoxazole (1a)
Following method 2 procedure for the 3,5-disubstituted isoxazole synthesis, phenylacetylene (54.9 µL, 0.5 mmol), benzaldoxime (90.9 mg, 0.75 mmol) and [bis(trifluoroacetoxy) iodo] benzene (323 mg, 0.75 mmol) were used to afford the white solid product after flash chromatography (silica gel, EtOAc/ Hexanes 1:5). M.p. 140.1 °C. TLC (20% EtOAc/ Hexanes): R_f 0.17. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (ddt, *J* = 11.0, 7.9, 1.8 Hz, 4H), 7.59 – 7.44 (m, 6H), 6.86 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.44, 163.01, 130.25, 130.04, 129.16, 129.04, 128.96, 127.50, 126.84, 125.87, 97.49, 76.72. GC-MS (*m/z*): 221. SMILES: c3ccc(c2cc(c1ccccc1)on2)cc3

3-Phenyl-5-(2-pyridinyl)isoxazole (1b)
Following method 1 procedure for the 3,5-disubstituted isoxazole synthesis, 2-ethynyl pyridine (61 µL, 0.6 mmol), benzaldoxime (55 µL, 0.5 mmol), and [bis(trifluoroacetoxy) iodo] benzene (323 mg, 0.75 mmol) were used to afford the white solid product after flash chromatography (silica gel, EtOAc/ Hexanes 1.5:10). M.p 79.3 °C. TLC (15% EtOAc/ Hexanes): R_f 0.22. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.91 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.85 – 7.76 (m, 3H), 7.46 – 7.37 (m, 3H), 7.30 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.20 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.75, 163.28, 150.08, 146.60, 137.16, 130.16, 129.01, 128.93, 126.88, 124.52, 120.92, 100.32, 76.71. GC-MS (*m/z*): 222. SMILES: c3ccc(c2cc(c1ccccn1)on2)cc3

5-(2-Fluorophenyl)-3-phenylisoxazole (1c)
Following method 1 procedure for the 3,5-disubstituted isoxazole synthesis, 1-ethynyl-2-fluorobenzene (68 µL, 0.600 mmol), benzaldoxime (55 µL, 0.5mmol), and [bis(trifluoroacetoxy) iodo] benzene (323 mg, 0.75 mmol) were used to afford clear crystals after flash chromatography (silica gel, EtOAc/ Hexane 1:10 → 1:5). M.p. 76.8 °C. TLC (10% EtOAc in hexane): R_f 0.43. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (td, *J* = 7.6, 1.8 Hz, 1H), 7.87 – 7.73 (m, 2H), 7.47 – 7.32 (m, 4H), 7.29 – 7.05 (m, 2H), 6.96 (d, *J* = 3.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.14, 163.12, 162.21, 159.40, 156.88, 130.66, 130.57, 129.97, 129.53, 129.06, 128.01, 127.98, 127.92, 127.68, 127.28, 126.65, 126.63, 125.85, 123.73, 123.69, 115.35, 115.13, 114.91, 114.79, 100.69, 100.58, 76.31, 76.20, 76.00, 75.68, -0.00. GC-MS (*m/z*): 239**.** SMILES: Fc1ccccc1c3cc(c2ccccc2)no3

3-(4-methoxyphenyl)-5-phenylisoxazole (2a)
Following method 1 procedure for the 3,5-disubstituted isoxazole synthesis, phenylacetylene (66 µL, 0.6 mmol), 4-methoxybenzaldhyde oxime (75.6 mg, 0.5 mmol), and [bis(trifluoroacetoxy) iodo] benzene (323 mg, 0.75 mmol) were used to afford the white solid product after flash chromatography (silica gel, EtOAc/ Hexanes 1:10). M.p. 99.3-101.3 °C. TLC (10% EtOAc in Hexanes): R_f 0.23. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 9.0, 2.3 Hz, 2H), 7.77 – 7.72 (m, 2H), 7.39 (dd, *J* = 9.6, 7.1 Hz, 3H), 6.94 – 6.84 (m, 2H), 6.71 (s, 1H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.17, 166.90, 163.34, 162.60, 161.03, 132.01,

131.60, 130.16, 129.00, 128.22, 127.58, 125.84, 122.62, 121.66, 114.34, 113.62, 97.28, 76.73, 55.43, 55.39, 51.88. GC-MS (*m/z*): 251. SMILES: COc3ccc(c2cc(c1ccccc1)on2)cc3

2-[3-(4-Methoxyphenyl)-5-isoxazolyl]pyridine (2b)

Following method 2 procedure for the 3,5-disubstituted isoxazole synthesis, 2-ethynylpyridine (51 µL, 0.5 mmol), 4-methoxybenzaldhyde oxime (113 mg, 0.75 mmol), and [bis(trifluoroacetoxy) iodo] benzene (323 mg, 0.75 mmol) were used to afford the slightly yellow solid crystals after flash chromatography (silica gel, EtOAc/ Hexanes 1:4). M.p. 100.9- 103.6 °C. TLC (25% EtOAc in Hexanes): R_f 0.23. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.86 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.81 – 7.70 (m, 3H), 7.26 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.13 (s, 1H), 6.96 – 6.81 (m, 2H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.46, 162.85, 161.12, 150.03, 146.64, 137.13, 132.15, 128.27, 124.44, 121.41, 120.88, 114.39, 113.65, 100.10, 77.27, 55.37. GC-MS (*m/z)*: 252. SMILES: COc3ccc(c2cc(c1ccccn1)on2)cc3

5-(2-Fluorophenyl)-3-(4-methoxyphenyl)isoxazole (2c)

Following method 2 procedure for the 3,5- disubstituted isoxazole synthesis, 1-ethynyl-2-fluorobenzene (57 µL, 0.5 mmol), 4-methoxybenzaldehyde oxime (113 mg, 0.75 mmol), and [bis(trifluoroacetoxy) iodo] benzene (323 mg, 0.75 mmol) were used to afford the white solid product after flash chromatography (silica gel, EtOAc/ Hexanes 1:5). M.p. 58.8 °C. TLC (20% EtOAc in Hexanes): R_f 0.23 ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 2H), 7.88 – 7.82 (m, 1H), 7.50 – 7.18 (m, 2H), 7.05 – 6.91 (m, 4H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.88, 163.33, 161.08, 131.60, 128.28, 127.69, 127.67, 124.74, 124.70, 122.62, 121.54, 116.35, 114.35, 101.52, 77.35, 55.42, 51.87. GC-MS (*m/z*): 269, 166 .

2-(5-Phenyl-3-isoxazolyl)pyridine (3a)

Following method 2 procedure for the 3,5-disubstituted isoxazole synthesis, phenylacetylene (55 µL, 0.5 mmol), pyradine-2-aldoxime (91.6 mg, 0.75 mmol), and [bis(trifluoroacetoxy) iodo] benzene (323 mg, 0.75 mmol) were used to afford the slightly yellow solid product after flash chromatography (silica gel, 1:4 EtOAc/ Hexanes). M.p. 95.4 °C. TLC (20% EtOAc in Hexanes): R_f 0.11. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (dq, *J* = 4.4, 1.5 Hz, 1H), 8.05 (dp, *J* = 8.0, 1.1 Hz, 1H), 7.82 – 7.69 (m, 3H), 7.45 – 7.33 (m, 3H), 7.28 (ddt, *J* = 7.7, 4.9, 1.5 Hz, 1H), 7.12 (d, *J* = 1.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.66, 163.78, 149.73, 148.58, 136.95, 130.26, 129.05, 127.45, 126.10, 125.87, 124.55, 121.68, 98.36, 77.38. GC-MS (*m/z*): 222. SMILES: c3ccc(c2cc(c1ccccn1)no2)cc3

3,5-Di-2-pyridinylisoxzaole (3b)

Following method 2 procedure for the 3,5-disubstituted isoxazole synthesis, 2-ethynyl pyridine (51 µL, 0.5 mmol), pyridine-2-aldoxime (91.6 mg, 0.75 mmol), and [bis(trifluoroacetoxy) iodo] benzene (323 mg, 0.75 mmol) were used for the reaction and after 7 hours the mixture was heated to 50 °C to run overnight to afford the yellow solid product after flash chromatography (silica gel, 1:10 acetone/ DCM). M.p. 159.6- 162.1 °C. TLC (10% acetone in DCM): R_f 0.24. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (ddt, *J* = 4.9, 1.7, 0.8 Hz, 2H), 8.03 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.86 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.75 (dtd, *J* = 9.5, 7.7, 1.8 Hz, 2H), 7.48 (s, 1H), 7.28 (dddd, *J* = 7.5, 6.1, 4.8, 1.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.88, 164.00, 150.20, 149.90, 149.33, 148.38, 146.56, 137.02, 124.46, 123.78, 121.74, 120.98, 101.23, 76.75. GC-MS (*m/z*): 223. SMILES: c3ccc(c2cc(c1ccccn1)on2)nc3.

2-[5-(2-Fluorophenyl)-3-isoxazolyl]pyridine (3c)

Following method 2 procedure for the 3,5-disubstituted isoxazole synthesis, 1-ethynyl-2-fluorobenzene (57 µL, 0.5 mmol), pyridine-2-aldoxime (91.6 mg, 0.75 mmol), and [bis(trifluoroacetoxy) iodo] benzene (323 mg, 0.75 mmol) were used to afford the white solid product (22 mg, 18.3% yield) after flash chromatography (silica gel, 1:5 EtOAc/ hexanes). M.p. 128.1 °C. TLC (20% EtOAc in Hexanes): R_f 0.59. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 8.15 (dt, *J* = 8.0, 1.1 Hz, 1H), 8.04 (td, *J* = 7.6, 1.8 Hz, 1H), 7.84 (td, *J* = 7.7, 1.8 Hz, 1H), 7.46 (dddd, *J* = 8.2, 7.1, 5.1, 1.8 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.32 (td, *J* = 7.6, 1.2 Hz, 1H), 7.24 (ddd, *J* = 10.9, 8.3, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.55, 164.53, 163.99, 160.51, 157.99, 149.82, 148.51, 136.92, 131.75, 131.66, 127.64, 127.62, 124.68, 124.64, 124.58, 121.76, 116.49, 116.27, 115.93, 115.80, 102.50, 102.39, 76.72. GC-MS (*m/z*): 240. SMILES: Fc1ccccc1c3cc(c2ccccn2)no3

4-(5-Phenyl-3-isoxazolyl)pyridine (4a)

Following method 1 procedure for the 3,5-disubstituted isoxazole synthesis, phenylacetylene (65.4 µL, 0.6 mmol), 4-pyridinaldoxime (61.1 mg, 0.5 mmol), and [bis(trifluoroacetoxy) iodo] benzene (323 mg, 0.75 mmol) were used to afford the white solid after flash chromatography (silica gel, acetone/ DCM 1:10). M.p. 162.1 °C. TLC (10% acetone in DCM): R_f 0.30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 – 8.67 (m, 2H), 7.79 (dd, *J* = 7.7, 2.0 Hz, 2H), 7.74 – 7.68 (m, 2H), 7.50 – 7.36 (m, 3H), 6.82 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.49, 161.05, 150.41, 136.87, 130.69, 129.17, 125.93, 121.08, 97.28, 77.34, 77.23, 77.03, 76.71. GC-MS (*m/z*): 222. SMILES: c3ccc(c2cc(c1ccncc1)no2)cc3

5-(2-Fluorophenyl)-3-(4-pyridinyl) isoxazole (4c)

Following method 1 procedure for the 3,5- disubstituted isoxazole synthesis, 1-ethynyl-2-fluorobenzene (68 µL, 0.6 mmol), 4-pyridinealdoxime (61 mg, 0.5 mmol), and [bis(trifluoroacetoxy) iodo] benzene (323 mg, 0.75 mmol) were used to afford white solid product after flash chromatography (silica gel, Hexanes/ EtOAc 1:5 → 2:5 gradient elution). M.p. 128.1-132.8 °C. TLC (40% EtOAc in hexane): R_f 0.16. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 – 8.69 (m, 2H), 7.97 (td, *J* = 7.5, 1.8 Hz, 1H), 7.78 – 7.73 (m, 2H), 7.42 (dddd, *J* = 8.3, 7.2, 5.2, 1.8 Hz, 1H), 7.26 (td, *J* = 7.6, 1.1 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.03 (d, *J* = 3.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.07, 132.23, 132.14, 127.68, 124.92, 124.89, 121.25, 116.52, 116.30, 101.47, 101.36, 76.71. GC-MS (*m/z*): 240. SMILES: Fc1ccccc1c3cc(c2ccncc2)no3

Results and Discussion:

A variety of hypervalent iodide reagents were employed to test the parameters of the cyclization reaction. In an effort to remove the need for a chromatographic separation, we tested a polymer-bound oxidant that we had developed many years ago.[16] This attempt resulted primarily in oxidation of the alkyne rather than the oxime and was abandoned. The use of bis(acetoxy)iodobenzene, both with and with and without the addition of catalytic amounts of TFA was also attempted,[9] but the reaction proved to be more sluggish. Likewise,

the reaction is enhanced by the use of a protic solvent. Presumably this solvent promotes the formation of iodoxybenzene *in situ*, which is likely the primary oxidant.

The products were characterized by HNMR, CNMR and GC/MS for both molecular weight and purity. Ten of the eleven products were of high purity (see Supplemental Information), with compound **2c** being contaminated with 4-fluorobenzoic acid methyl ester that was not amenable to chromatographic separation.

Typical side products (from GC/MS analysis of the reaction mix) include the derived nitriles from dehydration of the oximes and the methyl ester of the carboxylic acid derived from aldoxime hydrolysis, oxidation and esterification *in situ*. These are easily separated except in the case of compound **2c**.

Conclusion:

One of our objectives was to formulate a general approach to isoxazole formation that would be sufficiently robust to allow the construction of isoxazole libraries. We recommend that our Method 2, involving the sequential addition of the oxidant to such an end. Separation of byproducts remains a stumbling block and we continue to work on methods to obviate the need for a chromatographic purification.

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