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PART NO. 103047

Synthesis & Purification LETTERS

Multistep Synthesis and Purification of 1,2,3-Thiadiazoles Using "Bank-to-Bank" Transfer

The ability to run multi-step syntheses on a parallel organic synthesizer greatly enhances its capability. Addition of the Lower Luer Manifold Upgrade to the Quest 210 allows the connection of a variety of accessories with luer fittings to the reaction vessel outlets. By using a Teflon® transfer cannula with a luer fitting on one end and a septum luer on the other, reaction mixtures can be transferred from one bank of reaction vessels to the other, allowing multi-step syntheses on the Quest 210. To demonstrate this, we synthesized 1,2,3-thiadiazoles. The ketones required were prepared in reaction bank A. The reaction mixtures were quenched with MP-TsOH resin and the ketone solutions transferred to reaction vessels containing sulfonylhydrazine resin in bank B. After Hurd-Mori cleavage, 1,2,3-thiadiazoles products were purified using liquid-liquid extraction cartridges. Using this technique we were able to perform the parallel multi-step synthesis of 1,2,3-thiadiazoles on the Quest 210.

- ☑ Quest™ 210
- ☑ Quest Solid-Phase Extraction Rack
- ☑ Quest Lower Luer Manifold and Bank-to-Bank Transfer Cannulas
- ☑ Quest Funnel Manifold
- ☑ PS-TsNHNH$_2$ Resin
- ☑ MP-TsOH Resin

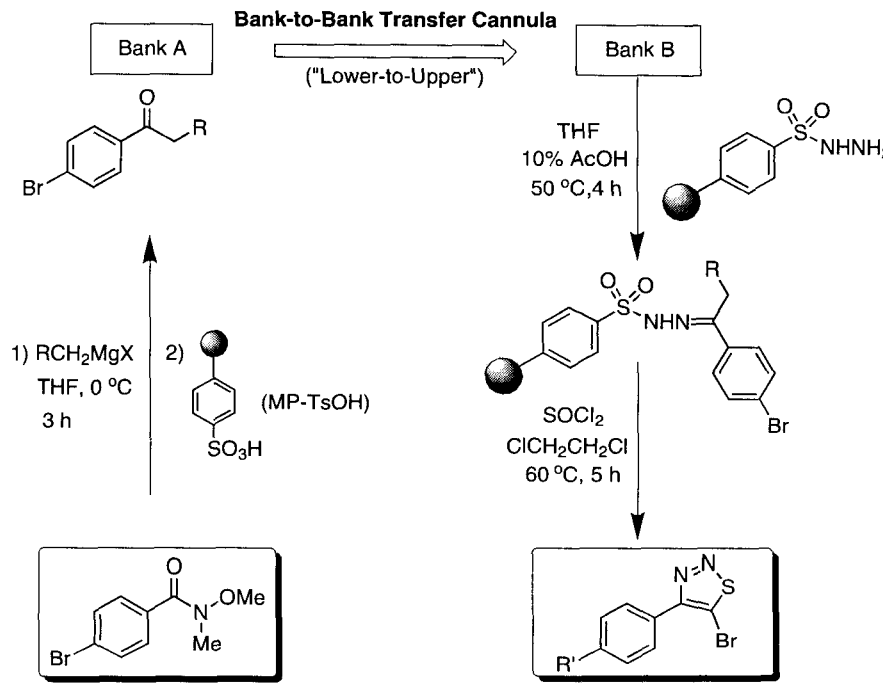
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INTRODUCTION

Many novel methodologies have been developed in the course of applying combinatorial solid phase[1] and solution phase[2] synthesis toward making compound libraries with potential biological and therapeutic significance. These include "catch and release"[3] and "resin capture"[4] strategies for the expedited workup and purification of compounds synthesized in solution. Here we demonstrate a catch and release strategy to synthesize 1,2,3-thiadiazoles. Ketones are prepared in solution on bank A of the Quest 210 organic synthesizer, transferred to a sulfonylhydrazine resin in bank B, and converted using further transformations to 1,2,3-thiadiazoles (**Scheme 1**).

1,2,3-Thiadiazoles are an important class of biologically active[5] compounds as well as useful intermediates in organic synthesis[6]. For example, 4,5-bis-(4'-methoxy-phenyl)-1,2,3-thiadiazole was found to be an active inhibitor of collagen-induced platelet aggregation in vitro.[5a] Many methods have been developed for the synthesis of 1,2,3-thiadiazoles,[5d,5c] including the Hurd-Mori cyclization of α-methylene ketones employing *p*-toluene-sulfonyl hydrazone intermediates.[7,8]

Argonaut Technologies supplies a gel-type polystyrene-sulfonylhydrazide resin (PS-Ts-NHNH$_2$) originally designed for carbonyl scavenging applications.[9,10] We felt



RCH$_2$MgX: CH$_3$MgCl, n-BuMgCl, EtMgBr, iso-BuMgCl, PhCH$_2$MgCl.

Scheme 1. Synthesis of 1,2,3-Thiadiazoles

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that the sulfonylhydrazide resin could also serve as a linker for carbonyl compounds and be used for 1,2,3-thiadiazole synthesis. In addition, we used several accessories that expand the capabilties of the Quest 210 organic synthesizer in order to facilitate the synthesis and purification of 1,2,3-thiadiazoles. These accessories include:

1) Bank-to-bank transfer cannulas
2) Funnel manifold
3) Solid phase extraction (SPE) rack
4) Septum luer plugs

MATERIALS

Reagents required for the synthesis of 1,2,3-thiadiazoles on the Quest 210 are outlined in **Table 1**.

EXPERIMENTAL PROCEDURE

All parallel synthesis transformations were performed on the Quest 210 organic synthesizer. A series of five Grignard reagents were used with a representative Weinreb amide in reaction vessels in bank A. The tetrahedral intermediates thus generated were quenched with MP-TsOH resin to afford aryl ketones. Parallel addition of MP-TsOH resin to reaction vessels was facilitated using the Quest funnel manifold. Ketones were then transferred via a bank-to-bank transfer cannula to reaction vessels containing PS-$TsNHNH_2$ resin in bank B to form polymer sulfonylhydrazones. Using a bank-to-bank transfer cannula to transfer reagents synthesized on bank A to bank B facilitates multistep solution-phase sequences. After sulfonylhydrazone formation and Hurd-Mori cyclizative cleavage, excess thionyl chloride was neutralized in parallel utilizing Extube™ extraction columns,[12,13] preloaded with saturated Na_2CO_3 and mounted on the Quest SPE rack. Final workup involved filtration and concentration of the products.

The Quest 210 was cleaned and prepared for synthesis as described in the *Quest 210 User Manual*. Septum luer plugs were used for reaction vessels on bank B. PS-$TsNHNH_2$ resin (200 mg, 2.4 mmol/g, 0.48 mmol) was loaded into five 5 mL Teflon® reaction vessels on bank A of the Quest 210. The reaction vessels containing the resin were then purged with nitrogen for 2 minutes. On bank B of the Quest 210, N-methoxy-N-methyl-*p*-bromobenzamide (215 mL, 1.25 mmol) was added into five 5 mL Teflon reaction vessels with 3 mL dry THF. The agitation parameters were programmed as follows: 2.5 sec, UpStroke: 1.5 sec, % Upward: 60%. The reaction vessels on bank B were cooled to 0 °C using a Julabo® recirculating chiller. Using Metered Gas to maintain an inert environment, the appropriate Grignard reagents (1.38 mmol, 1.1 equiv.): CH_3MgCl (3.0 M, 465 mL), n-BuMgCl (2.0 M, 695 mL), EtMgBr (3.14 M, 442 mL), *iso*-BuMgCl (2.0 M, 695 mL), $PhCH_2MgCl$ (2.0 M, 695 mL)) were then added to the reaction vessels through the septum luer plugs via syringe. Reaction mixtures were agitated at 0 °C for 3 hours.

While maintaining a gas flow using Metered Gas and Utility (bubbler attachment), the upper manifold luers were removed and the funnel manifold mounted. To each

Table 1. Materials Required

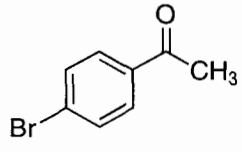
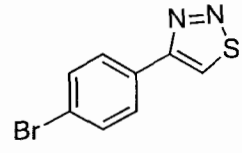
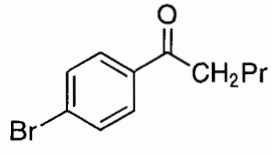
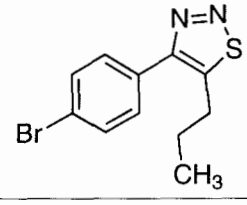
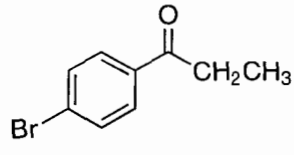
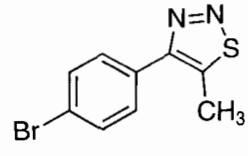
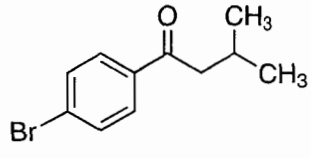
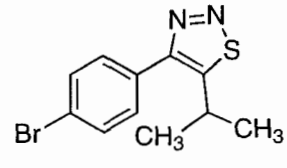
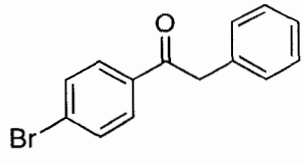
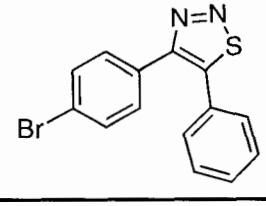
MATERIAL	SOURCE	PROPERTY	AMOUNT
PS-$TsNHNH_2$ resin	Argonaut	2.4 mmol/g	1.0 g
MP-TsOH resin	Argonaut	1.45 mmol/g	10 g
N-Methoxy-N-methyl-*p*-bromobenzamide	Prepared[11]	FW 244.09 d 1.434	1.08 mL
CH_3MgCl	Aldrich	3.0 M	465 µL
n-BuMgCl	Aldrich	2.0 M	695 µL
EtMgBr	Alfa Aesar	3.14 M	442 µL
iso-BuMgCl	Aldrich	2.0 M	695 µL
$PhCH_2MgCl$	Aldrich	2.0 M	695 µL
CH_3COOH	Fisher Scientific	FW 60.05 d 1.049	1.5 mL
$SOCl_2$	Aldrich	FW 118.97 d 1.631	3.5 mL

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reaction vessel was then added 1 gram (1.45 mmol/g, 1.45 mmol) of MP-TsOH through the Funnel Manifold. After reinsertion of the septum luer plugs, the reaction mixtures were agitated for 10 min at 0 °C, followed by addition of 0.3 mL of AcOH. The Manifold Control Valves on bank A were set to "Closed" and "Metered Gas" and the upper manifold luers removed. The shorter end of the bank-to-bank transfer cannula was attached to the luer ports and Metered Gas allowed to flow through for complete purging of the lines. The Manifold Control Valves were then set to "Closed" and "Vent." The female luer fittings were then attached to the male luer fitting under lower valve manifold to the adjacent RV position on bank B. The bank B manifold control valves were set to "Closed" and "Metered Gas." By toggling the RV lower manifold valve lever of bank B to the open position, Metered Gas pressure was used to transfer the solution to RVs of bank A. When the transfer was complete and the RV lower manifold valve lever closed, the bank A manifold control valves were set to "Closed" and "Metered Gas." The reaction vessels in bank A were then agitated at 50 °C for 4 hours. The vessels were cooled to room temperature, drained, and washed with THF (3 X), hexane (2 X), and dichloroethane (3 X). To perform product cleavage, 2.3 mL of dichloroethane and 700 mL of $SOCl_2$ (9.6 mmol, 20 equiv.) were added to each reaction vessel and the reaction mixtures agitated for 5 hours at 60 °C.

Five liquid-liquid extraction cartridges (Extube™ Extraction Columns)[13] were mounted on the SPE rack. To each cartridge was added 2.5 mL saturated Na_2CO_3 and the cartridges were allowed to soak for 10 min. The

Table 2. Thiadiazoles prepared via "resin capture" of ketones on the Quest 210

Entry	Ketone	Thiadiazole	Yield (%)	GC Purity (%)
1			98	100
2			82	94
3			77	97
4			59	97
5			67	98

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reaction mixtures (and three dichloroethane washes) were filtered through the liquid-liquid extraction cartridges into scintillation vials. The solutions were concentrated to afford the 1,2,3-thiadiazole products.

RESULTS AND DISCUSSION

The formation of support-bound sulfonylhydrazones from non-commercially available ketones was facilitated using "resin capture" wherein ketones synthesized in solution are captured as resin-bound sulfonylhydrazones (**Scheme 1, Table 2**). Five *p*-bromophenyl ketones were prepared in parallel on the Quest 210 organic synthesizer by reacting N-methoxy-N-methyl-*p*-bromobenzamide with a variety of Grignard reagents (THF, 0 °C). The reaction mixtures were then quenched with a macroporous polystyrene-sulfonic acid resin (MP-TsOH) to decompose the tetrahedral intermediate.[14] Acetic acid (10% v/v) was added and the ketone solutions were directly transferred via cannula to reaction vessels containing PS-$TsNHNH_2$ resin. The sulfonylhydrazone formation was complete in 4 h at 50 °C in the presence of acetic acid. After thionyl chloride cleavage (Hurd-Mori cleavage, dichloroethane, 60 °C, 5 h) and product purification (liquid-liquid extraction cartridges), thiadiazoles were obtained in high chemical yield and purity. A series of 1,2,3-thiadiazoles were prepared with various substituents at 5 position. All products were characterized by GC (GC method: 175 °C (3 min), ramp up to 300 °C (20 °C/min), 300 °C for 5 min.) and were found to have high purity (>90 % GC area). The 1,2,3-thiadiazoles were isolated with chemical yields ranging from 59-98%. All compounds were characterized by ^1H and ^{13}C NMR (see spectroscopic data section). Bis-aryl compounds similar to those shown in entry 5 are of great interest since antithrombotic compounds have been found to bear aromatic substituents at both 4 and 5 positions of the 1,2,3-thiadiazole ring.

SPECTROSCOPIC DATA

Gas chromatography, ^1H NMR, ^{13}C NMR and MS (APCI) for 1,2,3-thiadiazole compounds are provided below:

Entry **1**, 4-(4'-bromophenyl)-1,2,3-thiadiazole: ^1H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1 H, =CH), 7.93 (d, 2 H, J = 8.7 Hz, Ar-H), 7.65 (d, 2 H, J = 8.7 Hz, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.68, 132.24, 129.97, 129.63, 128.72, 123.50 ppm.

Entry **2**, 4-(4'-bromophenyl)-5-n-propyl-1,2,3-thiadiazole: ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (m, 4 H, Ar-H), 3.02 (t, 2 H, J = 7.7 Hz, $-CH_2-$), 1.78 (m, 2 H, $-CH_2-$), 1.01 (t, 3 H, J = 7.4 Hz, $-CH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.03, 153.12, 131.89, 130.34, 120.27, 123.00, 27.50, 24.95, 13.48 ppm; MS (APCI) showed [M +1]+: 283.0 (calcd for $C_{11}H_{11}N_2SBr$: 282.1).

Entry **3**, 4-(4'-bromophenyl)-5-methyl-1,2,3-thiadiazole: ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (m, 4 H, Ar-H), 2.71 (s, 3 H, $-CH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.46, 146.55, 132.76, 131.91, 130.07, 123.02, 10.10 ppm.

Entry **4**, 4-(4'-bromophenyl)-5-isopropyl-1,2,3-thiadiazole: ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, 2 H, J = 8.4 Hz, Ar-H), 7.56 (d, 2 H, J = 8.4 Hz, Ar-H), 3.51 (septet, 1 H, J = 6.6 Hz, -CH-), 1.39 (d, 6 H, J = 6.6 Hz, $-(CH_3)2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.39, 157.71, 131.92, 130.50, 130.34, 123.05, 26.85, 25.56 ppm.

Entry **5**, 4-(4'-bromophenyl)-5-phenyl-1,2,3-thiadiazole: ^1H NMR (300 MHz, $CDCl_3$): δ 7.51 (m, 5 H, Ph-H), 7.44-7.33 (m, 4 H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.31, 151.07, 131.82, 131.60, 130.48, 129.83, 129.18, 129.13, 127.51, 123.18 ppm; MS (APCI) showed [M +1]+: 317.2 (calcd for $C_{14}H_9N_2SBr$: 316.2).

CONCLUSIONS

- A multistep, solution/solid-phase sequence for the synthesis of 1,2,3-thiadiazoles employing "resin capture" of ketones has been performed on the Quest 210 using the lower luer manifold upgrade.
- The transfer of ketones prepared *in situ* was facilitated using the Quest bank-to-bank transfer cannula accessory.
- Ketones were captured to the solid support as sulfonylhydrazones using PS-$TsNHNH_2$ resin.
- Cleavage of resin-bound sulfonylhydrazones was accomplished using thionyl chloride to afford 1,2,3-thiadiazoles without silica gel chromatography.
- Parallel product purification was performed using liquid-liquid extraction cartridges and the Quest SPE rack.

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13. Extube™ liquid-liquid extraction cartridges (part number 1219-8003, 3 mL aqueous capacity) were purchased from Varian Sample Preparation Products, Harbor City, CA. The cartridges were preloaded with 2.5mL saturated Na_2CO_3 for 10 min. before use.
14. MP-TsOH resin (1.1-1.6 mmol/g, macroporous polystyrene-co-divinylbenzene) is commercially available from Argonaut Technologies.

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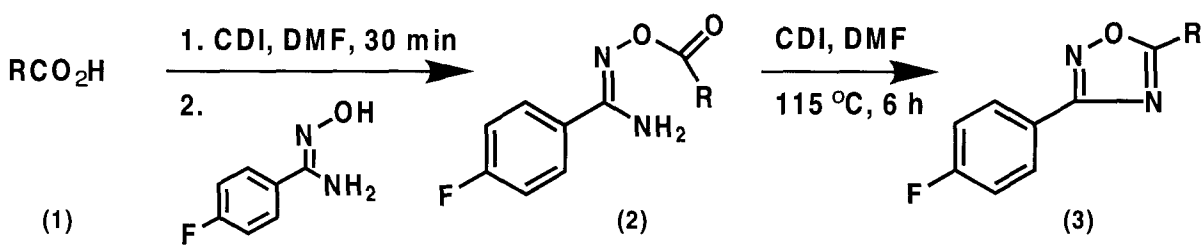
Use of In-line Purification Cartridges with the Lower Luer Manifold Upgrade on the Quest 210

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In-line purification of compounds on the Quest 210 is more efficient and less costly than using off-line techniques. Luer purification cartridges filled with various separation media are available from a number of vendors (e.g. Alltech Associates, Varian, etc). The Quest Lower Manifold Luer Upgrade allows direct attachment of these cartridges to the Quest 210 and facilitates the in-line purification of compounds. This technique was demonstrated by synthesizing five 1,2,4-oxadiazoles. Each oxadiazole was synthesized in duplicate. One of the pair of oxadiazoles was analyzed after liquid-liquid extraction and filtration; the other product was filtered through a Florisil cartridge attached to the Quest 210. Oxadiazoles purified in-line showed up to 10% higher purity over the crude reaction products.

PROCEDURE

Scheme 1 shows the general synthesis of 1,2,4-oxadiazole compounds derived from 4-fluorobenzamidoxime:



Scheme 1.

In a typical experimental procedure, 0.5 mL of a 0.5 M carboxylic acid solution (1, 0.25 mmol) in DMF was added to 10 mL reaction vessels (RVs) on the Quest 210, followed by addition of 0.275 mL of 1.0 M solution (0.275 mmol) of 1,1'-carbonyldiimidazole (CDI) in DMF. After mixing for 30 min, 0.5 mL of 0.55 M 4-Fluorobenzamidoxime solution (0.275 mmol) in DMF was added and the resulting solution was mixed for 4 h at 25 °C. A further 0.275 mL of 1.0 M CDI (0.275 mmol) in DMF was added and the reaction mixtures were heated to 115 °C for 6 h to effect cyclodehydration (*Caution: gas evolution!*). After cooling to room temperature, 4 mL of CH_2Cl_2 was added to each vessel, and the solutions were washed with 2 x 2 mL H_2O, 1 x 2 mL 1 N HCl, 1 x 2 mL sat. $NaHCO_3$, and 1 x 2 mL brine with the top aqueous layers removed via pipet. The CH_2Cl_2 layers were dried in situ using $MgSO_4$. One of each duplicate was filtered through 900 mg Florisil cartridges (Alltech Part No. 210059) which were pre-wetted with CH_2Cl_2 and attached to the luer fittings of the lower manifold (see section below for more details). The other reaction replicates were drained without purification. All products were analyzed for purity by GC.

CARTRIDGE PURIFICATION

Florisil cartridges were pre-wetted with CH_2Cl_2 by assembling them together in a chain and pushing solvent through using a disposable polypropylene syringe. The female ends of the cartridges were then attached to the male luer fittings on the lower manifold and "locked in" with a gentle twisting motion. Scintillation vials were then

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placed in the adjustable collection rack. The rack was adjusted to the correct height for collection of samples by turning the wing nuts until the height was uniform and the rack was level. Once the height of the rack was adjusted so that the cartridge tip was inside the lip of the scintillation vials, the toggle switch on the Quest was opened to the drain position. The metered gas control valve was turned to the lowest setting and the control knobs were turned to "Metered Gas" and "Closed" positions. The metered gas valve was slowly turned counterclockwise to increase the pressure until the solvent flowed from the cartridges with light to medium dripping (Note: "Pouring" causes poor separation). Once the liquid levels in the RVs reached the bottom (not allowing air to dry out the cartridge), a further 4 mL of DCM was added to the RVs for rinsing, and the cartridges were allowed to drain dry.

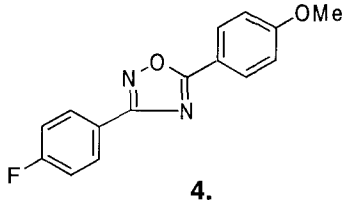
RESULTS

Table 1 summarizes the results from the study. It is clear from the GC data of products 4-8 that in-line filtration through Florisil enhanced the product purities as much as 10 %. In addition, the Florisil cartridges absorbed yellow colored impurities from the crude reaction products.

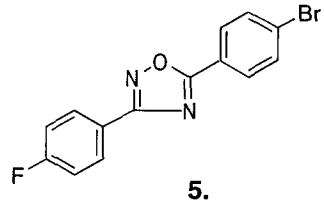
Table 1.

Entry	Florisil Cartridge	Carboxylic Acid (1)	Product Oxadiazole	% Wt. Yield	Product Appearance	Area % Purity[1]
1A	Y	p-anisic acid	4	49	White solid	95
1B	N	p-anisic acid	4	53	Yellow solid	85
2A	Y	4-bromobenzoic acid	5	60	White solid	82
2B	N	4-bromobenzoic acid	5	60	Yellow solid	73
3A	Y	4-cyanobenzoic acid	6	61.3	White solid	72
3B	N	4-cyanobenzoic acid	6	62.3	Yellow solid	67
4A	Y	cyclopentanecarboxylic acid	7	61	Colorless oil	97
4B	N	cyclopentanecarboxylic acid	7	62	Yellow oil	88
5A	Y	4-pentenoic acid	8	57	Colorless oil	98
5B	N	4-pentenoic acid	8	59	Yellow oil	98

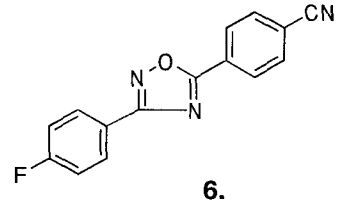
1. GC Analysis (HP-5 phenylmethylsilicone column (175 °C, 3 min), 20 °C/min to 300 °C).



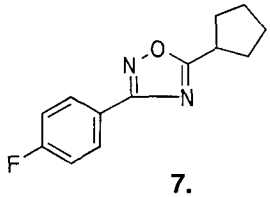
4.



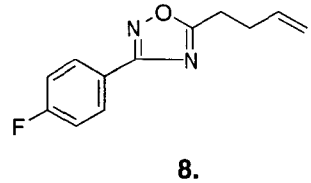
5.



6.



7.



8.

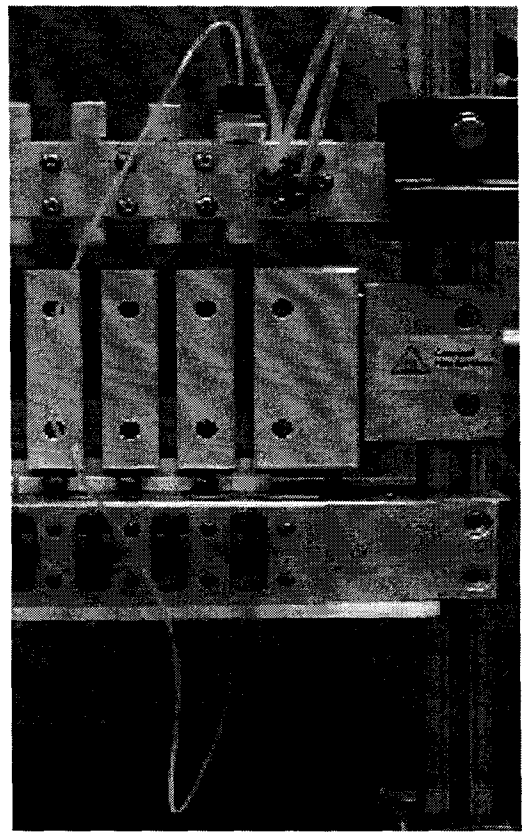
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QUEST™ Operational Tip

Bank-to-Bank Transfer Cannula Protocol

DESCRIPTION



The Quest 210 bank-to-bank transfer cannula may be used to transfer reaction solutions from Bank A through the lower luer manifold of the Quest 210 to reaction vessels on bank B through the upper manifold luer port. This cannula allows the efficient transfer of reaction solutions under an inert environment. Multiple cannulas may be used to transfer banks of reaction vessels (For an example of bank-to-bank transfer, see: *Synthesis & Purification Letter* #4, Argonaut Technologies.)

INSTRUCTIONS

STEP 1: Purging the Cannula Line

1. Place reaction vessels into Bank B (receiving side).
2. Attach the female luer end(s) of the cannula(s) to the lower manifold luer fittings on Bank B.
3. Open the lower manifold drain valves. Turn the upper manifold membrane valve switch to "Open." Rotate the control valves to "Drain Gas" and "Closed" and flush with nitrogen to purge the cannula line(s) of any previous solvent.
4. Remove the cannula(s).

STEP 2: Attachment of the Cannula(s) for Transfer

1. Insert the septum luer plug end(s) of the cannula(s) into the upper manifold of Bank B (receiving).
2. Rotate the Quest to Bank A (source side).
3. Attach female luer end(s) of the cannula(s) onto the lower luer fittings on Bank A opposite to those on Bank B (i.e. position 1 drains to position 11).
4. Flush Bank B reaction vessels with nitrogen by turning Bank B control valves to "Utility 1" and "Metered Gas" for one minute. Then return the control valves to "Closed" and "Closed."

STEP 3: Solution Transfer

1. Toggle open the lower manifold drain valves on Bank A (source) to allow drainage.
2. Turn the control valves on Bank A to "Closed" and "Metered Gas" and push the solution(s) out of Bank A into Bank B (receiving).
3. Rinse as needed by addition of solvent into Bank A's reaction vessels.

STEP 4: Cleaning the Transfer Cannula

1. Unplug the cannula end(s) from Bank B and place the tubes into a waste receptacle.
2. Rinse the lines by addition of appropriate solvent into Bank A reaction vessels and purge the system to waste using Drain Gas.

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