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Telescoped Sequence of Exothermic and Endothermic Reactions in Multistep Flow Synthesis

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Abstract:

A multi-step sequential flow synthesis of isopropyl phenol is demonstrated, involving 4-steps exothermic, endothermic, and temperature sensitive reactions like nitration, reduction, diazotization and high temperature hydrolysis. Nitration of cumene with fuming nitric acid produces 2 and 4-nitrocumene which is converted into respective cumidines by the hydrogenation using Pd/Ni catalyst in H-cube with gravity separation. Hydrolysis of in-situ generated diazonium salts in the boiling acidic conditions is carried out using integration of flow and microwave-assisted synthesis. 58 % of 4-isopropyl phenol was obtained. The sequential flow synthesis can be applied to synthesize other organic compounds involving this specific sequence of reactions.

Keywords: Multistep Flow Synthesis, Nitration, Reduction, Diazotization, Phenol-Verkochung

1. Introduction:

Translation of batch process to continuous flow synthesis provides a promising technique for scale-up of exothermic, multiphase, and temperature sensitive reactions. Smaller dimensions help to enhance heat & mass transfer rates, reduce the equipment size, energy consumption, and thereby reduce reaction time with increase in production capacity. All these features help to achieve an economical process. In flow synthesis, dead time is almost negligible when automated and integration of multistep in continuous synthesis eliminates laborious off-line isolation of intermediates. Multi-step flow synthesis and purification of Ibuprofen,¹ synthesis of alkaloid natural product Oxomaritine,² a library of 5-amino-2-aryl-2H-[1,2,3]-triazole-4carbonitriles,³ Suzuki-Miyaura cross coupling reaction,⁴ process intensification of the synthesis of poly(vinyl butyral),⁵ diazotization with subsequent reactions⁶, Taxadienone synthesis involving 2 copper mediated addition, a Diels-Alder reaction, palladium catalyzed Negishi coupling reaction,⁷ rhodium-catalysed, syngas-mediated C–C bond formation for hydroformylation of styrenes,⁸ and so many other multistep flow synthesis have been successfully demonstrated and reported by academia as well as by industries.⁹⁻¹¹ Continuous flow synthesis of a few important molecules viz. HIV NNRTI Doravirine,¹² Vildagliptin an oral antibiotic drug¹³, Efavirenz,¹⁴ etc. is also reported in the literature with improved yield. Glasnov et al. have reported multistep flow synthesis of Boscalid involving Suzuki-Miyaura cross-coupling and heterogeneous catalytic hydrogenation.¹⁵ Cantillo et al. have developed multistep continuous-flow process for the synthesis of triaminophloroglucinol using sequential nitration/reduction of phloroglucinol.¹⁶ Chen and Buchwald have designed a multistep synthesis consisting of a C-N bond formation-hydrogenation-diazotization-cyclization sequence starting from 2-chloronitroben-zenes and amines to synthesize 1-substituted benzotriazoles.¹⁷

Among the several multistep synthesis, one of the important sequence is the aromatic nitration followed by its reduction and then diazotization followed by hydrolysis. This sequence is followed for the synthesis of aromatic alcohols used as intermediates in the fine and specialty chemicals industry and also as API (viz. phenylrephren hydrochloride). Here, we have used this sequence for flow synthesis of isopropyl phenol, which is useful organic intermediate for synthesis of agrochemicals and perfumery products.^{18, 19} It is also used for the production of phosphorus containing plasticizers instead of cresol, as diphenylisopropylphenyl phosphate is

less toxic than tricresylphosphate.¹⁸ Generally, isopropyl-phenols are synthesized by either rearrangement of saturated alkylphenylethers or by the selective oxidation of diisopropylbenzene. In the rearrangement approach first an alkyl phenyl ether is synthesized by reaction of phenol with an alkyl halide in the presence of potassium hydroxide under reflux condition. Rearrangement of this alkylphenylether takes place in sulfuric acid and glacial acetic acid solution which gives predominantly the ortho isomer as the major product.²⁰ The second approach involves oxidation of p-di-isopropylbenzene in a two stages: (i) liquid phase oxidation of p-di-isopropyl benzene to monohydroperoxide by atmospheric oxygen, which follows radical mechanism, followed by (ii) acid catalyzed decomposition of the monohydroperoxide into isopropyl phenol in the presence of a cation exchange resin. The yield of monohydroperoxide depends on the temperature and distillation rate. Literature data shows 98% yield at 90 °C and at a distillation rate of 0.05-0.07 l/hr.²¹ Safe handling of organic peroxide needs special attention. Isopropyl phenol can also be synthesized by Fe_2O_3 catalyzed rapid oxidation of arylboronic acids in the presence of atmospheric oxygen under solar visible range light irradiation,²² and via a three step reaction starting from the reduction of nitrocumene (Ranev Ni catalyst, 130 °C, 15 kg/cm² and distillation give 90% yield) followed by diazotization and hydrolysis (steam distillation, 60% yield) which involves many separation and purification steps.²³ In such a sequence comprising of exothermic reactions (viz. nitration, reduction and diazotization) and handling of sensitive and reactive intermediates (diazonium salt), flow synthesis seems to be a better approach.²⁴⁻²⁹ Fully continuous flow diazotization-hydrolysis has recently been reported for synthesis p-cresol starting from p-toluidine as starting material. Optimized reaction temperature and low concentration has enhanced yield of p-cresol as well as reduced byproducts.30

In this work, isopropylphenol is synthesized in a 4-step continuous flow process with special emphasis on the hydrolysis reaction following a classical approach (see Schematics 1). Commercially available cumene was chosen as starting material, upon nitration of cumene followed by reduction, diazotization and hydrolysis gives isopropyl phenol with complete elimination of separation and isolation steps. Among these steps, the first three steps are known to be feasible in flow synthesis and a good amount of literature is available in the recent time. For these three reactions, rapid mixing, high interfacial mass transfer rates, excellent temperature control through efficient heat transfer and with adequate residence time, the reactions usually

show enhanced yields of the products.³¹⁻³³ However, the last step of converting an aniline into a phenol is a classical conversion known as "Phenol-Verkochung".³⁴ It is a SN1 type reaction of the diazonium salt with water in the presence of concentrated acids at high temperature, which yields respective phenols.^{35, 36} Although Phenol-Verkochung is well –known reaction, here we demonstrate it for the first time in continuous mode under highly acidic conditions. This reaction needs excess water under boiling conditions. The reaction should have relatively higher activation energy as even in the acidic environment, phenol formation happens in a short time only close to boiling conditions. Although Phenol-Verkochung reaction is known, here we demonstrate a continuous microwave method for the first time under highly acidic conditions.



Schematic 1: Classical approach for synthesis of isopropylphenol from cumene via multistep approach involving 1) nitration (FNA: Fuming nitric acid), 2) catalytic hydrogenation, 3) diazotization and 4) hydrolysis

2. Experimental Section:

Experimental set-up used for continuous nitration of cumene is shown in schematics 2. Typical setup consisted of two continuous syringe pumps (*Holmarc Opto-Mechatronics, Pvt. Ltd. India*). Stainless steel syringes were mounted on syringe pump to pump nitric acid (50 mL volume) while PTFE syringes were used for the pump for dosing cumene. These syringes were connected to SS316 tubes (1/8" o.d.) which were further connected to AMaR1 micromixer (*Amar Equipments Pvt. Ltd., India*) followed by a 1/8" helical coil of 10 m length to maintain residence

time. The reactor assembly was immersed in a constant temperature bath (ME-12, Julabo GmbH, *Germany*) to maintain the system at isothermal condition. The entire assembly had four outlets (one immediately after the micromixer i.e. after 2 mL volume and remaining along the length at about every 3.33 m) connected to needle valves for sampling. The flow rates of the both reactants were varied to achieve the desired mole ratio as well as the residence time. To extract nitrocumene in organic phase, the pinched tube reactor of 36 mL volume was used and organic and aqueous layer was separated using inline gravity separator as shown in schematics 2. For analysis of samples, known quantity of samples were collected at the different outlets (corresponding to different residence times), in a fixed quantity of ice-cold-water. A known quantity of toluene (Merck Life Science Pvt. Ltd.) was used to extract the organic phase from these samples. The extracted organic phase was washed thrice with water followed by brine and separated by gravity. Trace quantity of water was removed by passing the organic phase through a bed of anhydrous sodium sulphate. Products were confirmed by GCMS and NMR. Conversion, vield and selectivity was estimated using gas chromatography (Thermo Fischer trace GC Ultra, Column HP-5, i.d. = 0.25 mm, L = 30 m and FID detector). Nitrobenzene was used as an internal standard.



Schematic 2: Experimental setup for nitration of cumene followed by in-line quenching and separation.

To the outlet of nitration reactor, toluene was dosed for continuous extraction of organic phase (the mixture of Nitrocumenes) in toluene using a pinched tube reactor and the outlet was subjected to a continuous settler where the phase separation happened by gravity and the organic layer was continuously fed to the next step of reduction. H-cube® (*ThalesNano Nanotechnology*)

Inc., Hungary) with different catalyst Raney-Ni and Pd/Ni was used with temperature range of 40 to 100 °C and pressure range of 10 to 50 bar (see Schematics 3). Internal volume of the catalyst cartridge was 0.3 mL. The nitro-derivatives of cumene were passed through the H-cube® at flow rates over a range of 0.2-2 mL/min and samples were collected for each experiment (see Table 1). These samples were analyzed without any separation or isolation using GC with HP-5 column and a FID detector. Nitrobenzene was used as an internal standard. The analysis showed that the outlet stream contained 16.7% 2-cumidine and 59.4% 4-cumidine (yield are on the basis of Cumene).



Schematic 3: Experimental set-up for nitrocumene reduction using H-cube followed by cumidine salt generation using a CSTR.

After hydrogenation of nitro-cumene was dissolved in toluene, cumidines were subjected to diazotization. Before diazotization, it was converted into (substituted) ammonium salt by treatment with HCl and water, for which a continuous stirred reactor (also known as CSTR or mixed flow reactor) was used (see setup in Schematic 3). This (substituted) ammonium salt is completely soluble in water, and aqueous phase was separated by gravity. Peristaltic pump was used to flow this aqueous phase containing (substituted) ammonium salt to react with 1.2 equivalent NaNO₂ (10%) solution. The NaNO₂ was injected using syringe pumps with PTFE syringe and mixed with (substituted) ammonium salts in T mixer (see the schematic 4). This reaction was carried out at 5 $^{\circ}$ C in 4.5 mL coiled reactor and reaction solution maintained 113 seconds residence time. In order to estimate yield of diazonium salt by HPLC, the reaction mixture at the outlet of the reactor was collected in several vials containing 2 to 10 ml of aqueous solution of β -naphthol (0.45 M) and NaOH (1.5 M)/.^{37, 38} The samples was collected over a

period of 15–30 s to maitain required stoichiometry to give Sudan-I dye and the completion of reaction was monitored using HPLC.



Schematic 4: Experimental setup for the diazotization of cumidine salt.

The diazonium salt from the outlet of the previous step was directly fed into the CSTR placed in a continuous microwave oven operated at 210 W, 2.45 GHz (*Ragatech Pvt. Ltd. India*), at the flow rate of 2.4 mL/min at 80 °C (residence time $\sim 4 - 13.4$ min depending upon volume of CSTR, see the reaction setup in Schematic 5). HCl (36% aq. solution) was used to provide acidic media for hydrolysis at high temperature.³⁴ The collected sample was extracted in organic phase using toluene. Organic layer was separated by gravity. After thrice water wash followed by brine wash, sample was directly submitted to GC analysis with HP-5 column and FID detector. On using 16 mole sulfuric acid, 5% 2-isopropylphenol with 4% isopropylphenol was obtained in PFR, while on using 2 mole of HCl in microwave 58% 4-isopropyl was achieved with 2% 2-isopropylphenol (yields are on the basis of cumene). NMR and GCMS were used for product conformation.

3. Result and discussions

In the first step commercially available cumene was chosen as starting material and nitration was performed using fuming nitric acid being a greener reagent avoiding the use of sulfuric acid.³⁹ Isoproyl group in cumene is ortho/para (o:p) directing and gives more para-isomer and negligible amount of meta-isomer. The o:p isomer ratio depends on nitrating agent and solvent. Initially,

nitration reactions were performed with 1 mole of nitric acid in residence time range of 2.64-10 min, maximum 38% conversion was achieved in residence time of 10 min. In order to get complete conversion of cumene, 2 moles of fuming nitric acid was used at 30 °C and 40 °C, at both temperatures and achieved in the range 65 and 66% conversion respectively at 10 min residence time (see Figure 1), which clearly shows that nitrating reagent is limiting reagent for this reaction. Using larger quantities of the fuming nitric acid (4 moles) at the same temperatures resulted in very rapid reaction and exceedingly rapid heat generation. Even the outlet stream was dark in color with a few impurities getting formed (mostly dinitro derivatives, confirmed from GC Mass). Hence, further experiments were carried out at lower temperatures (0 °C and 10 °C). On using 4 moles of fuming nitric acid 99.6% conversion was achieved with 19.5%, 1% and 79% yield for 2-nitrocumene, 3-nitrocumene and 4-nitrocumene, respectively in 6.4 min residence time at 10 °C. Rest of the 0.5% mass was impurities that could not be isolated. In another set of experiments at 0 °C, complete conversion was achieved in 8.2 min with almost identical outlet composition. Thus it was possible to get complete conversion of the substrate by achieving a suitable combination of temperature and residence time. Reaction was guenched inline using ice-cold water and toluene was added continuously to this stream for extraction of organic compound from aqueous phase using a pinched tube.⁴⁰



Figure 1: Graphical representation of influence of reaction temperature and residence time on the conversion of cumene.

To achieve maximum separation efficiency, pinched tube reactor (1/8" o.d., 10 mL volume) was used for liquid-liquid extraction which enhances mass transfer rates.⁴⁰ Toluene layer containing nitro derivatives was then continuously separated by liquid-liquid separator. The organic stream was subjected to continuous reduction.

Extracted nitrocumene solution exhibits concentration of 0.642 M. First reduction experiment using H-cube® was carried out using Raney-Ni catalyst at 100 °C and at 40 bar with solution of same molarity at 0.3 mL/min. However, no conversion was achieved at this condition due to much smaller catalyst quantity loaded in the catalyst cartridge compared to the substrate concentration. In view of this, nitrocumene solution was diluted to 0.1068 M and 0.0222 M using toluene and hydrogenation was carried out at the conditions mentioned before (see table 1). This resulted in only 10% and 13.83% yield at 40 bar pressure indicating that the catalyst was inappropriate for reduction of nitrocumene and hence for all further experiments Pd-Ni (100mg) was used as the catalyst.⁴¹ Nitrocumene solution (0.018 M) in toluene was subjected for its reduction with Pd-Ni catalyst over a temperature range of 40 to 100 °C and pressure range of 10 to 50 bar with flow rate of 0.2 mL/min. At 100 °C and 40 bar pressure, 76.8% yield was achieved with 16.7% 2-cumidine and 59.4% 4-cumidine.

Without any further separation or isolation steps this cumidine mixture was treated with HCl and water to generate (substituted) ammonium ion in a CSTR. HCl was continuously added with the help of a syringe pump that generated water soluble (substituted) ammonium ion and the water was also continuously added to dissolve this (substituted) ammonium salt. At room temperature, 30 min residence time was found be sufficient for dissolution. Subsequently, the (substituted) ammonium ion containing aqueous phase and organic phase separated using a gravity separation unit. This (substituted) ammonium ion was treated with 1.2 equivalents NaNO₂ (10%). The aromatic diazonium salts can be a very unstable intermediate and can decompose above 5 °C or it can undergo coupling reaction resulting in ethers or anhydride molecules, which is beyond the scope of the present work. Thus retaining suitable temperature that avoids decomposition reaction is necessary along with optimal reaction time. Various reports are available on flow synthesis of unstable diazonium intermediate at different temperatures.^{42, 43} Therefore, diazotization reaction was carried out in a residence time range of 30 to 120 s at 0 °C. 100%

diazotization was achieved with a residence time of 113 s, which was also confirmed via coupling with β -naphthol.

On hydrolysis at higher temperature, diazonium salts are expected to give corresponding phenols. It is known that this hydrolysis reaction follows first order kinetics with water being in far excess and thus only the concentration of diazonium salt governs the rate of reaction.⁴⁴ Following this aspect, the mixture of diazonium salts of 2-cumidine and 4-cumidine from the previous steps were directly injected to a tubular reactor (of 9.5 mL volume) having multiple outlets corresponds to different residence times. The coiled reactor was immersed in constant temperature bath to provide isothermal conditions. Since, the reaction is facilitated only at higher temperatures, experiments were carried out at 70 °C, 80 °C and 90 °C. However, the maximum yield was 10% implying that either it needs stronger acidic media or higher temperature or both together. It was thought desirable to transfer phenol in organic phase to enhance the reaction in aqueous phase by avoiding possibility of lowering the reactant concentration in aqueous phase. An organic solvent having lower dielectric constant would help as it does not get significantly

Table 1: Details of reaction parameters for reduction of nitrocumene mixture dissolved in toluene, with flow rate of 0.2 mL/min except in case of 0.642 molar solution, it's 0.3 mL/min. Yields are calculated using the GC data and are on the basis of nitrocumene. (H-cube catalyst cartridge: *Raney-Ni, ** Pd-Ni)

Nitrocumene	Temp.	Р	Cumidine isomer		% yield
(mol/L)	(°C)	(bar)	2	4	
0.642*		40	-	-	-
0 107*		40	4.50	5.88	10.39
0.107		60	1.72	2.72	4.44
0.0445*	100	20	3.48	4.87	8.35
0.0115	100	40	4.85	6.27	11.12
		20	3.27	4.61	7.88
0.0222*		40	5.79	8.03	13.83
		50	3.42	5.71	9.13

	40	20	1.0	7.3	8.43
	60	20	6.6	32.7	39.70
	80	10	9.6	43.5	53.52
		20	13.7	53.1	67.45
0.01836**	100	10	13.7	53.0	67.32
		20	16.4	58.3	75.35
		30	16.3	58.6	75.62
		40	16.7	59.4	76.79
		50	16.7	58.6	76.02

heated. This makes the system two phase and using a pinched tube facilitated the mass transfer of phenol from aqueous to organic phase. Hence, the next set of experiments was carried out using sulfuric acid. On using 16 moles of H_2SO_4 at 80 °C in a residence time of 4.2 min, the highest yield was 39% (see Table 2 section Tubular reactor). Longer residence time resulted in significant loss in the yield due to decomposition of diazonium salt as coupling of phenol with undecomposed diazonium salt and their is formation of tar.^{45, 46} Also, slow heating of the reaction mixture through an immersed tubular reactor also led to decomposition of diazonium salt.

The approach using sulfuric acid led to generation of water vapors containing nitrophenols, which could be avoided to some extent by using lower number of moles of H_2SO_4 and higher temperature in further experiments. Moreover to avoid the volume of expansion due to evaporation, further experiments were carried out in a continuous stirred tank reactor (CSTR) rather than in a tubular reactor. CSTR attached to a condenser was used as it helped releasing the water vapors from the reaction mass and its condensation to a steady state without affecting the residence time. This also ensured that no pressure is built-up in the reactor, which is an unsafe situation. In order to achieve rapid heating under stirring, the conventional method of circulation of heating fluid through jacket was insufficient to achieve rapid heating compared to reaction rates, a CSTR without any jacket was used and placed inside a microwave oven with inbuilt magnetic stirring, having inlet and outlet ports and a condenser to condense the condensable

vapors and release non-condensable gases (see schematics 5). CSTR was a favoured choice of reactor as it helps rapid mixing, release of vapours avoiding pressure built-up in the reactor, with a microwave while the heating rate remains constant using CSTR helped change residence time independently.



Schematic 5: Experimental step for microwave-assisted continuous flow hydrolysis of diazonium salt.

This also helped to achieve a localized heating in a much shorter time. Initial continuous microwave experiments at 140 W power at 80 °C with 7 minutes residence time resulted in a total 41.7% yield of the phenols in which 10.5 % 2-isopropylphenol and 31.1 % 4-isopropylphenol was obtained (see Table 2, section microwave). At 210 W the yield increased to 55.4%, however at 240 W the yield decreased to 44.9%. The temperature inside the reactor measured using an IR gun (*Testo*) was found to be about 98 °C. Despite circulating ice cold water in the condenser brown fumes of isopropyl phenol were visible at the outlet of the condenser. Sulfuric acid being a very strong hydrolyzing agent, controlling the reaction rates under rapid heating was relatively difficult. In order to control the rate of hydrolysis further experiments were carried out using 2 mole of HCl at 210 W, which resulted in 61.7% yield with 3.3% 2-isopropylphenol and 58.4% 4-isopropylphenol in 13 minute residence time. This yield of 4-isopropylphenol is close to the observations in the literature.³⁴ In order to avoid any spark inside the reactor, it was necessary to ensure that no charring happens and no carbon deposition takes place on the surface of reactor or connecting joints.²¹ Further increase in residence time or

microwave power resulted in rapid generation of brown fumes and lower yield of the desired product in solution. Hence, 210 W power for microwave, 13 min residence time with 2 mol HCl) was considered as optimum for this reaction step.

Table 2: Details of reaction parameters for the hydrolysis of diazonium salt (yields are on the basis of diazonium salt). [#] Pinched tube tubular reactor, $*H_2SO_4$ catalyst, **HCl catalyst, - without catalyst, the HCl used in the preparation of diazonium salt carried forward for hydrolysis reaction).

	Temp OC	Catalyst Residence		Selectivi	Overall	
	remp. C	mole	time (min)	2-IPP	4-IPP	yield %
Tubular reactor in circulating bath	70	-	4	8.43	0.98	2.5
	80	-	4	11.32	2.6	4.4
	90	-	4	22.84	7.2	10.3
	60	8*	6	5.51	1.91	7.4
	60	16*	6	11.64	0.85	12.5
	70	16*	6	16.15	2.09	18.3
	80	16*	4	32.76	6.27	39.0
	80	16*	9	21.86	3.51	25.4
	70#	-	15	11.36	34.9	30.2
Microwave	140w, 20%	-	7	10.53	31.16	41.7
	210w, 30%	-	13	15.82	39.56	55.4
	240w, 35%	-	13	14.98	29.9	44.9
	210w, 30%	0.8**	13	10.9	47.1	58.0
	210w, 30%	2**	13	3.3	58.4	61.7

Upon integrating the hydrolysis step with the previous steps of continuous nitration, hydrogenation and diazotization (see schematic 5), the analysis of reaction mass showed 3.3% yield of 2-isopropylphenol and 58.4% yield of 4-isopropylphenol. For the isolation of the phenolic isomers, we used column chromatography using 10% ethyl acetate/petroleum ether and

also crystallization using methanol/hexane (1:1) mixture. In crystallization protocol, almost quantitative yield of 4-isopropylphenol (melting point 59–60 °C) was obtained with 2-isopropylphenol remaining in the liquid (melting point ~ 12–16 °C). Upon further recrystallization, 4-isopropylphenol was isolated in pure form with 52.3% yield.



Schematic 6: Integrated multistep multi step flow synthesis of isopropylphenol.

The purpose of this work was to not only demonstrate the telescoped 4-step integration of flow synthesis of isopropyl phenols but to also show that the classical approach of transforming an aniline to a phenol works very well and can be improved through synergy of flow synthesis and microwave heating. In this specific example, the overall reaction time of 21 hours in batch synthesis for all 4 steps was seen to be reduced by at least 25 times with no intermittent isolation stages. More such examples can be demonstrated using this approach.

4. Conclusions

4-step integrated continuous flow synthesis of isopropylphenol has been established with reduction of overall process time from 21 hours to 50 min with complete elimination of any intermittent isolation, separation, and purification steps. The sequence of reactions includes exothermic reactions like nitration and hydrogenation^{47, 48}, temperature sensitive and unstable diazonium intermediate and endothermic continuous hydrolysis. The last stage of hydrolysis follows the classical approach of reacting diazonium salt with water under strong acidic and at boiling conditions. The entire sequence of stages covers a very wide range of experimental conditions with the final stage under microwave to achieve rapid heating. The reaction sequence followed cumene nitration with fuming nitric acid that gives 2 and 4-nitrocumene, which gives respective cumidines upon reduction using H-cube with Pd/Ni catalyst. Upon diazotization of

mixture of cumidines in acidic environment followed by high temperature continuous hydrolysis in a microwave gives 2-isopropyl phenol and 4-isopropyl phenol with complete elimination of intermittent separation, isolation and purification steps. The yield of 4-isopropylphenol after purification was 52.3%. The hydrolysis step was seen to be extremely sensitive to acidic environment as well as microwave power and hence should be optimized for individual anilines separately. The approach can be used for the synthesis of other useful intermediates for agrochemicals and pharmaceutical industry.

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Description of Supporting Information: Supporting information includes the NMR spectra for various intermediates and products and GC and GC-MS methods and chromatograms for various intermediates and products that are formed at various stages in this multistep synthesis.

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Four step flow synthesis involving nitration, reduction, diazotization and hydrolysis

163x121mm (144 x 144 DPI)