Organic Process Research & Development **2003**, *7,* 10–16

Articles

Process Design and Scale-Up of the Synthesis of 2,2′:5′,2′′-Terthienyl

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Abstract:

The objective of this study was the design of a scaleable process for the synthesis of 3−4 mol of α-terthienyl from 2,5-dibromothiophene and thienylmagnesium bromide in a 10-L stirred tank reactor. In THF the Grignard reagent, thienylmagnesium bromide, was readily formed from 2-bromothiophene and magnesium. To avoid crystallization the maximal concentration was limited to 1.4 M. Furthermore, the novel combination of THF and $NiCl_2$[bis(diphenylphosphino)benzene] allows for fast double coupling of the Grignard reagent with 2,5-dibromothiophene. The concentration of catalyst could be limited to 0.5 mol % based on the amount of 2,5-dibromothiophene. An adapted workup procedure was developed, in which *n*-octane was used to separate the magnesium salts from the desired product. The reaction was performed in a (semi)batch-wise operated reactor. A global model for the coupling step proved to predict the results at 0.1-, 1-, and 10-L scales very accurately. The heat of reaction evolved in the coupling step was valorized and could be handled easily. Mixing of the feed stream and the reactor content proved to be another important factor in the scaling-up of the α-terthienyl synthesis.

Introduction

In the fine chemical industry most chemicals are produced in (semi)batch-wise operated multipurpose plants. Short-market life cycles and relatively low production volumes characterize the wide variety of chemicals produced in these plants. The demand for a short time-to-market of new chemicals is a challenge for batch process design. A fast and systematic approach is required in the scale-up that allows an early recognition of scale-up issues before (pilot) plant process implementation.[1] To develop tools and a methodology for fine chemical scale-up of catalytic batch processes, the synthesis of 2,2′:5′,2′′-terthienyl (α-terthienyl) was selected. This compound is one of the most general building blocks in the field of conducting polymers.[2]

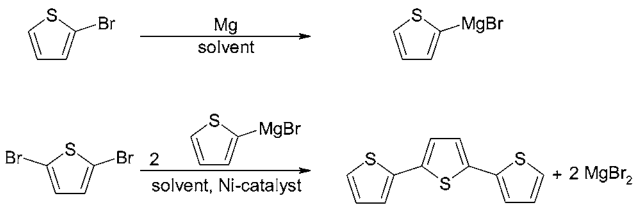

Figure 1. **Selected two-step synthesis of α-terthienyl: a Grignard synthesis of thienylmagnesium bromide followed by its Ni(0)-catalyzed coupling with 2,5-dibromothiophene.**

Many synthetic routes towards α-terthienyl are reported,[3] but most of them are not applicable to large-scale production since hazardous solvents or reactants or both, or too many reaction steps with low yields are involved. A two-step preparation involving the formation of thienylmagnesium bromide and its subsequent Ni(0)-catalyzed coupling with 2,5-dibromothiophene (TBr_2) was selected, see Figure 1.

The optimization comprised amongst other things the selection of a suitable solvent—preferably the same in both steps, the concentration of the reactants, the reaction temperatures and, in addition, an efficient catalyst for the coupling step. Since both reaction steps are exothermic, a reaction calorimetric study was performed to determine the heat of reaction. With the results found during the optimiza-

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(1) (a) Hulshof, L. A. The Red Queen's Race in Fine Chemical Scale-Up. Presented at the 3rd International Conference on Organic Process Research and Development, Montreal, Canada, July 10−12, 2000 (this article describes the contours of a novel methodology in fine chemical scale-up as derived from an analysis of the causes of various batch surprises upon scale-up). (b) Nollen, E. A. C. *Continuous versus Batch in Fine Chemicals Industry*; Stan Ackermans Institute: Eindhoven, The Netherlands, 1999. (c) Spanjers, M. A. J. C. M. *A Novel Approach for Fine Chemicals Process Development*; Stan Ackermans Institute: Eindhoven, The Netherlands, 2000 (examples of b and c are related to the production of *R,S*-*β*-acetylthioisobutyrate).

(2) (a) Roth, S. R. *One-Dimensional Metals*; VCH: Weinheim, 1995. (b) Miller, J. S. *Adv. Mater.* **1993**, *5*, 587. (c) McQuade, D. T.; Pullen, A. E.; Swager, T. M. *Chem. Rev.* **2000**, *100*, 2537. (d) Pei, J.; Yu, W. L.; Huang, W. *Macromolecules* **2000**, *33*, 2462. (e) Semenikhin, O. A. *Electrochim. Acta* **2001**, *47*, 171. (f) Leclerc, M.; Donat-Bouillud, A. *Chem. Mater.* **1997**, *9*, 2815. (g) Buvat, P. *Synth. Met.* **1999**, *101*, 17. (h) Sicot, L.; Lorin, F. A.; Nunzi. J. M.; Raimond, P. *Synth. Met.* **1999**, *102*, 991. (i) Miller, L. L.; Mann, K. R. *Acc. Chem. Res.* **1996**, *29*, 417. (j) Gangopadhyay, R.; De, A. *Chem. Mater.* **2000**, *12*, 608.

(3) Tourillon, G. *Handbook of Conducting Polymers*; Skotheim, T. A., Ed.; Marcel Dekker: New York, 1986. α-Terthienyl has been prepared by ring-closure of 1,4-bis(2-thienyl)-butane-1,4-dione[14] and of 1,4-bis(2-thienyl)-1,3-butadiyne.[15] It has also been prepared by Pd-catalyzed aryl−aryl coupling of the Stille[16] and Suzuki type.[17] Most frequently, however, the Ni-catalyzed aryl−aryl Kumada coupling is selected.[18] While Pd catalysts serve as aryl−aryl coupling mediators with boronates and stannanes (Suzuki; Stille), the use of nickel catalysts definitely is to be preferred with Grignard reagents (Kumada). In comparison with other homogeneous aryl−aryl coupling methods the described Ni-dppp-catalyzed coupling of 2-thienylmagnesium bromide with 2,5-dibromothiophene in diethyl ether necessitates minor quantities of catalyst, presumably reflecting the intrinsic high reactivity of the system aryl Grignard-Ni^0-aryl halide. The replacement of the solvent (diethyl by dipropyl ether),[19] of the halide (dibromide by diiodide)[20] and of the catalyst (Ni-dppp by Ni-dppf)[21] has been investigated.

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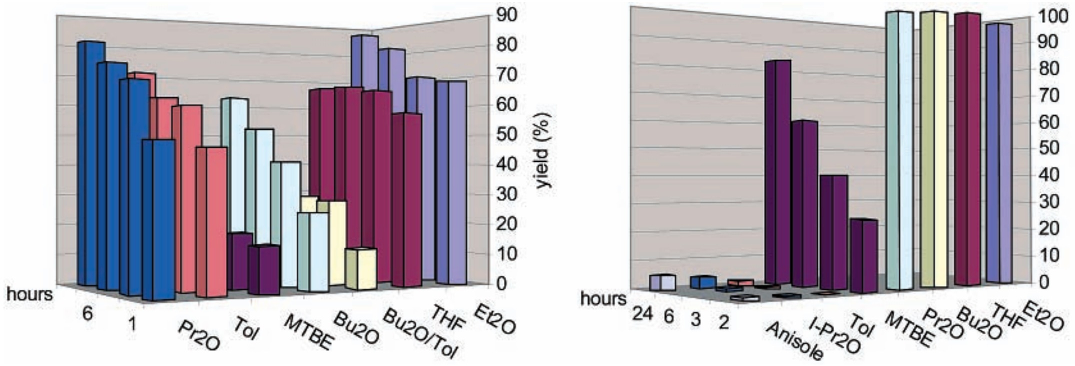

Figure 2. **Yields of products in the formation of the Grignard reagent (right), and of α-terthienyl (left) respectively in various solvents as a function of time, 1.5 mol % $NiCl_2$(dppp) was used as catalyst in the coupling step. The temperature was at reflux for diethyl ether (35 °C) and THF (67 °C); other solvents were heated to 90 °C. At 100% conversion the concentration of the Grignard reagent was approximately 2 mol/L.**

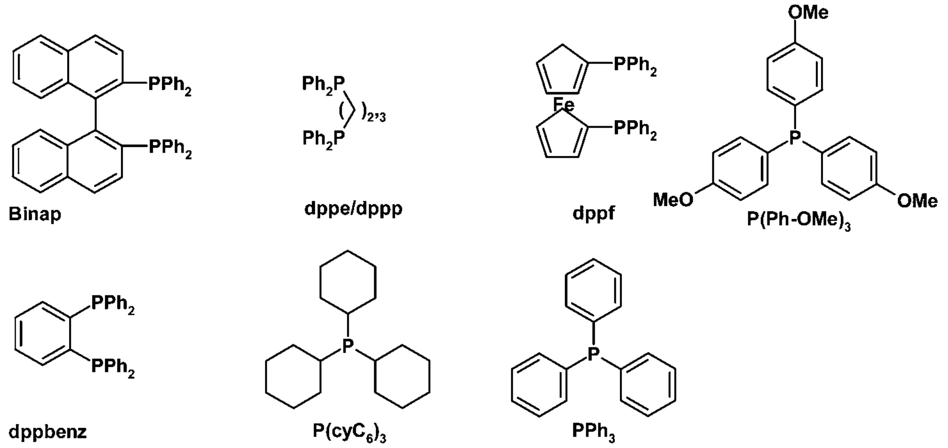

Figure 3. **Various ligands screened to tune the selectivity and activity of the Ni catalyst.**

tion of the reaction system and kinetic data for the coupling reaction a semibatch process was designed for the production of α-terthienyl on a 10-L scale in a fully automated (semi)-batch-wise operated reactor.[4]

Optimization Studies

Solvent Selection. Most nickel-catalyzed coupling reactions between a Grignard reagent and a bromo compound are carried out in diethyl ether in the literature.[5] Since diethyl ether is not appropriate for scale-up, a number of more applicable solvents were selected. The selected solvent should be cheap, not harmful to the environment, and easy to recover. Additionally, the reactions should proceed with high conversion rates in the solvent to increase productivity and reduce production costs.

Ethers are known to be good solvents for both the Grignard and coupling reactions; therefore, a screen of ethereal solvents was carried out. The length and type of the ether alkyl chains influenced the results as is depicted in Figure 2.

Several solvents performed well in the Grignard step as becomes apparent from Figure 2. For the coupling step diethyl ether remained the best solvent, with di-*n*-propyl ether and THF as good alternatives.

The differences in yields are caused by variations in the solubility of the catalysts and in stabilization by the solvent. Finally, THF was selected as the most favorable solvent for both steps since it gave reasonably high yields and is commercially available in large quantities.

Glymes have been considered as solvent for this process. However, it turned out that the ligating power of monoglyme is so high that it stabilizes the active nickel catalyst, giving rise to a colorless and inactive $NiCl_2$•monoglyme complex. Hence, glymes were also abandoned for the formation of the Grignard reagent.

Catalyst Selection. Variation of the phosphine ligands attached to nickel changes the activity of the nickel catalysts. Apart from steric and electronic effects of more or less electron-rich ligands the bite angle of the ligand plays a crucial role.[6] Several ligands (Figure 3) were selected for screening on selectivity and productivity. The results are depicted in Figure 4.

A substantial difference in activity of the catalysts in different solvents was observed (see Figure 4). In THF the best catalysts seem to be $NiCl_2$(dppe) and particularly $NiCl_2$-

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(4) (a) This reactor is described in: Soldaat, A. *Chemisch2weekblad* **1999**, *8*, 18. (b) Hersmis, M. C.; Spiering, A. J. H.; Waterval, R. J. M.; Meuldijk, J.; Vekemans, J. A. J. M.; Hulshof, L. A. *Org. Process Res. Dev.* **2001**, *5*, 54.

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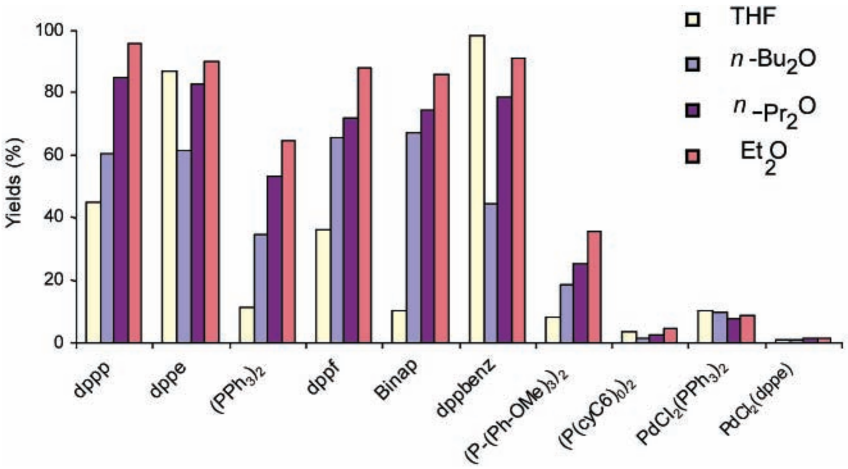

Figure 4. **Screening tests for various catalysts in selected solvents (THF, di-*n*-butyl ether, di-*n*-propyl ether, and diethyl ether). Except for the two at the right, $NiCl_2$ is used as metal center. The procedure for the screening tests is given in the Experimental Section.**

(dppbenz). The bite angles of these ligands are comparable. In di-*n*-butyl ether and di-*n*-propyl ether several catalysts showed a similar but inferior activity.

Optimization of the Reaction System. In the screening tests for the solvent and catalyst the combination of THF with $NiCl_2$(dppbenz) gave remarkably high yields of the desired α-terthienyl. This system was selected for further optimization tests. Factors such as concentration of the catalyst, concentration of 2,5-dibromothiophene in the reaction mixture, temperature of the reaction mixture, and the addition rate of the Grignard reagent have been included in this study.

In Figures 5−10 the yields are given as a function of time.

Higher temperatures increased the reaction rate as expected. In experiments at low temperatures the activity of the catalyst started to decrease when the conversion reached about 60%. At elevated temperatures this fall in performance was not observed. This is presumably due to product inhibition by a reversible coordination of α-terthienyl to the Ni center.

At room temperature an optimum addition time of 15 min for the Grignard reagent was determined on 0.1-L scale. Faster addition resulted in product inhibition again, while slower addition diminished the concentration of the Grignard reagent and hence the reaction rate. When the temperature was increased, this effect disappeared. At this addition rate of the Grignard reagent the rate of heat production was modest, and no severe precautions had to be taken to control the reaction temperature.

The results in Figure 7 demonstrate that the reaction rate with decreasing amounts of catalyst decreases more than proportionally. The lower productivity with 0.5 mol % catalyst could be improved by an increase in temperature.

The concentration of the TBr_2 influenced the reaction rate, see Figure 8. Another effect of high concentration was a decrease in selectivity, giving more 2,2′-bithiophene as the major byproduct. Therefore, the maximal concentration of TBr_2 was fixed at 0.4 M.

Increasing the excess of the Grignard reagent favored the reaction rate. Unfortunately, the formation of undesired 2,2′-bithiophene was also related to the amount of Grignard reagent used. To guarantee a high selectivity the excess of Grignard reagent was set at 5%.

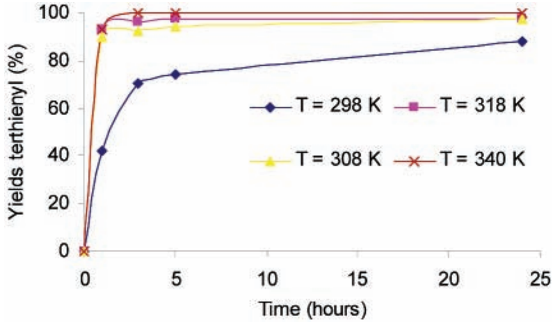

Figure 5. **Influence of the temperature in K, $[TBr_2]_0$ = 0.4 M, 0.5% $NiCl_2$(dppbenz), t_{add} (Grignard) = 15 min.**

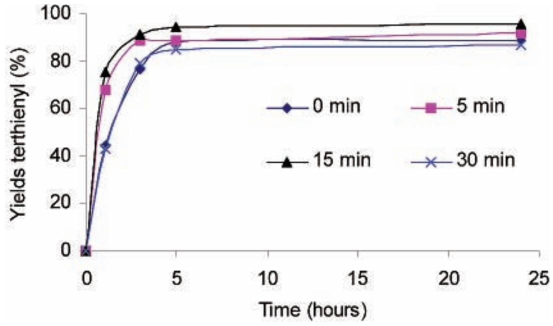

Figure 6. **Influence of the addition time of the Grignard reagent, $[TBr_2]_0$ = 0.4 M, 1.5% $NiCl_2$(dppbenz), 25 °C.**

Conclusions of the Optimization Study. The coupling reaction should be performed at reflux temperature (see Figure 5). The addition rate is not important for the final yield when a sufficiently high temperature is applied, and it allows control of the temperature (see Figure 6). The amount of catalyst can be reduced to 0.5 mol % (see Figure 7) at reflux, and the catalyst cannot be recycled. Recycling of the catalyst at higher loadings was not considered. Finally, a concentration above 0.4 M of the starting material gives lower yields (see Figure 8).

On the basis of the above-mentioned conclusions a reaction procedure was developed at 100-mL scale (see Experimental Section).

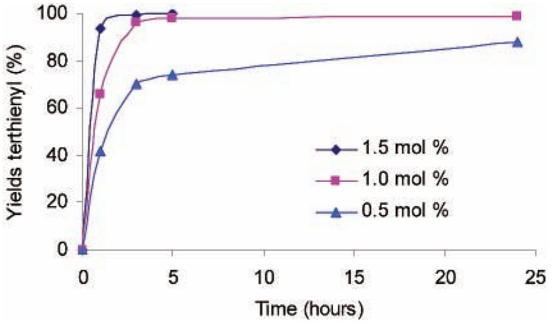

Figure 7. **Influence of the amount of catalyst, $[TBr_2]_0 = 0.4$ M, t_{add} (Grignard) = 15 min, 25 °C.**

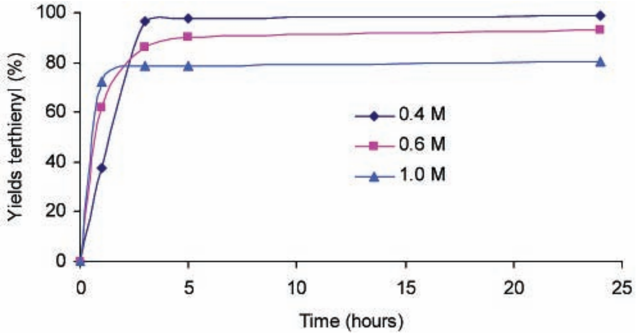

Figure 8. **Influence of $[TBr_2]_0$, 0.5% $NiCl_2$(dppbenz), t_{add} (Grignard) = 15 min, 25 °C.**

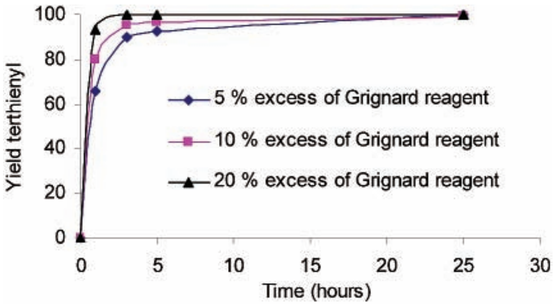

Figure 9. **Influence of the excess of the Grignard reagent, $[TBr_2]_0 = 0.4$ M, 0.5% $NiCl_2$(dppbenz), t_{add} (Grignard) = 15 min, 25 °C.**
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Workup

The traditional workup for reactions involving Grignard reagents is the addition of water, followed by an extraction step.[7] This method could not be used for a scaleable process since it was found that THF formed soluble complexes with magnesium salts. These complexes remained in the organic phase and led to an off-spec product. A new workup method had to be developed. Addition of *n*-octane, removal of THF by distillation, and heating the *n*-octane to reflux led to dissolution of all α-terthienyl. After siphoning off the α-terthienyl solution, the precipitated magnesium salts were washed with hot *n*-octane (110 °C) twice. The total volume of *n*-octane (approximately 1.5 times the original amount of THF) was allowed to cool to room temperature, yielding bright yellow α-terthienyl as product (95% yield). The purity of the α-terthienyl could be improved from 95 to 99% by recrystallization either from *n*-octane, *n*-hexane, or *n*-butanol as depicted in Figure 10.

Two crystallization cycles from *n*-octane yielded α-terthienyl with the desired purity.

Scale-Up of the α-Terthienyl Synthesis. In the scale-up of the α-terthienyl synthesis three aspects proved to be important. First the mixing of the feed stream, second the heat transfer to remove the heat of reaction, and finally the handling of the suspension containing magnesium salts during workup.

The desired degree of feed-stream mixing was determined by visual inspection and was accomplished at a stirring speed of 400 rpm at 1-L scale. At this stirring speed the heat transfer between the reactor content and the jacket was sufficient to remove the heat of reaction. The heats of reaction for the Grignard synthesis and the coupling step were measured with a Mettler Toledo RC1/e reaction calorimeter. The results are shown in Table 1. The adiabatic temperature rise (ΔT_{ad}) was calculated in the usual way.[8]

By feeding the Grignard reagent to a solution of 2,5-dibromothiophene the heat that had to be removed could be controlled. The feeding time was calculated by simultaneous solution of the mass and energy balances:

$$\frac{dV(t)}{dt} = F_{in} \tag{1}$$

$$\frac{d(V(t)C_A)}{dt} = F_{in}C_{A,in} + V(t)R_A \tag{2}$$

$$\frac{d(T_r m(t)C_p(t))}{dt} = F_{in}\rho_{in}C_{p,in}(T_{in} - T_r) + UA(T_j - T_r) + (-\Delta_R H R_A V(t)) \tag{3}$$

where

F_{in} = feed stream (m^3/s)
C_A = concentration of the feed ($kmol/m^3$)
m = reaction mass (kg)
R_A = reaction rate of the feed ($kmol/m^3 \cdot s$)
C_p = heat capacity of the reactor contents (1200 J/kg·K)
$\Delta_r H$ = reaction heat production (kJ/kmol)
U = heat exchange coefficient (45 $J/m^2 \cdot K \cdot s$)
A = heat exchange area (m^2)
T_j = temperature of the jacket (K)
T_r = temperature of the reaction mass (K)

The feeding time is governed by the requirement that the temperature of the reaction mixture should be 67 °C. This is theoretically met when the addition times for the Grignard reagent were 35 min at 1-L and 65 min at 10-L scale, respectively. In practice the addition times were shorter.[9]

The magnesium salts formed during the reaction precipitated when *n*-octane was fed to the reactor. These salts showed a tendency to stick to the reactor wall when mixing was not efficient. A pitched-blade impeller was used, and according to measurements the lowest stirring rate to keep

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(7) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. In *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Vogel, A. I., Ed.; Longman Scientific & Technical: Harlow, UK; Wiley: New York; 1989.

(8) $\Delta T_{ad} = -\frac{\Delta_r H C_0}{m C_p}$
with $\Delta_r H$ = heat of reaction (kJ/mol), C_0 = total amount of the starting material (mol of 2-bromothiophene and 2,5-dibromothiophene in the Grignard synthesis and the coupling step, respectively), m = total mass of the reaction mixture (kg), C_p = heat capacity of the reactor contents (kJ/kg·K).

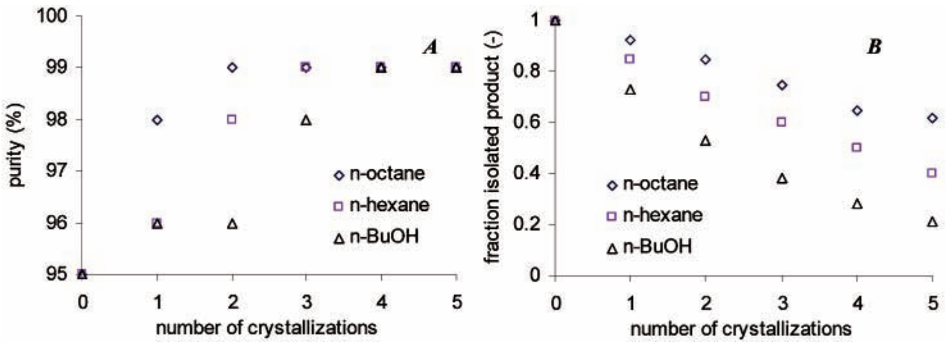

Figure 10. **Purity of α-terthienyl obtained after repeated crystallizations (A) and the fraction of isolated product, compared to the initial amount of crude α-terthienyl (B).**

Table 1. **Reaction enthalpies and the adiabatic temperature rise for both reaction steps**

	C_0 (mol)	$\Delta_r H$ (kJ/mol)	M (kg)	C_p (kJ/kg·K)	ΔT_{ad} (°C)
Grignard synthesis	0.84 (2-bromothiophene)	−471.90[a]	0.650	1.85	329.64
coupling step	0.40 (2,5-dibromothiophene)	−248.13[b]	0.900	2.03	54.32

[a] Based on 2-bromothiophene. [b] Based on 2,5-dibromothiophene.

the solids in suspension was 360 rpm. According to the "Zwietering" relation 4 a just-suspended stirring rate (N_{min}) of 380 rpm was predicted.[10]

$$N_{min} = S_1 \upsilon^{0.1} d_p^{0.2}\left(g\left(\frac{\rho_s - \rho_l}{\rho_l}\right)\right)^{0.45}\left(100\frac{m_s}{m_l}\right)^{0.13}\left(\frac{T}{D}\right)S_2 D^{-0.85} \quad (4)$$

where

N_{min} = lowest stirring rate (rpm)
D = diameter of the impeller (m)
S_1, S_2 = constants (for the Rushton turbine: $S_1 = 1.4$, $S_2 = 1.5$; pitched-blade: $S_1 = 0.9$, $S_2 = 1.5$)
ν = kinematic viscosity (m²/s)
d_p = particle diameter (m)
g = gravity constant (m/s²)
ρ_s, ρ_l = density of the solid and liquid phase (kg/m³)
m_s, m_l = total mass of solids and liquid, respectively (kg)
T = reactor diameter (m)

The following relations for the cake resistance (r) and filterability (k) could be used to predict the behavior of a suspension upon filtration,[11] and this could be used in the selection of a proper filtration unit:

$$r = t_{filter}\frac{2\Delta PA}{HV\eta} \quad (5)$$

$$k = \frac{HV}{At_{filter}\Delta P} \quad (6)$$

where

t_{filter} = filtration time (s)
ΔP = pressure drop (9×10^4 Pa)
A = filtration area (2×10^{-3} m²)
H = cake height (m)
V = filtration volume (1×10^{-4} m³)

In Table 2 the cake resistance and filterability are collected for three different suspensions. The cake resistance and filterability determine the filtration type at different scales.[12]

The filterability and cake resistances of various suspensions shown in Table 2 indicate that a good separation between the solid and liquid phases is possible by pressure filtration or centrifugation.

The synthesis of α-terthienyl was performed on 1-L scale according to the optimized recipe as mentioned before. The yields were comparable to the small-scale experiments, and the reaction heats could be handled smoothly. The results of the 1-L experiments are summarized in Table 3.

To ensure the control of the temperature in the reactor the Grignard reagent was fed over 40 min. In the first run it was noticed that mixing between the feed stream and the reactor content was very poor. In the second and third run, mixing was improved by higher impeller speeds and an increased clearance between the pitched-blade impeller and the reactor bottom. The overall yield of isolated α-terthienyl after crystallization was in all cases between 90 and 92% based on 2,5-dibromothiophene (98% purity).

Ten-Liter Experiment. On 10-L scale[4] the recipe was identical to the procedure used at 1-L scale multiplied by a factor of 6 (maximal filling of the reactor). The stirring speed during the reaction was scaled according to eq 7[13]

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(9) The addition time of the 10-L run was estimated from the mass and energy balances to be 65 min and turned out to be 60 min, whereas the addition time for 1-L scale was estimated to be 35 min, and in practice 40 min. The addition times for the Grignard reagent were estimated under the requirement that the temperature of the reaction mixture was 67 °C (reflux). For 1000-L scale the addition time was estimated to be 4 h. No chances of accumulation in the experimentals were ever observed. The temperature rise after additions was complete before heating to reflux was started. On larger scale when the Grignard would be added at higher temperatures, reflux would be advantageous for even a shorter addition time due to the removal of heat by improvement of the heating transfer capacity of the condenser.

(10) Zwietering, Th. N. *Chem. Eng. Sci.* **1957**, *8*, 244.

(11) (a) Svarovsky, L. *Kirk-Othmer Encyclopedia of Chemical Technology*; John Wiley & Sons: New York, 1994. (b) Meeten, G. H.; Smeulders, J. B. A. F. *Ind. Eng. Chem. Res.* **1996**, *35*, 4810. (c) Motta Raimondo (Oxon Italia Spa.). CH623057, May 15, 1981.

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(13) Custers, J. P. A.; Hersmis, M. C.; Meuldijk, J.; Vekemans, J. A. J. M.; Hulshof, L. A. *Org. Process Res. Dev.* **2002**, *6*, 645.

Table 2. **Filtration times, cake heights, cake resistance, and filterability for different suspensions**

run	filtration times (s)	cake heights (m)	cake resistance (m^{-2})	filterability (m^3/kg)
magnesium salts in a solution of α-terthienyl in THF	64	0.024	1.92×10^{12}	1.88×10^{-9}
magnesium salts in *n*-octane at 110 °C	28	0.014	1.36×10^{12}	2.91×10^{-9}
α-terthienyl in *n*-octane at room temperature	16	0.013	6.38×10^{12}	5.23×10^{-9}

Table 3. **One-liter synthesis of α-terthienyl, 200 mL of THF with TBr_2 in the reactor, 600 mL of 1.4 M Grignard solution is added in 40 min, pitched-blade impeller**

run	[Br_2T] (mol/dm^3)	% catalyst ($NiCl_2$[dppbenz])	excess of Grignard reagent (%)	temperature (°C)	stirring speed (rpm)	yield T_3 (%)[a]
1	0.5	0.5	10	30−67	300	95
2	0.5	0.5	5	40−67	400	95
3	0.3	0.25	5	40−67	400	98

[a] After 1.5 h, based on 2,5-dibromothiophene and determined by GC analysis.

$$\left(\frac{N_{\min}}{D^{-0.85}}\right)_{s} = C\left(\frac{N_{\min}}{D^{-0.85}}\right)_{l} \tag{7}$$

where C = correction factor, $C = 0.9$ for $V < 10$ L, and $C = 1$ for $V > 10$ L for a pitched-blade impeller.

With eq 7 the stirring speed needed for the suspension of particles formed during the reaction was calculated to be at least 280 rpm on a 10-L scale. The actual stirring rate applied in the 10-L experiment was also 280 rpm.

The Grignard reagent was fed to the 2,5-dibromothiophene solution in 60 min. The heat of reaction was used to heat up the reactor content as could be calculated from eqs 1−3. After addition of the entire amount of Grignard reagent, the reaction mixture was stirred for another 30 min at reflux temperature, leading to complete conversion of the 2,5-dibromothiophene.

The conversion of 2,5-dibromothiophene at different scales could be described very accurately by simultaneous solution of eqs 1−3 as becomes obvious in Figure 11.

When the reaction was complete, THF was distilled off; in the meantime *n*-octane was added slowly. The *n*-octane solution was heated to reflux temperature. The impeller was stopped, and the magnesium salts that settled on the bottom were separated from the α-terthienyl solution by siphoning off the latter into another vessel to crystallize. The final conversion was 100% with a selectivity of 92%. The main byproduct was 2,2′-bithiophene. After a second crystallization the yield of bright yellow colored α-terthienyl was 85% with a purity of 98.7%.

Conclusions

A novel combination of THF and $NiCl_2$(dppbenz) has proven to be very efficient in the coupling as a solvent/catalyst combination in the coupling of 2,5-dibromothiophene with 2 equiv of thienylmagnesium bromide. THF is applicable as solvent in the large-scale production of α-terthienyl since it gives a high yield and purity.

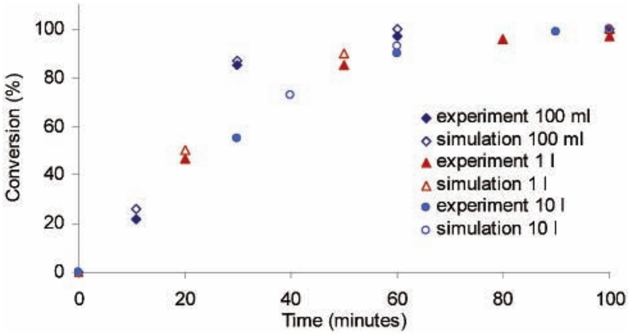

Figure 11. **Conversion of 2,5-dibromothiophene as a function of time at different reaction scales. $T = 60$ °C, [T_3] = 0.4 M, 0.5 mol % $NiCl_2$(dppbenz), addition time Grignard reagent (1.4 M): 15 min (0.1 L), 40 min (1 L), and 60 min (10 L).**

In addition, the optimization study includes concentration of the reactants, reaction temperature, addition rate of the Grignard reagents, and excess of the Grignard reagent. The highest conversions are 99% with a selectivity of 92%. This means that some of the byproduct formation occurs via a parallel reaction.

A workup procedure has been developed to obtain the desired purity (99%). In this procedure THF is distilled off while hot *n*-octane is fed to the reaction mixture. The magnesium salts precipitate while α-terthienyl stays in solution. After filtration/siphoning off the solution, it is cooled, and the α-terthienyl is obtained in good yields. A simple model for the semibatch reactor is able to describe the coupling step adequately. Finally, the scale-up to 10 L has been successful.

Experimental Section

General Experimental. $NiCl_2{\cdot}6H_2O$ was obtained from Aldrich. 2,5-Dibromothiophene (95% pure), and 2-bromothiophene (97% pure) were also purchased from Aldrich. Ligands for the preparation of the catalysts were purchased from different suppliers in purity varying between 95 and 98%. All chemicals were used without further purification. All solvents were distilled prior to use and stored under dry

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argon gas on activated molecular sieves. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Varian Gemini 300, 400, or 500 MHz. The proton chemical shifts were calibrated to tetramethylsilane (TMS), whereas the carbon chemical shifts are reported in ppm downfield of TMS using the resonance of the deuterated solvent as the internal standard. GC analyses were performed using a Zebron ZB-35 column on a Perkin-Elmer autosystem. Conversion and yields were determined with the aid of 1,3,5-tri-*tert*-butylbenzene as the internal standard. Reaction calorimetric tests were performed on 1-L scale in a RC-1. Large-scale reaction was carried out in a 10-dm^3 fully automated (semi)batch-wise operated reactor. This Belatec reactor is able to perform under a variety of conditions: a temperature range from −50 to 200 °C, solvent distillation, different agitator types, a pressure range from 0.03 to 1.1 bar. The reactor is controlled by a PLC, a special computer, which monitors physical data (batch history) and secures optimal process and safety conditions.[4]

Procedure for Screening Tests. An oven-dried 40-mL Radley Carousel reaction tube was flushed with argon before it was charged with 2,5-dibromothiophene (10 mL of 0.4 M) dissolved in the solvent of choice, mixed with catalyst (1.5 mol %) and 2-thienylmagnesium bromide (10 mL 0.9 M). This mixture was stirred at room temperature during 5 h. Small aliquots were taken for GC analyses.

Syntheses of Different Catalysts. In a 100-mL flask $NiCl_2 \cdot 6H_2O$ was dispersed in methanol. The dispersion was thoroughly purged with argon for 2 h. The different ligands were added (1.1 equiv), and the resulting dispersions were stirred during 24 h at reflux temperature. The color of the solid in the dispersion changed from green to orange/red (except for the synthesis of $NiCl_2$[dppf], where a purple solid was formed). After filtration and drying under vacuum the solids were stored under argon and used without further purification. Yields varied around 95% for all syntheses. The purity was checked by elemental analysis and UV absorption.

Original Procedure for the Synthesis of α-Terthienyl. A solution of 2.5 equiv of 2-thienylmagnesium bromide in diethyl ether was reacted with 2,5-dibromothiophene in the presence of a catalytic amount $NiCl_2$[dppp]. After 5 h at reflux, 0.1 M HCl was added, and the mixture was extracted with toluene. The volume of toluene was reduced by distillation, and the product was obtained by the addition of cold methanol. After recrystallization yields up to 60% were reported.[5b]

New Procedure for the Synthesis of α-Terthienyl (100-mL Scale). During the formation of the Grignard reagent, 2-bromothiophene, (0.07 mol, 11.41 g) was added in 1 h to a slurry of 1.3 equiv of magnesium turnings in anhydrous THF (50 mL). Addition was carried out at reflux temperature. After addition of all 2-bromothiophene the mixture was kept at reflux temperature during 1 h. The stirrer was stopped, the Grignard reagent was filtered to remove the excess of magnesium, and the resulting solution was kept under a blanket of argon prior to use. Treatment of a sample of 2-thienylmagnesium bromide with water revealed the disappearance of 2-bromothiophene by GC and NMR.

In the coupling reactions the Grignard reagent (50 mL, 1.4 M) was added in 15 min to a solution of 2,5-dibromothiophene (0.030 mol, 7.26 g) in THF (20 mL) at room temperature. In the latter solution the catalyst, $NiCl_2$ [dppbenz] (0.15 mmol, 60 mg) was dispersed. After addition of the Grignard reagent the temperature was raised to reflux temperature.

In the workup *n*-octane (50 mL) was added in 2 min, and the THF was distilled off. The resulting suspension of magnesium salts and α-terthienyl in *n*-octane was heated to 110 °C followed by siphoning of the hot *n*-octane solution. The magnesium salts were washed twice with 25 mL of hot *n*-octane, and the combined *n*-octane fractions were cooled to room temperature, yielding α-terthienyl as a bright yellow product after smooth filtration and drying under vacuum (6.72 g, yield 90%).

^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.20$ (s, 2H), 7.11 (s, 2H), 7.06 (s, 2H), 7.01 (s, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz): $\delta = 137.07$, 136.14, 127.84, 124.26, 77.00.

Ten-Liter Scale. During the formation of the Grignard reagent 2-bromothiophene (7 mol, 1141 g) was added in 4 h to a slurry of 1.3 equiv of magnesium turnings in THF (4.5 L). Addition was carried out at reflux temperature. After addition of all 2-bromothiophene the mixture was kept at reflux temperature during 1 h. The stirrer was stopped, the Grignard reagent was filtered to remove the excess of magnesium, and the resulting solution was kept under argon prior to use.

In the coupling reactions the Grignard reagent (4.5 L, 1.56 M) was added in 45 min to a solution of 2,5-dibromothiophene (3 mol, 726 g) in THF (2 L) at room temperature. In this solution the catalyst, $NiCl_2$ [dppbenz], (14 mmol, 8.29 g) was dispersed. After addition of the Grignard reagent the temperature rise was complete ($T_{r,max} = 338$ K), and the reaction mixture was heated to reflux temperature for another hour.

In the workup *n*-octane (5 L) was added, and the THF was distilled off at atmospheric pressure. The resulting suspension of Mg salts in *n*-octane was heated to 110 °C. The hot *n*-octane solution was siphoned off, and the salts were washed twice with hot *n*-octane (2.5 L). The combined *n*-octane fractions were cooled to room temperature, yielding α-terthienyl as a bright yellow product after a smooth filtration and drying under vacuum (678.5 g, yield 90.8%). A second crop could be obtained by cooling the *n*-octane to 253 K (50.6 g, total yield 97.5%).

Acknowledgment

We thank DSM Fine Chemicals and the departments SMO and SPD of the Eindhoven University of Technology for financial support. Also the excellent assistance by Tim Baks is gratefully acknowledged.

Received for review April 19, 2002.

OP020044N