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# On the Fischer Indole Synthesis of 7-Ethyltryptophol—Mechanistic and Process Intensification Studies under Continuous Flow Conditions

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Supporting Information

**ABSTRACT:** 7-Ethyltryptophol, a key intermediate in the synthesis of the anti-inflammatory agent etodolac, was produced by Fischer indole synthesis of 2-ethylphenylhydrazine and 2,3-dihydrofuran under continuous flow conditions. The reaction generates several undesired byproducts and therefore product yields could not be improved above 40−50%. The mechanism of this transformation was studied in detail and the structure of the byproducts carefully elucidated. Despite the only moderate product yield, the synthesis of 7-ethyltryptophol by this protocol remains interesting compared to alternative methods and starts from inexpensive reagents. The developed process is executed in an environmentally benign solvent (methanol) and, importantly, the majority of byproducts can be removed from the 7-ethyltryptophol product by a straightforward extraction process.

## INTRODUCTION

Tryptophol and tryptophol analogues are common intermediates in the synthesis of several important pharmaceutically active molecules including tryptamine-based pharmaceuticals, such as certain members of antimigraine drugs of the triptan family (e.g., Sumatriptan, rizatriptanm and zolmitriptan; Figure 1),[1,2] the alpha-1 selective adrenoceptor antagonist indoramin,

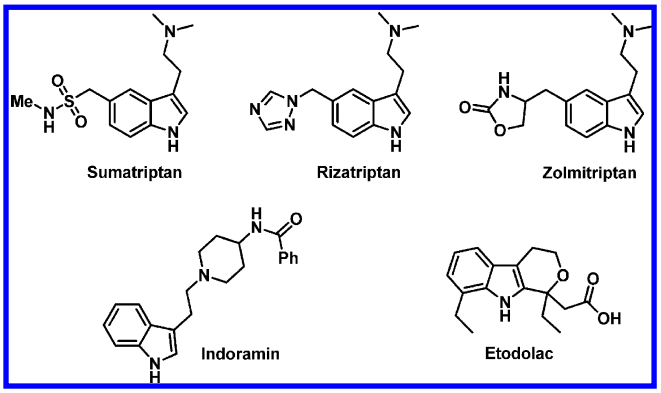


**Figure 1.** Selected pharmaceutically important indoles derived from tryptophol analogues.

or compounds based on the pyranoindole structure, such as etodolac.[3,4] Etodolac is a potent anti-inflammatory and analgesic compound synthesized from 7-ethyltryptophol (7-ET, cf. **3a** in Scheme 2) as the key intermediate.[3,4]

Different methods for the synthesis of indoles bearing a C-3 hydroxyethyl side chain are described in the patent and scientific literature. For example, 7-ET was prepared from the 7-ethyl-3-indolylglyoxylate by reduction with $LiAlH_4$, while the indolylglyoxylate was formed from 7-ethylindole and oxalyl chloride.[3] Other methods for the synthesis of tryptophols include aldol condensation of ketones with isatins and subsequent reduction of the 3-substituted-dioxyindoles,[2a] palladium catalyzed coupling of an iodoaniline species with protected butynol derivatives,[2b] or alkylation of the indole or indolyl-metal salt with ethylene oxide or with ethylene glycol under pressure.[5] The formation of 7-ET by a Fischer indole synthesis from 2-ethylphenylhydrazine hydrochloride and dihydrofuran (DHF), as disclosed by Demerson and Humber[6] and Stevensen et al.,[7] clearly would be a simpler and cheaper alternative, but unfortunately the reaction produces a lot of side products and 7-ET is generally isolated from the reaction as a tarry solid or sticky oil in poor yields (less than 50%) and requires column chromatography for purification.[2c,d,4,6,7] A related strategy for the one-pot synthesis of various tryptophol and tryptophol homologues by a Fischer indole synthesis was described in 2004 by Campos and co-workers (Scheme 1).[8] Substituted phenylhydrazine hydrochlorides **1** were mixed with cyclic enol ethers in DMA/$H_2O$ as solvent in the presence of sulfuric acid. The hydrazones **2** were formed in situ from the hydrazine hydrochloride and the enol ether, and the ensuing [3,3]-rearrangement of the respective ene-hydrazine at 100 °C provided 3-substituted indoles **3** in good yields after chromatography.[8] The major side product was the adduct **4**, which evidently is derived from a further reaction of the indole product with unconsumed enol ether.[8] Several subsequent papers have described modifications of this protocol, such as the use of Montmorillonite-K10 or mesoporous MCM-41 as

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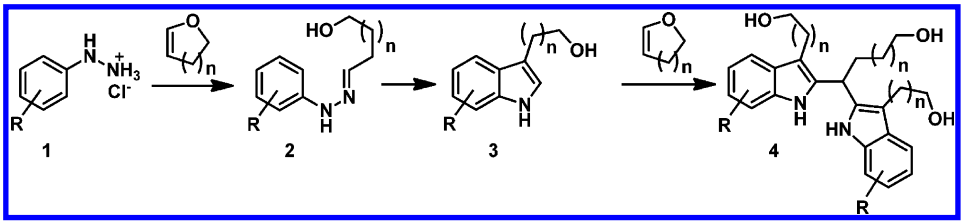
**Scheme 1. Synthesis of Tryptophol and Homologs from Arylhydrazines and Cyclic Enol Ethers**



**Scheme 2. Continuous Flow Synthesis of 7-ET 3a[11]**

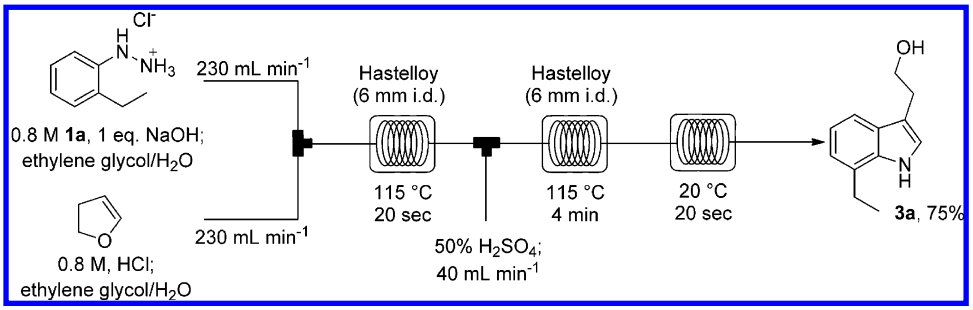



**Table 1. Yields of 7-ET for Flow Reactions Performed at Different Reaction Temperatures and Residence Times with 1 equiv of DHF and 1.2 equiv of $H_2SO_4$ (Scheme 2)[a]**

| entry | flow feed A [g min$^{-1}$] | flow feed B [g min$^{-1}$] | flow feed C [mL min$^{-1}$] | temp. [°C] | RT module 1 [min] | RT module 2 [min] | total RT [min] | yield 7-ET (incl. HPLC assay)[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | 4.3 | 4.3 | 0.5 | 108 | 0.6 | 5.1 | 6.2 | 39 |
| 2 | 5.3 | 5.3 | 0.7 | 108 | 0.5 | 4.1 | 5.1 | 37 |
| 3 | 7.2 | 7.2 | 0.9 | 108 | 0.4 | 3.0 | 3.7 | 36 |
| 4 | 4.3 | 4.3 | 0.5 | 115 | 0.6 | 5.1 | 6.2 | 36 |
| 5 | 5.3 | 5.3 | 0.7 | 115 | 0.5 | 4.1 | 5.1 | 38 |
| 6 | 7.2 | 7.2 | 0.9 | 115 | 0.4 | 3.0 | 3.7 | 50 |
| 7 | 4.3 | 4.3 | 0.5 | 122 | 0.6 | 5.0 | 6.1 | 24 |
| 8 | 5.3 | 5.3 | 0.7 | 122 | 0.5 | 4.1 | 5.1 | 39 |
| 9 | 7.2 | 7.2 | 0.9 | 122 | 0.4 | 3.0 | 3.7 | 43 |

[a]Conditions: feed A: 0.8 M 2-ethylphenylhydrazine hydrochloride **1a**, 1 equiv NaOH in ethylene glycol/$H_2O$; feed B: 0.8 M DHF, 0.008 equiv HCl in ethylene glycol/$H_2O$; feed C: 50% $H_2SO_4$; RT module 1: Hastelloy C-22 flowplate and PFA coil (2.8 and 2 mL); RT module 2: Corning glass reactor and stainless steel coil (5.6 and 38 mL). [b]Yields are based on quantitative HPLC analysis (%) of samples after extraction and removing of solvent. RT = residence time.

heterogeneous catalysts.[9,10] It was argued that the use of heterogeneous catalysts reduces dimerization and polymerization of the tryptophol owing to the shape and size selectivity of these catalysts.[10]

The synthesis of 7-ET **3a** from 2-ethylphenylhydrazine hydrochloride **1a** and DHF on a kilogram scale was reported in 2011 by Su and co-workers (Scheme 2).[11,12] The reaction was performed as a continuous flow process in three consecutive tube reactors. The hydrazine hydrochloride **1a** was neutralized first with 1 equiv of NaOH in ethylene glycol/water as solvent. DHF, also dissolved in ethylene glycol/water as solvent, was stirred for 10 min at room temperature in the presence of hydrochloric acid to open the enol ether to the 4-hydroxybutyraldehyde. These two solutions were pumped into a T-joint and further through a first residence tube heated to 115 °C where the hydrazone **2a** was formed. After the first residence loop, 50% aqueous sulfuric acid was fed in to catalyze the Fischer indolization which then occurred in a second residence loop at 115 °C. The processed reaction mixture was finally quenched in a third residence coil held at 20 °C. The authors hypothesized that, by performing this reaction as a two-stage process, the DHF (or aldehyde) is consumed in the first residence tube and no DHF (or aldehyde) should be present during indolization in the second tube reactor, and therefore, no adduct **4a** should be formed. Indeed, the reported yields of 7-ET **3a** increased from 45% for a one-pot batch process to 75% for the two-stage continuous flow process.[11]

This apparently very elegant procedure and the reported high yields of 7-ET **3a** achieved by this method encouraged us to establish an analogous continuous flow process for the synthesis of 7-ET in our laboratories. Unfortunately, however, all of our attempts to synthesize 7-ET following the above-mentioned protocol provided the desired product in rather moderate yields only (50% at best). In this publication, we discuss some of the mechanistic and process chemistry details of this industrially very relevant transformation, and provide rationalization on why the yields in this particular Fischer indole synthesis are difficult—if not impossible—to improve.

## RESULTS AND DISCUSSION

**Replication of the Reaction Conditions Reported by Su and Coworkers.** Our initial experiments were aimed to reproduce the continuous flow protocol described by Su and co-workers (Scheme 2).[11] The two feed solutions (feed A:


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**Table 2. Yields of 7-ET for Flow Reactions Performed with Different Stoichiometries of DHF and $H_2SO_4$ at 115 °C Reaction Temperature.**[a]

| entry | flow feed A [g min$^{-1}$] | flow feed B [g min$^{-1}$] | flow feed C [mL min$^{-1}$] | equiv of DHF | equiv of $H_2SO_4$ | RT module 1 [min] | RT module 2 [min] | total RT [min] | yield 7-ET (incl. HPLC assay)[b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 7.2 | 7.2 | 0.9 | 1.0 | 1.2 | 0.4 | 3.0 | 3.7 | 41 |
| 2 | 7.0 | 7.7 | 0.9 | 1.1 | 1.2 | 0.3 | 3.0 | 3.7 | 44 |
| 3 | 6.7 | 8.1 | 0.8 | 1.2 | 1.2 | 0.3 | 3.0 | 3.6 | 35 |
| 4 | 7.2 | 7.2 | 0.7 | 1.0 | 1.0 | 0.4 | 3.1 | 3.8 | 41 |
| 5 | 7.3 | 7.3 | 0.6 | 1.0 | 0.8 | 0.4 | 3.1 | 3.8 | 38 |
| 6 | 7.2 | 7.2 | 0.9 | 1.0 | 1.2 | 0.4 | 3.0 | 3.7 | 41 |

[a]Conditions: feed A: 0.8 M 2-ethylphenylhydrazine hydrochloride **1a**, 1 equiv NaOH in ethylene glycol/$H_2O$; feed B: 0.8 M DHF, 0.008 equiv HCl in ethylene glycol/$H_2O$; feed C: 50% $H_2SO_4$; RT module 1: Hastelloy C-22 flowplate and PFA coil (2.8 and 2 mL); RT module 2: Corning glass reactor and stainless steel coil (5.6 and 38 mL). [b]Yields are based on quantitative HPLC analysis (%) of samples after extraction and removing of solvent. RT = residence time.

hydrazine hydrochloride and NaOH in ethylene glycol/water; feed B: DHF and HCl in ethylene glycol/water) were pumped by two gear pumps into the first reactor module consisting of a plate microreactor, wherein the two feed solutions were mixed, and an ensuing residence loop. The reaction mixture leaving the first module was combined with 50% aqueous sulfuric acid, fed via a syringe pump into a second reactor module. The second module again consisted of a plate microreactor and a consecutive residence loop. The reaction mixture was cooled in a third residence loop and was collected in a collection vessel under nitrogen (for more details, see Experimental Section). The collected mixtures were extracted with MTBE/$H_2O$, the solvent removed under vacuum, and the content of 7-ET **3a** in the samples were determined by quantitative HPLC analysis (see Experimental Section for details).

Flow experiments with this setup under reaction conditions adopted from the work of Su and co-workers (i.e., ~0.8 M solutions of starting materials, 115 °C reaction temperature in both reactor modules, 30 s and 4 min residence time in reactor module 1 and 2, respectively) led to the 7-ET **3a** in product yields of only 35−41% based on quantitative HPLC analysis of the obtained samples (Table 1, entry 5). Increasing or decreasing the temperature of module 1 and 2 and/or altering the total residence time in the reactor by varying the flow rates of the three feeds did not give any notable improvement. Often, it was observed that the yields of 7-ET **3a** increased when the residence time was shortened, even though a full consumption of hydrazone was no longer achieved. This was particularly obvious for the reactions performed at 122 °C where the yields decreased from 43% to 24% when the total residence time in the reactor was increased from 3.7 to 6 min (Table 1, entry 7 to 9). The best result in this set of experiments was a yield of 50% of 7-ET, obtained at 115 °C with a total residence time of 3.7 min (Table 1, entry 6). Varying the residence times of the reaction mixture in the individual reactor modules by adding a second residence tube to module 2 (residence volume of 38 + 38 mL) or by replacing the 2 mL tube of module 1 by a 6 mL tube did not show any significant effect on the reaction at a reaction temperature of 115 °C (see Tables S1 and S2 in the Supporting Information). Also, adjusting the flow rates of the individual feeds to change the stoichiometry (1.0, 1.1, and 1.2 equiv of DHF) or the concentration of sulfuric acid (0.8, 1.0, and 1.2 equiv of $H_2SO_4$) had very little effect, and the yields of 7-ET **3a** were consistently around 40% only (see Table 2). Formation of black, tarry materials in the second reactor module after sulfuric acid was fed in was observed in all of these reactions. The tarry compounds were not detectable by HPLC, but they precipitated during the reaction and repeatedly blocked the channels of the microreactor.

**Dimerization and Oligo-/Polymerization of 7-ET 3a.** It is well-known that indoles form dimers, trimers, and oligomers under acidic conditions by electrophilic attack of the 3-protonated species on the indole nucleus of an unprotonated species.[13] Even though pure 7-ET was rather stable under various conditions and just slowly decomposed in the presence of sulfuric acid (Figure 2), it rapidly decomposed when both

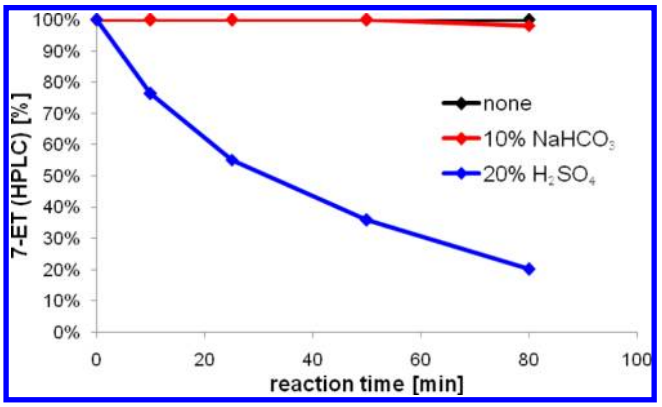


**Figure 2.** Decomposition of pure 7-ET **3a** in MeOH/$H_2O$ at 150 °C (sealed vessel microwave irradiation) based on quantitative HPLC analysis of the reaction mixtures. Conditions: 1 mmol 7-ET **3a**, additive in 1.5 mL MeOH/$H_2O$ 2:1. The main product in the reaction with $H_2SO_4$ was the O-methylated 7-ET.

DHF and strong acids were present. For example, the isolated and purified 7-ET heated together with 0.5 equiv of DHF and 1 equiv of HCl in MeOH/$H_2O$ as solvent decomposed completely within 15 s at 130 °C. The main compound detected by HPLC was the adduct **4a** (Scheme 3). In addition to adduct **4a**, a significant amount of tarry, polymeric material was formed which was insoluble in both aqueous and unpolar organic solvents and precipitated upon extraction of the

**Scheme 3. Formation of Adduct 4a**

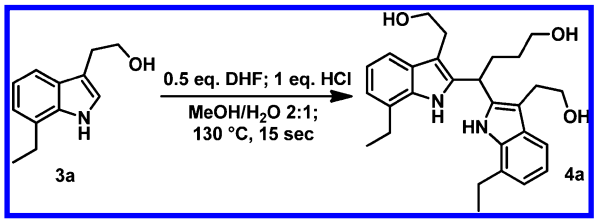



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**Table 3. HPLC Purity (Peak Area Integration at 215 nm) and Yields of 7-ET (quant. HPLC) for Batch Reactions Performed with Different Additives[a]**

| entry | solvent | additive [mol %] | $t$ [min] | hydrazone **2a** | 7-ET **3a** | adduct **4a** | 7-ET yield (HPLC)[b] |
|---|---|---|---|---|---|---|---|
| 1 | MeOH/$H_2O$ | $NaHCO_3$ [10] | 5 | 16 | 78 | 2 | **37** |
| 2 | | $NaHCO_3$ [10] | 15 | 6 | 84 | 3 | **38** |
| 3 | | $NaHCO_3$ [10] | 50 | 3 | 85 | 4 | **39** |
| 4 | | none | 5 | 8 | 81 | 4 | **39** |
| 5 | | $H_2SO_4$ [20] | 5 | 1 | 76 | 18 | **39** |
| 6 | | $H_2SO_4$ [40] | 5 | 0 | 51 | 43 | **21** |
| 7 | *i*-PrOH/$H_2O$ | $NaHCO_3$[c] [10] | 5 | 12 | 77 | 2 | **36** |
| 8 | | none | 5 | 5 | 79 | 5 | **35** |
| 9 | | $H_2SO_4$ [20] | 5 | 1 | 78 | 10 | **35** |
| 10 | MeCN/$H_2O$[c] | $H_2SO_4$ [20] | 5 | 0 | 47 | 41 | **17** |
| 11 | THF/$H_2O$[c] | $H_2SO_4$ [20] | 5 | 7 | 78 | 6 | **40** |
| 12 | DMA/$H_2O$ | $H_2SO_4$ [20] | 5 | 10 | 83 | 2 | **43** |
| 13 | | $H_2SO_4$ [40] | 5 | 2 | 84 | 5 | **45** |
| 14 | | $H_2SO_4$ [80] | 5 | 0 | 72 | 19 | **37** |

[a]Conditions: 1 mmol 2-ethylphenylhydrazine hydrochloride **1a**, 1 equiv of DHF in 1.5 mL solvent/$H_2O$ 2:1 at a reaction temperature of 130 °C (sealed vessel microwave irradiation). [b]Yields are based on quantitative HPLC analysis (%) of the crude reaction mixtures. [c]An organic and an aqueous liquid phase separate during the reaction.

reaction mixture. The adduct **4a** was isolated in 43% product yield by column chromatography from this experiment.

To get further insight into the Fischer indole synthesis of 7-ET **3a**, a set of experiments was performed with a variety of acidic or basic additives in different organic solvent/water mixtures as solvents. The reactions were performed as one feed continuous flow reactions with premixed reagents in a Hastelloy tube reactor (9.8 mL, 1/8 in. o.d.; see Experimental Section for details) heated in an oil bath or as one-pot batch reactions in glass vials heated on a hot plate or in a microwave reactor (see Experimental Section for details). Water is required as a cosolvent to dissolve the 2-ethylphenylhydrazine hydrochloride **1a** and to keep the solution homogeneous during the reaction, i.e., prevent precipitation of $NH_4Cl$ during the reaction. The main side product of the reaction of hydrazine hydrochloride **1a** with DHF detectable by HPLC was the adduct **4a**. Further side products detected in minor amounts were 2-ethylphenol and a compound which appeared to be a positional isomer of 7-ET (it had the same mass and fragmentation pattern). Significant amounts of the adduct **4a** were formed in the presence of sulfuric acid or other acidic catalysts in all solvents tested (Table 3) and the yields of 7-ET in the processed reaction mixtures were below 50% in all of these reactions (yields were determined from the crude reaction mixture by quantitative HPLC). Without any acid catalyst, formation of the adduct was reduced and its formation was almost completely suppressed when the reaction was performed in the presence of a mild base such as $NaHCO_3$, triethylamine or pyridine. Unfortunately, consumption of the hydrazone became rather slow in the presence of a base and the overall yield of 7-ET did not increase. Adduct formation also depended strongly on the solvent and it was considerably less in protophilic solvents such as DMA/$H_2O$, NMP/$H_2O$, or DMF/$H_2O$. The p$K_a$ of protonated amides (~ −0.5) is higher than the p$K_a$ of protonated MeOH (−2.2) or water (−1.7) and, presumably, amide-based solvents buffer the reaction mixture somewhat and thus suppress dimerization of 7-ET. Indolization of the hydrazone, however, was significantly slower in these solvents and, again, the overall yield did not increase (Table 3). For more data of reactions under flow and batch conditions, see Figures S1−S9 and Tables S4−S6 in the Supporting Information. Overall, the yields of 7-ET **3a** were around 40% with surprising indifference regarding the reaction conditions.

Even though the reaction without any acid catalyst required several minutes (e.g., around 8 min at 150 °C) to obtain an essentially full consumption of the hydrazone (HPLC at 280 nm), the yields of 7-ET **3a** did not increase any further after the first few minutes of reaction (Figure 3 and Figure S1 in the Supporting Information). Apparently, the rate of decomposition of 7-ET becomes comparable to the rate of its formation after a few minutes and then even exceeds it. Interestingly, the yields of 7-ET consistently increased with increasing reaction temperature in the investigated temperature range (Figure 3). Analogous behavior, but with shorter reaction times to attain the optimum yield at a particular reaction temperature, was also observed with acids being present in the solution (Figure 4).

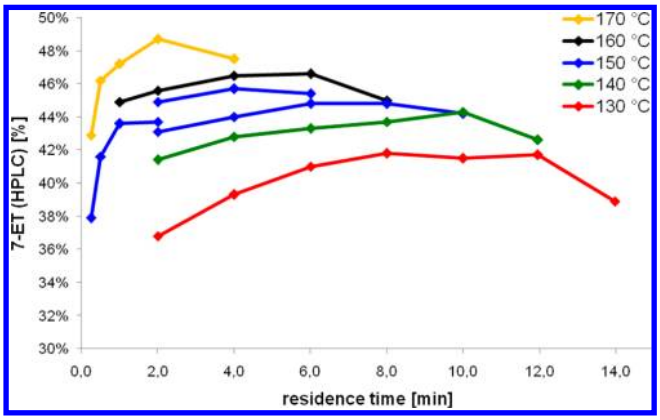


**Figure 3.** Yields of 7-ET (quantitative HPLC analysis of the crude reaction mixtures) for flow reactions performed without any catalyst in a Hastelloy tube reactor (9.8 mL; 1/8 in. o.d.). Conditions: 1 feed: 0.4 M 2-ethylphenylhydrazine hydrochloride **1a**, 1 equiv DHF in MeOH/$H_2O$ 2:1; 40 bar back pressure.

An important factor may be the efficiency with which the hydrazone is formed. As described above, dimerization and oligo/polymerization requires the presence of DHF and, thus, ought to be diminished when DHF is consumed by hydrazone formation in the preceding step. In MeOH/$H_2O$ as solvent, the


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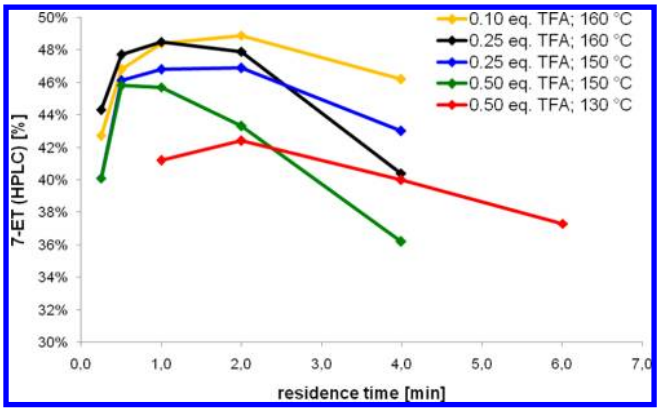
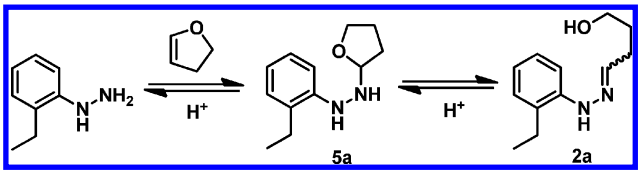



**Figure 4.** Yields of 7-ET (quantitative HPLC analysis of the crude reaction mixtures) for flow reactions performed with TFA as catalyst in a Hastelloy tube reactor (9.8 mL; 1/8 in. o.d.). Conditions: 1 feed: 0.4 M 2-ethylphenylhydrazine hydrochloride **1a**, TFA, 1 equiv DHF in MeOH/$H_2O$ 2:1; 40 bar back pressure.

DHF reacts very rapidly in the presence of the hydrazine hydrochloride even at room temperature. $^1$H NMR monitoring in deuterated MeOH/$H_2O$ showed that the $^1$H NMR signals of DHF disappear within 10 to 15 min (see Figure S10 in the Supporting Information). Three distinct compounds were detected in this reaction, but the main product was apparently not the hydrazone **2a**, but a compound tentatively assigned to the tetrahydrofuran **5a** (Scheme 4). In contrast, hydrazone

**Scheme 4. Equilibration of Hydrazone and Hydrazine/DHF in Non-Solvolytic Solvents**




formation proceeded cleaner in THF/$H_2O$ as solvent (see Figure S11 in the Supporting Information) and the crude hydrazone could be isolated from this mixture in 75% product yield. However, the yields of 7-ET were virtually identical for reactions in THF/$H_2O$ compared to MeOH/$H_2O$ as solvent.

Furthermore, comparable product compositions as observed for reactions with hydrazine hydrochloride **1a** and DHF—forming various amounts of adduct **4a** as side-product—were also obtained when the hydrazone **2a** was isolated and subsequently used for the indolization, indicating a fast equilibration of hydrazone and hydrazine/DHF under the employed reaction conditions (Table 4). In fact, the adduct **4a** was formed even when the reaction was performed with the isolated hydrazone **2a** in non-solvolytic (non-nucleophilic) solvents such as MTBE (Table 4, entries 2–5). Equilibrium concentrations of DHF in the reaction mixture thus seem to be unavoidable and an advantage of a flow process with three feeds and two consecutive residence tubes (cf. Scheme 2)[11] over flow reactions with premixed reagents, and one residence tube is not expected.

**Selectivity of the [3,3]-Rearrangement.** As indicated above (and in more detail in the Supporting Information), even though dimerization of 7-ET **3a** could be mostly prevented by adjusting the pH of the reaction mixture, the 7-ET yields were invariably below 50% regardless of the catalyst, solvent, reaction temperature, or reaction time. In large part, this seemed to be owed to oligo/polymerization of 7-ET in the presence of DHF. Additionally, however, it must be stressed that the [3,3]-sigmatropic rearrangement of the ene-hydrazine intermediate **6a** may produce two isomeric nonaromatic species, **7a** and **8a** (Scheme 5). Importantly, only **7a** can rearomatize to form 7-ET **3a** after cyclization and expulsion of ammonia from the cyclic aminal. The intermediate **8a**, on the other hand, will form a nonaromatic dienylimine (**9a**) after cyclization of the transitional diimine intermediate **8a**.[14,15] Dienylimines of this kind have been isolated and characterized on a few occasions, providing good evidence for the accepted reaction mechanism of the Fischer indolization.[15]

A nonaromatic compound, which appears to have the structure of the dienylimine **9a**, along with small amounts of 2-ethylaniline could be isolated from the crude reaction mixture by extraction with MTBE/$H_2O$, neutralization of the water phase with $NaHCO_3$, and subsequent re-extraction of the water phase with EtOAc. Notably, dienylimine **9a** does not absorb UV light strongly and is therefore not easily detectable with HPLC-UV/vis and, further, elutes together with remaining hydrazine and the 2-ethylaniline. However, GC-FID and $^1$H NMR analysis of the reaction mixtures after extraction with sat. $NaHCO_3$/EtOAc indicated that the 7-ET/dienylimine ratio is around 3:1 for reactions in the presence of 20% of $H_2SO_4$ as the catalyst (see Figure 5 and Figure S12 in the Supporting Information). 2-Ethylaniline, isolated together with the dienylimine **9a**, is probably formed by thermal decomposition of the 2-ethylphenylhydrazine **1a**.[16] Attempts to purify the dienylimine **9a** from the aniline by crystallization or by chromatography were unsuccessful because of its susceptibility to decomposition.

For model compound **2b** (cf. Scheme 6), full MP2 calculations[17] with the 6-311+G(d,p) basis set using the *Gaussian 09* package[18] indicate that the energy barrier for the uncatalyzed [3,3]-rearrangement to the position occupied by the o-ethyl group is not even 0.5 kcal mol$^{-1}$ higher than the

**Table 4. HPLC Purity (Peak Area Integration at 215 nm) and Yields of 7-ET (quant HPLC) for Batch Reactions Performed with the Isolated Hydrazone 2a**[a]

| entry | solvent | additive | t [min] | hydrazone **2a** | 7-ET **3a** | adduct **4a** | 7-ET yield (HPLC)[b] |
|---|---|---|---|---|---|---|---|
| 1 | MeOH/$H_2O$ | 1 equiv HCl | 1 | 0 | 50 | 37 | **20** |
| 2 | MTBE | 0.5 equiv $H_2SO_4$ | 1 | 56 | 25 | 2 | **7** |
| 3 | MTBE | 1 equiv TFA | 1 | 31 | 44 | 0 | **13** |
| 4 | MTBE | 1 equiv TFA | 6 | 8 | 61 | 5 | **22** |
| 5 | MTBE | 2 equiv TFA | 1 | 0 | 58 | 26 | **30** |

[a]Conditions: 1 mmol hydrazone **2a**, additive in 1.5 mL solvent at a reaction temperature of 150 °C (sealed vessel microwave irradiation). [b]Yields are based on quantitative HPLC analysis (%) of the crude reaction mixtures.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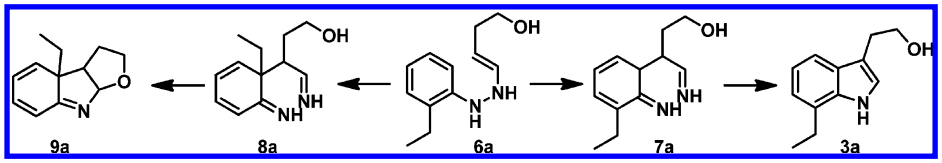
**Scheme 5.** [3,3]-Rearrangement of Ene-Hydrazine 6a



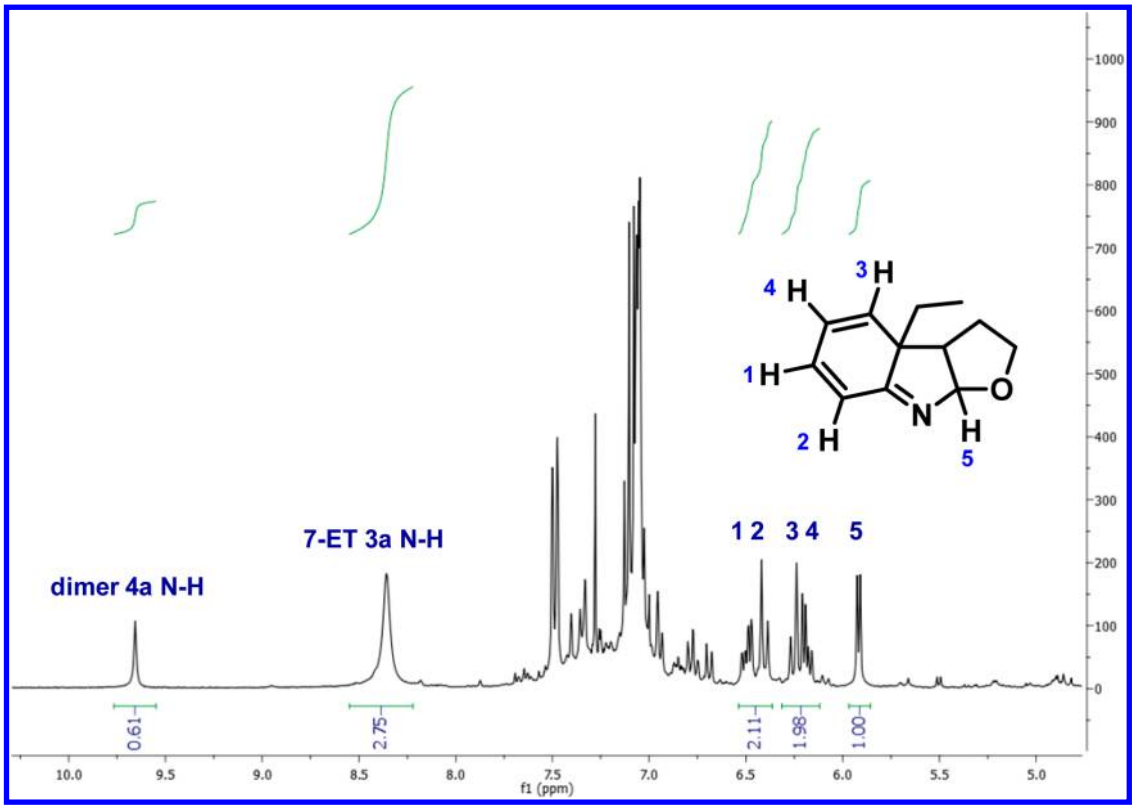
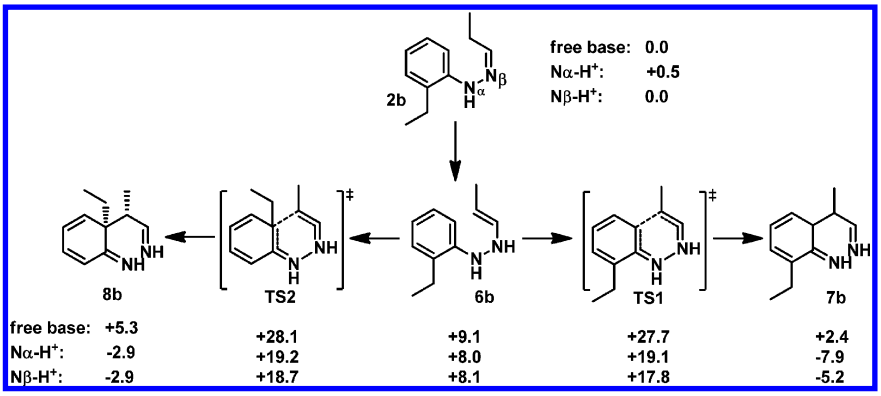




**Figure 5.** $^1$H NMR analysis of a sample containing dienylimine **9a** after extraction of the reaction mixture with sat. $NaHCO_3$/EtOAc. Conditions: 1 mmol 2-ethylphenylhydrazine hydrochloride **1a**, 1 equiv DHF, 1.5 mL MeOH/$H_2O$ 2:1; 20% $H_2SO_4$; 5 min reaction temperature at 130 °C.

**Scheme 6. Relative Free Energies for the Intermediates and Transition Structures Involved in the Uncatalyzed and Proton Promoted Transformation of Hydrazone 2b to Diimine 7b and 8b Calculated at the MP2/6-311+G(d,p) Level**[a]




[a]Relative free energies ($\Delta G$ in kcal mol$^{-1}$) for the uncatalyzed and proton-catalyzed reaction are given relative to the free energy of the free hydrazone or the N$\beta$-protonated hydrazone, respectively.

barrier for the rearrangement to the free position (energy barriers of, respectively, 28.1 and 27.7 kcal mol$^{-1}$ were calculated with respect to the hydrazone).[19,20] Solvation effects using MeOH as solvent were included for geometry optimizations, and frequency analyses using the SMD solvation model (a more detailed description of these calculations with comparison of all calculated energies on MP2 and M06−2X levels are given in the Supporting Information).[21] Protonation on either of the nitrogen atoms decreases the energy barrier for the rearrangement substantially ($\Delta\Delta G^{\ddagger}$ is around 9−10 kcal mol$^{-1}$; Scheme 6). The N$\beta$ protonated pathway is thereby slightly favored by 1.3 and 0.5 kcal mol$^{-1}$ for the attack on the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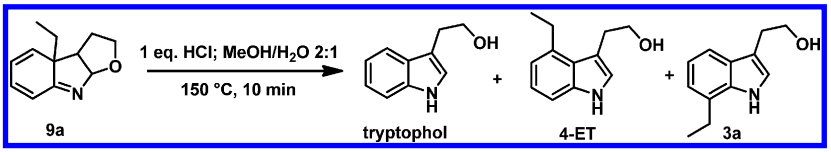
**Scheme 7. Elimination and Migration of the Ethyl Group of Dienylimine 9a**




free and occupied position, respectively. Protonation of the N$\beta$ nitrogen stabilizes the transition structure for the rearrangement to the free position more than the alternative transition structure, and thus, protonation should increase the selectivity towards the desired product. However, the difference in the energy barriers with 0.9 kcal mol$^{-1}$ is still rather low and good regioselectivities for this reaction therefore cannot be expected.

Both elimination[14a,15c] and migration (1,2-[14c,d] and 1,4-migrations[14c]) of the alkyl-group of the dienylimine intermediate with accompanied rearomatization to the dealkylated or isomeric indole derivative were reported. A 1,2-migration of the ethyl group of the protonated dienylimine **9a** to the adjacent carbon would form 4-ET after rearomatization and would explain the origin of the regioisomer of 7-ET detected in the reaction mixtures. However, heating the isolated, crude dienylimine **9a** for 10 min to 150 °C in the presence of an acid in MeOH/$H_2O$ as solvent gave three main products in a roughly 1:3:1 mixture after column chromatography (Scheme 7 and Figure 6). The first product was identified as tryptophol by its mass and by comparison with an authentic sample prepared form phenylhydrazine hydrochloride and DHF. The two other products had the mass of ethyltryptophol and were assigned to 4-ET and 7-ET, respectively, by comparing the HPLC trace of dienylimine **9a** after heating with the HPLCs obtained from the reaction mixture of a 7-ET synthesis and a mixture of a reaction with the 3-ethylphenylhydrazine hydrochloride and DHF (see Figure 6 and Figure S13 in the Supporting Information). 7-ET may be formed from the dienylimine by a sigmatropic [1,5]-shift of the ethyl group or by two consecutive [1,2]-shifts.[22] Interestingly, the dienylimine **9a** was not detected in the reaction mixture by $^1$H NMR analysis in the absence of acids even though the same side products (tryptophol and 4-ET) were observed by HPLC (Figure 6).

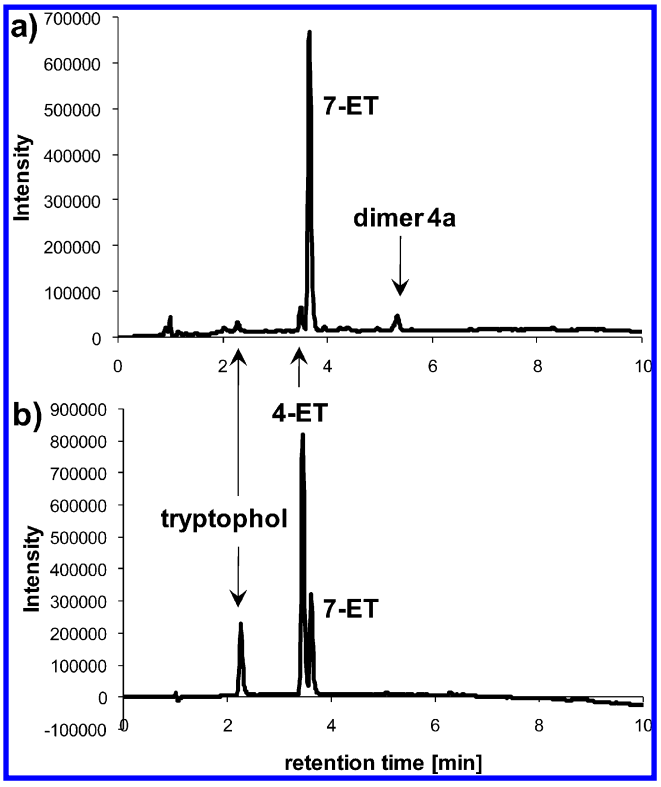


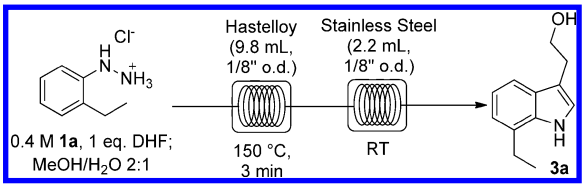

**Figure 6.** Comparison of HPLC traces of reaction mixtures (215 nm) of (a) 7-ET synthesis: Conditions: 1 mmol 2-ethylphenylhydrazine hydrochloride **1a**, 1 equiv DHF, 1.5 mL MeOH/$H_2O$ 2:1; 20 s reaction time at 170 °C (sealed vessel microwave heating) and (b) dienylimine **9a** after heating for 10 min at 150 °C in MeOH/$H_2O$ in the presence of 1 equiv of HCl (after column chromatography).

## CONCLUSIONS

Efforts to synthesize the industrially important building block 7-ET **3a** by a direct reaction of ethylphenylhydrazine hydrochloride **1a** with DHF provided 7-ET in yields of 40−50% (quantitative HPLC). Polymeric material, apparently formed by a follow-up reaction of 7-ET with DHF, was generated in all transformations performed in this study. In addition, two molecules of 7-ET reacted with DHF to form a dimer type structure **4a** under acidic conditions and the [3,3]-rearrangement of the ene-hydrazine to the position occupied by the ethyl-group led to dienylimine **9a** as an isolable side product (this is one of very rare examples where this dienylimine actually could be isolated). Migration of the ethyl-group of the dienylimine **9a** forms 4-ET as a minor side product. Even though no or only small amounts of adduct **4a** were observed when the reaction was performed in the presence of a mild base or without any acidic catalyst, the yields of 7-ET did not increase.

Despite the moderate product yield, it must be emphasized that both the 2-ethylphenylhydrazine **1a** and DHF are inexpensive and readily available starting materials. Furthermore, the developed process is operationally simple, can be executed in the absence of strong acids or bases using an environmentally benign solvent, and importantly, the majority of side products can be removed from the product simply by extraction. Residence times of only a few minutes are required at temperatures of 150−170 °C, thus allowing a high throughput even with rather compact reactors with residence loops of small volume. The final experimental setup used in the present study comprising a single syringe pump, a Hastelloy loop immersed into an oil bath, a short stainless steel loop to cool the processed reaction mixture, and a back-pressure regulator (Scheme 8). The crude product was isolated by

**Scheme 8. Continuous Flow Synthesis of 7-ET**





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extraction, and further purification could readily be accomplished by precipitation of polymeric material, remaining in the product after extraction, with unpolar solvents, such as a mixture of MTBE/petroleum ether (PE). Thus, heating a solution of the hydrazine hydrochloride **1a** (0.4 M) and 1 equiv of DHF in MeOH/$H_2O$ 2:1 for 3 min at 150 °C produced 39% of 7-ET **3a** (corrected for purity based on quantitative HPLC) after extraction and treatment of the extracted product with MTBE/PE in a HPLC purity (215 nm) of 92%. Analytically pure and crystalline 7-ET was obtained by extraction and subsequent column chromatography in 41% product yield.

## EXPERIMENTAL SECTION

**General.** $^1$H NMR spectra were recorded on a Bruker 300 MHz instrument. $^{13}$C NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts ($\delta$) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. GC-FID analysis was performed on a Trace-GC (ThermoFisher) with a flame ionization detector using a HP5 column (30 m × 0.250 mm × 0.025 $\mu$m). After 1 min at 50 °C, the temperature was increased in 25 °C min$^{-1}$ steps up to 300 °C and kept at 300 °C for 4 min. The detector gas for the flame ionization is $H_2$ and compressed air (5.0 quality). GC-MS spectra were recorded using a Thermo Focus GC coupled with a Thermo DSQ II (EI, 70 eV). A HP5-MS column (30 m × 0.250 mm × 0.025 $\mu$m) was used with Helium as carrier gas (1 mL min$^{-1}$ constant flow). The injector temperature was set to 280 °C. After 1 min at 50 °C, the temperature was increased in 25 °C min$^{-1}$ steps up to 300 °C and kept at 300 °C for 4 min. Low-resolution mass spectra were obtained on a Shimadzu LCMS-QP2020 instrument using electrospray ionization (ESI) in positive or negative mode. Analytical HPLC (Shimadzu LC20) analysis was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 $\mu$m) at 37 °C using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.0 mL min$^{-1}$ (the following gradient was applied: linear increase from solution 30% B to 100% B in 8 min, hold at 100% solution B for 2 min), or on a Agilent 1100 with a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 $\mu$m) using a mobile phase A (water/methanol/THF 700:160:60 (v/v/v)) and B (water/acetonitrile 300:700 (v/v)) at a flow rate of 1.3 mL min$^{-1}$ (isocratic 62% mobile phase A and 38% mobile phase B). For quantitative HPLC, calibration curves were established with analytically pure 7-ET as calibration standard. These calibration curves were used to translate the integrated peak areas from the HPLC analysis into absolute quantities. TLC analyses were performed on precoated (silica gel 60 HF254) plates. All chemicals were purchased from commercial sources and were used without further purification. 2-Ethylphenylhydrazine hydrochloride and DHF were purchased from Shandong Xinhua Pharmaceutical Company Limited and Zhejiang Realsun Chemical Industry Co. Ltd., respectively. Chromatographic purification was done on an automated flash-chromatography system (SP1, Biotage) using cartridges packed with KP-SIL, 60 Å (40−63 $\mu$m particle size), and ethyl acetate/petroleum ether mixtures as eluents.

**Three Feed Continuous Flow Reactions (Scheme 2).** 2-Ethylphenylhydrazine hydrochloride **1a** (144.5 g; 0.829 mol) was dissolved in ethylene glycol/water (656.2 g/161.4 g) and 25% aqueous NaOH was added (134.7 g; 0.842 mol NaOH). DHF (56.7 g; 0.805 mol) was stirred at room temperature with HCl (0.74 g 32% aqueous HCl; 6.52 mmol) in ethylene glycol/water as solvent (723.2 g/288.8 g). The two solutions were introduced into a plate microreactor (Flowplate A6 reactor with SZ mixers, 2.8 mL) by two gear pumps (Reglo-Z; Ismatec) and the combined solution passed through a first residence coil (2 mL PFA tube, 1/8 in. o.d.). 50% $H_2SO_4$ was fed in by a syringe pump (MDP1f; MMT GmbH) and was combined with the effluent reaction mixture of the first residence coil in a second plate microreactor (Corning glass reactor NIM 06-017-C, 5.6 mL). The mixture passed through a second residence coil (1/8 in. o.d., 38 mL). The two plate reactors and the two residence coils were heated to the temperature indicated in the Tables 1 and 2. The reaction mixture was finally cooled to room temperature in a PFA tube (1/8 in. o.d., 2 mL) and collected in a flask under nitrogen. The processed reaction mixtures were neutralized with NaOH to pH7 and the crude 7-ET was isolated by extraction with $H_2O$/MTBE. The isolated product was analyzed by quantitative HPLC.

**One Feed Continuous Flow Reactions (Scheme 8).** 2-Ethylphenylhydrazine hydrochloride **1a** was dissolved in the respective solvent. Additives and DHF were added under stirring. The reaction mixture was pumped through a Hastelloy tube reactor (9.8 mL, 1/8 in. o.d.), which was heated in an oil-bath, by a syringe pump (ISCO; Teledyne). The reaction mixture passed a stainless steel coil (2.2 mL, 1/8 in. o.d.) which was cooled in a water bath to room temperature and the reaction mixture left the reactor through a back-pressure regulator (30 to 50 bar). The processed reaction mixture was analyzed by quantitative HPLC. The crude 7-ET was isolated by extraction with MTBE/$H_2O$ or toluene/$H_2O$ and the isolated product was again analyzed by HPLC. Additional purification can be accomplished by precipitation of polymeric material remaining in the product after extraction with unpolar solvents, such as MTBE/PE.

**Batch Reactions.** 2-Ethylphenylhydrazine hydrochloride **1a** was dissolved in the respective solvent. Additives and DHF were added under stirring. The reaction mixture was heated to the desired temperature either in a Biotage Initiator 8 EXP microwave reactor or on a hot plate. The processed reaction mixture was analyzed by HPLC. The crude 7-ET was isolated by extraction with MTBE/$H_2O$ or toluene/$H_2O$ and the isolated product was again analyzed by HPLC.

*7-Ethyltryptophol **3a**.* $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.27 (s, 1H), 7.52 (d, $J$ = 7.2 Hz, 1H), 7.17−7.04 (m, 3H), 3.93 (t, $J$ = 6.4 Hz, 2H), 3.06 (t, $J$ = 6.4, 2H), 2.88 (q, $J$ = 7.6 Hz, 2H), 1.39 (t, $J$ = 7.6 Hz, 2H); MS (pos. ESI): $m/z$ = 190 (M +H$^+$).

*Adduct **4a**.* $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 9.35 (s, 2H), 7.35 (d, $J$ = 7.6 Hz, 2H), 7.05 (t, $J$ = 7.5 Hz, 2H), 6.97 (d, $J$ = 7.0 Hz, 2H), 4.68 (t, $J$ = 7.7 Hz, 1H), 3.98 (t, $J$ = 5.2 Hz, 4H), 3.61 (t, $J$ = 5.3 Hz, 2H), 3.20−3.05 (m, 4H), 2.76 (q, $J$ = 7.4 Hz, 4H), 2.48 (br s, 3H), 2.44−2.35 (m, 2H), 1.67−1.51 (m, 2H), 1.30 (t, $J$ = 7.7 Hz, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 137.19, 134.66, 128.00, 126.38, 120.05, 119.33, 115.71, 108.36, 62.81, 62.41, 36.62, 30.70, 29.98, 27.60, 23.82, 13.75;MS (pos. ESI): $m/z$ = 449 (M+H$^+$).

*Dienylimine **9a**.* $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 6.48 (ddd, $J$ = 9.7, 5.2, 0.8 Hz, 1H), 6.39 (d, $J$ = 9.7 Hz, 1H),6.23 (d, $J$ = 9.4 Hz, 1H), 6.17 (ddd, $J$ = 9.5, 5.2, 1.0 Hz, 1H),5.91 (d, $J$ = 4.8 Hz, 1H), 3.88−3.79 (m, 1H), 3.57 (dd, $J$ = 16.0, 7.6 Hz, 1H), 2.78 (dt, $J$ = 10.3, 5.2 Hz, 1H), 1.91 (ddt, J = 12.7, 10.1, 7.6 Hz, 1H), 1.71−159 (m, 1H), 1.59−1.47 (m, 1H), 1.33 (dt, $J$ = 10.6, 5.9 Hz, 1H), 0.87 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (75


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MHz, $CDCl_3$) $\delta$ = 179.89, 138.30, 134.64, 123.47, 122.08, 103.47, 67.18, 60.75, 49.97, 34.18, 28.44, 9.33; MS (pos. ESI): $m/z$ = 190 ($M+H^+$).

*Butanal, 4-Hydroxy-, 2-(2-Ethylphenyl)hydrazone* ***2a.*** 10 mmol of 2-ethylphenylhydrazine hydrochloride were dissolved in 20 mL THF/$H_2O$ 1:1. One equivalent of DHF was added and the mixture was stirred for 35 min at room temperature. The mixture was extracted with $Et_2O/H_2O$ to provide the crude hydrazone **2a** as a orange oil in 76% product yield. The product was further purified by flash chromatography ($CHCl_3$/MeOH) to give 62% hydrazone **2a**. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ =7.51−7.37 (m, 1H), 7.26−7.08 (m, 3H), 6.89−6.82 (m, 1H), 3.74 (t, $J$ = 6.2 Hz, 2H), 2.60−2.34 (m, 4H), 1.92−1.81 (m, 2H), 1.27 (t, $J$ = 7.5 Hz, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ = 142.46, 141.62, 128.12, 127.10, 126.01, 119.64, 112.97, 62.25, 29.53, 28.89, 23.60, 13.31; MS (pos. ESI): $m/z$ = 207 ($M+H^+$).

## ■ ASSOCIATED CONTENT

### Supporting Information

Additional experimental information. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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(20) It should be mentioned that density functional theory (DFT) calculations at the M06−2X/6-311+G(d,p) level greatly overestimated the energy barriers for the [3,3]-rearrangement (see Table S7 in the Supporting Information and ref 19 for details). In addition, the DFT calculation failed to predict the concerted nature of the sigmatropic rearrangement of the N$\beta$-protonated ene-hydrazine intermediate to the carbon atom occupied by the ethyl group and favored N-N bond cleavage without C-C bond formation instead.

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(22) The product derived from the model substrate **2b** after cyclization of the diimine **8b** and expulsion of ammonia would be a nonaromatic **3a**-ethylindole. The energy barrier for the 1,2-migration of the ethyl group of this compound to form the 4-ethylindole was calculated at the MP2/6-311+G(d,p) level to be only14.7 kcal $mol^{-1}$ and is thus lower than the barrier calculated for the [3,3]-rearrangement. Obviously, formation of the cyclic hemiaminal ether **9a**, rather than the **3a**-ethylindolyl ethanol, makes the dienylimine sufficiently stable to be an isolable compound. This is one of only very rare examples where a dienylimine of this kind actually could be isolated. See also ref 15.