Synthesis of compounds with interest for the pharmaceutical industry from plastic waste

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Abstract – In this work is reported, for the first time, the reductive depolymerization of polybutylene succinate (PBS) and poly(4-hydroxybutyrate) (P4HB) plastic waste with good yields using the environmentally friendly systems $MoO_2Cl_2(H_2O)_2$/silane and KOH/$PhSiH_3$. We also developed a new synthetic strategy for the sustainable synthesis of compounds with interest for the pharmaceutical industry from plastic waste. In this context, the first example of the synthesis of a drug, the anticancer Busulfan and an aspirin derivative, from PBS and P4HB plastic waste with moderate overall yields, is also described.

Keywords – Plastic waste, P4HB, PBS, reductive depolymerization, busulfan, aspirin derivative.

Introduction

Plastic is present in many of our everyday objects including in packaging, sportswear, healthcare, automobile industry, electrical and electronic goods, agriculture, in construction, etc.[1] For example, Delta Q eQo coffee capsules, a Portuguese coffee, are made from PBS. The huge consumption of this coffee produces large quantities of capsules that go to domestic waste (Fig 1.a). Plastic also has several applications in health tools, for example, in surgical suture that can be made from P4HB (Fig. 1.b).[2]

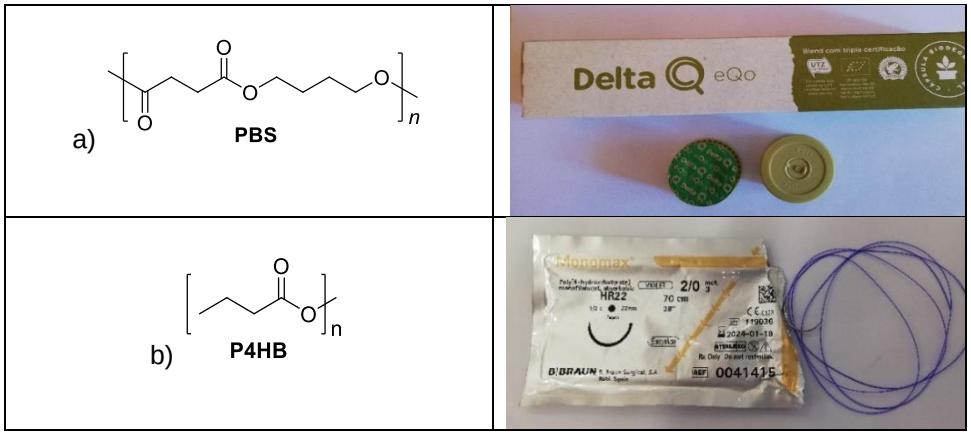


Figure 1 - a) Delta Q eQo coffee capsules made of PBS; b) Surgical suture made of P4HB.

The massive use of plastic has led to enormous increase of plastic waste.[3-4] Plastic pollution represents not only a global environmental crisis but also a loss of valuable resources.[5] The use of plastic waste as a potential cheap resource for the production of value-added products or raw materials for the chemical and pharmaceutical industries can contribute to reduce the impact of plastic pollution on the environment and the oceans.

In recent years, reductive depolymerization has emerged as an excellent alternative methodology for the valorization of plastic waste and has gained strength as it allows to transform plastic waste into value-added products, which cannot be obtained by other recycling processes.[6-9]

In this work we investigated, for the first time, the reductive depolymerization of the aliphatic polyesters P4HB and PBS. We also studied the sustainable synthesis of compounds with interest for the industry pharmaceutical, including the anticancer drug busulfan (Fig. 2), from these plastic wastes.[10]

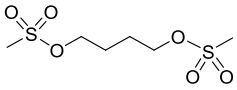


Figure 2 – Structure of busulfan.

Discussion and results

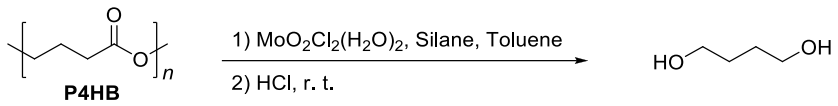
Initially, in this work we studied the reductive depolymerization of the two aliphatic polyesters PBS and P4HB. To the best of our knowledge, there are no methodologies reported in the literature for the reductive depolymerization of these polyesters. The reductive depolymerization of P4HB investigated using the catalytic system silane/$MoO_2Cl_2(H_2O)_2$, previously developed in our group,[9] employing different silanes as the reducing agents, including $PhSiH_3$, $(EtO)_2MeSiH$, PMHS (poly(methylhydrosiloxane)) and TMDS (1,1,3,3-tetramethyldisiloxane).

The reductive depolymerization of P4HB was initially carried out in the presence of 2 mol% $MoO_2Cl_2(H_2O)_2$ using 1 or 3 equivalents of PMHS in toluene at reflux temperature for 24 h. These reactions led to the formation of 1,4-butanediol with 39% and 52% yields, respectively (Table 1, entries 1 and 2). The reductive depolymerization of P4HB was also studied using $(EtO)_2MeSiH$ (3 equiv.) as the reducing agent and $MoO_2Cl_2(H_2O)_2$ (2 mol%) as the catalyst, producing 1,4-butanediol with 50% yield after 24 h at reflux temperature (Table 1, entry 3). This diol was also obtained in 55% yield in the reaction of P4HB with $PhSiH_3$ (3 equiv.) in the presence of 5 mol% of $MoO_2Cl_2(H_2O)_2$ (Table 1, entry 4).

To evaluate the efficiency of the catalytic system $MoO_2Cl_2(H_2O)_2$/TMDS in the depolymerization of P4HB, this reaction was explored using different amounts of $MoO_2Cl_2(H_2O)_2$ and TMDS using toluene as solvent, at reflux and ambient temperatures. The best yield of 1,4-butanediol (72%) was observed in the presence of 5 mol% $MoO_2Cl_2(H_2O)_2$ and 3 equivalents of TMDS after 24 h at reflux (Table 1, entry 5).

When a depolymerization was carried out with smaller amounts of both catalyst and TMDS, the diol was formed with about 50% (Table 1, entries 6-8). When the depolymerization of P4HB with the $MoO_2Cl_2(H_2O)_2$/TMDS system was carried out at room temperature, this reaction did not occur, demonstrating the effect of temperature on P4HB depolymerization (Table 1, entry 9).

Table 1 - Reductive depolymerization of P4HB with the catalytic system $MoO_2Cl_2(H_2O)_2$/Silane.[a]



Entry	Catalyst (mol%)	Silane	Silane (equiv.)	Temp. (ºC)	Time (h)	Yield (%)[b]
1	2	PMHS	1	110	24	39
2	2	PMHS	3	110	24	52
3	2	$(OEt_3)_2MeSiH$	3	110	24	50
4	5	$PhSiH_3$	3	110	24	55
5	5	TMDS	3	110	24	72
6	2	TMDS	2	110	24	52
7	2	TMDS	3	110	24	59
8	5	TMDS	2	110	24	52
9	5	TMDS	3	r. t.	48	No reaction
10	5	TMDS	3	110	24	65[c]

[a]The reactions were carried out with 0.5 mmol of P4HB, obtained from a surgical suture. [b]Yields were determined by ^1H NMR using mesitylene as the internal standard. [c]The reaction was carried out using 2.0 mmol of P4HB.

To study the possible scale-up of this methodology, the depolymerization of P4HB was performed from 2 mmol (0,172 g) of this polyester with the catalytic system $MoO_2Cl_2(H_2O)_2$/TMDS, also leading to the formation of 1,4-butanediol with good yield (65%) (Table 1, entry 10). This result is very interesting because it suggests the possible application of this cheap and environmentally friendly catalytic system in the large-scale production of 1,4-butanediol, contributing to reduce the use of fossil resources.

In this work was also explored the possible use of the catalyst $MoO_2Cl_2(H_2O)_2$ (5 mol%) in several catalytic cycles in the reductive depolymerization of P4HB carried out with TMDS, and we concluded that this catalyst can be used in at least 8 cycles, producing 1,4-butanediol with good yields (Fig 3).

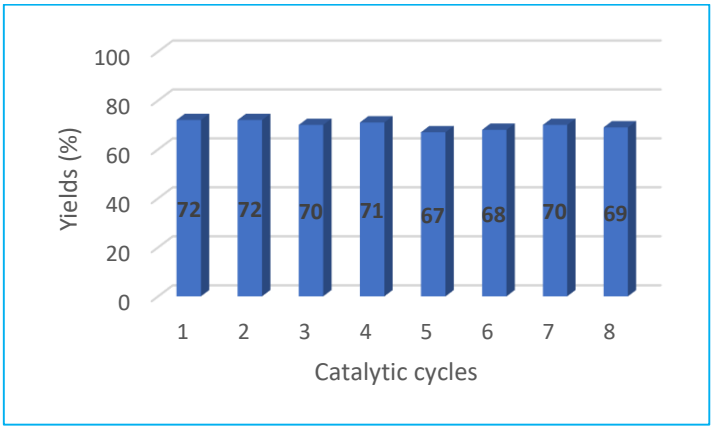
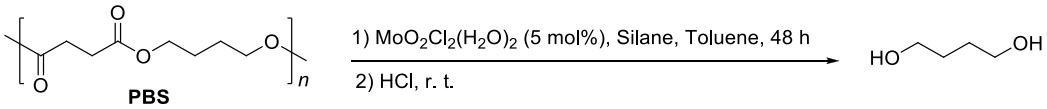


Figure 3 – Use of $MoO_2Cl_2(H_2O)_2$ in multiple catalytic cycles in the reductive depolymerization of P4HB.

The reductive depolymerization of polyester PBS, obtained from Delta Q eQo coffee capsules, cut into small pieces, was also investigated with the catalytic system $MoO_2Cl_2(H_2O)_2$/silane (Table 2). The depolymerization of PBS was initially investigated using PMHS as the reducing agent and $MoO_2Cl_2(H_2O)_2$ as the catalyst. The reaction performed with 5 mol% of catalyst and 2 equivalents of PMHS gave 1,4-butanediol with 48% yield after 48 h (Table 2, entry 1). When this reaction was carried out using 6 equivalents of PMHS, this diol was obtained with 72% yield (Table 2, entry 2). Then, the depolymerization of PBS was studied using $PhSiH_3$ (6 equiv.) in the presence of 5 mol% of $MoO_2Cl_2(H_2O)_2$, producing 1,4-butanediol with 67% yield after 48 h at reflux temperature (Table 2, entry 3). The reductive depolymerization of PBS carried out with TMDS (6 equiv.) and 5 mol% of $MoO_2Cl_2(H_2O)_2$, led to the formation of 1,4-butanediol with the best yield (75%) after 24 h at reflux temperature (Table 2, entry 4), while using 4 equivalents of TMDS was obtained a yield of 48% (Table 2, entry 5). In contrast, at room temperature this reaction did not occur (Table 2, entry 6). Finally, we also successfully applied the catalytic system $MoO_2Cl_2(H_2O)_2$/TMDS to the depolymerization of 2,0 mmol (0,344 g) of PBS, obtaining 1,4-butanediol with 69% yield (Table 2, entry 7).

Table 2 – Reductive depolymerization of PBS with the catalytic system $MoO_2Cl_2(H_2O)_2$/Silane.[a]



Entry	Silane	Silane (equiv.)	Temp. (ºC)	Yield (%)[b]
1	PMHS	2	110	48
2	PMHS	6	110	72
3	$PhSiH_3$	6	110	67
4	TMDS	6	110	75
5	TMDS	4	110	48
6	TMDS	6	r. t.	No reaction
7	TMDS	6	110	69[c]

[a]The reactions were carried out with 0.25 mmol of PBS, obtained from a Delta Q eQo coffee capsule. [b]Yields were determined by ^1H NMR using mesitylene as the internal standard. [c]The reaction was carried out using 2.0 mmol of PBS.

The development of efficient methodologies for the depolymerization of plastic waste in the absence of a metallic catalyst is also an extremely important issue that must be addressed. Nolan et al.[11] a reported new procedure for the reduction of esters using the system KOH/$PhSiH_3$ providing the corresponding alcohols with good yields, however, this catalyst has never been used in the reductive depolymerization of plastic waste. Based on the work on Nolan, we decided to apply this methodology to the depolymerization of PBS and P4HB.

The reductive depolymerization of P4HB was performed with KOH (0.4 equiv.) and $PhSiH_3$ (3 equiv.) in toluene at reflux temperature during 24 h, producing 1,4-butanediol with 95% (Table 3,

entry 1). A similar reaction using only 2 equivalents of $PhSiH_3$ also led to the formation of 1,4-butanediol but with a lower yield of 38% (Table 3, entry 2). In contrast, at room temperature, no product was formed (Table 3, entry 3).

When the reductive depolymerization of PBS, obtained from the coffee capsule, was carried out with KOH (0.8 equiv.) and $PhSiH_3$ (6 equiv.) in toluene, at 110ºC for 48 h, producing 1,4-butanediol with 51% of yield (Table 3, entry 4).

Table 3 – Reductive depolymerization of P4HB and PBS using the system KOH/$PhSiH_3$.[a]

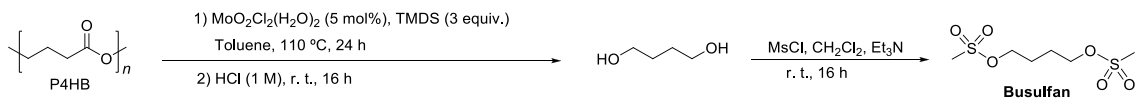
Entry	Polyester	KOH (equiv.)	$PhSiH_3$ (equiv.)	Temperature (ºC)	Time (h)	Yield (%)[a]
1	P4HB	0.4	3	Reflux	24	95[b]
2	P4HB	0.4	2	Reflux	24	38[b]
3	P4HB	0.4	3	r. t.	24	No reaction[b]
4	PBS	0.8	6	Reflux	48	51[c]

[a]Yields were determined by ^{1}H NMR using mesitylene as the internal standard. [b]The reactions were carried out with 0.5 mmol of P4HB, obtaining from surgical suture. [c]The reaction was carried out with 0.25 mmol of PBS, obtained from a Delta Delta Q eQo coffee capsule.

This result demonstrates, for the first time, the applicability of the KOH/$PhSiH_3$ system in the reductive depolymerization of plastic waste. Beyond the good yield obtained from the reductive depolymerization of P4HB, this system also has the advantage of using cheap base and a non-metallic catalyst.

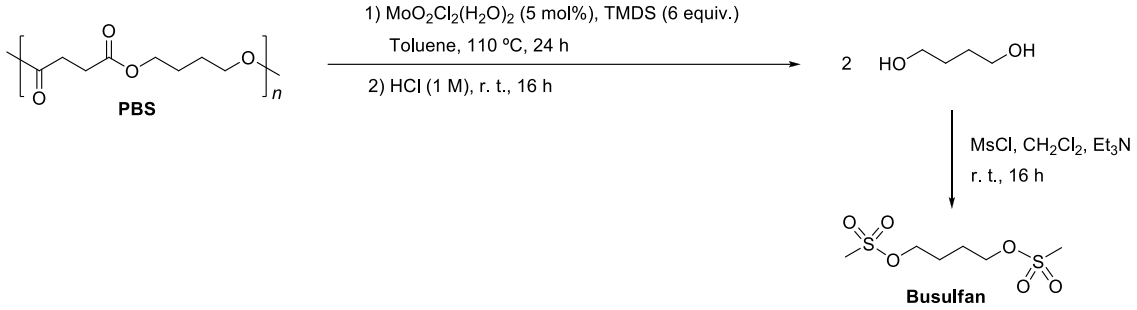
Our next goal was the valorization of 1,4-butanediol, obtained from the depolymerization of PBS and P4HB waste, in the synthesis of compounds with interest to the pharmaceutical industry. Then, we decided to investigate the synthesis of the anticancer busulfan from PBS and P4HB waste.

A sample of P4HB, obtained from a surgical suture, was initially converted to 1,4-butanediol by reductive depolymerization with the catalytic system $MoO_2Cl_2(H_2O)_2$/TMDS, followed by hydrolysis. The 1,4-butanediol obtained was directly mesylated, without further purification, by reaction with methanesulfonyl chloride and triethylamine in dichloromethane at room temperature, producing busulfan in moderate overall yield (42%) (Scheme 1). This result is very encouraging and this method could contribute to the more sustainable production of this drug.



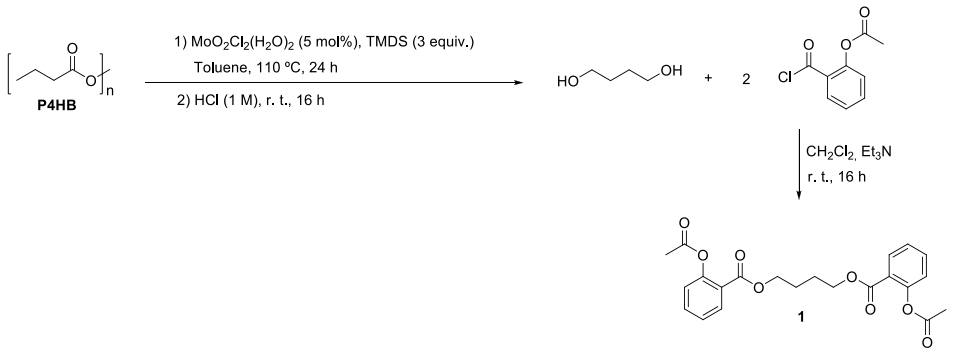
Scheme 1 - Synthesis of busulfan from a P4HB surgical suture.

A similar procedure was also developed for the synthesis of busulfan from PBS, obtained from a Delta Q eQo coffee capsule, also leading to the production of this anticancer drug with moderate overall yield of 37% (Scheme 2).



Scheme 2 - Synthesis of busulfan from PBS waste, obtained from a Delta Q eQo coffee capsule.

In this work, the application of 1,4-butanediol in the synthesis of the aspirin derivative **1** was also explored following a synthetic strategy similar to the one developed for the preparation of busulfan. Thus, a plastic waste sample of P4HB (obtained from a surgical suture) was depolymerized using the catalytic system $MoO_2Cl_2(H_2O)_2$/TMDS, followed by hydrolysis, producing 1,4-butanediol. Then, the synthesis of the aspirin derivative **1** was performed by reacting 1,4-butanediol with *O*-acetylsalicylic chloride and triethylamine in dichloromethane at room temperature, giving compound **1** in moderate overall yields (44%) (Scheme 3).



Scheme 3 - Synthesis of aspirin derivative **1** from P4HB waste.

Using a similar synthetic strategy, the aspirin derivative **1** was also prepared with an overall yield of 43% from PBS (obtained from a delta coffee capsule) by reductive depolymerization with the catalytic system $MoO_2Cl_2(H_2O)_2$/TMDS, followed by hydrolysis, and acylation with *O*-acetylsalicylic chloride.

The compound **1** contains two aspirin moieties linked by the 1,4-butanediol chain. The presence of these two moieties could improve the pharmacological activity of this compound compared to the aspirin.

Conclusion

This work describes the first example of the production of a pharmaceutical, the anticancer busulfan, from PBS and P4HB plastic waste, obtained from the domestic or hospital waste, with moderate overall yields. This research demonstrates a completely new strategy for the valorization of plastic waste and for the sustainable synthesis of drugs.

The reductive depolymerization of PBS and P4HB waste was also studied for the first time with the systems $MoO_2Cl_2(H_2O)_2$/TMDS and KOH/$PhSiH_3$. These methodologies have the advantage of using a cheap and environmentally catalyst or using a non-metallic catalyst producing 1,4-butanediol with good yields.

1,4-Butanediol, obtained from the depolymerization of P4HB and PBS, was also applied in the synthesis of the aspirin derivative **1** with moderate overall yields.

This simple synthesis of busulfan from plastic waste proves that it is possible to apply these wastes to the production of extremely important compounds and paves the way for other fascinating applications of plastic waste.

Experimental

1 - Reductive depolymerization of P4HB and PBS with the catalytic system $MoO_2Cl_2(H_2O)_2$/TMDS

A mixture of P4HB or PBS (2.0 mmol), $MoO_2Cl_2(H_2O)_2$ (5 mol%) and TMDS (3-6 equiv.) in toluene (10 mL) was heated at reflux (24-48 h). After cooling the reaction mixture at room temperature, a solution of HCl 1M (3 mL) was added and the mixture was stirred for more 16 h at room temperature. The reaction mixture was partitioned between dichloromethane (20 mL) and H_2O (15 mL) and separated. The aqueous layer was re-extracted with dichloromethane (2 x 20 mL) and the combined organic fractions were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo obtaining the 1,4-butanediol. ^{1}H NMN (300 MHz, $CDCl_3$): 3.68 (t, *J* = 5.46 Hz, 5.59 Hz, 4H, 2 CH_2), 2.07 (brs, 2H, 2 OH), 1.68 (t, *J* = 5.67 Hz, 5.64 Hz, 4H, 2 CH_2) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): 62.6, 29.8 ppm.

2 - Reductive depolymerization of P4HB and PBS with the system $PhSiH_3$/KOH

To the solution of P4HB or PBS (0.5-0.25 mmol) in toluene (3 mL) was added KOH (0.4-0.8 equiv.) and $PhSiH_3$ (3-6 equiv.) and the reaction mixture was stirred at reflux temperature during 48 h. The yield of 1,4-butanediol was determined by ^{1}H NMR using mesitylene as the internal standard.

3 - Synthesis of busulfan from P4HB or PBS waste

A mixture of P4HB or PBS (2.0 mmol), $MoO_2Cl_2(H_2O)_2$ (5 mol%) and TMDS (3-6 equiv.) in toluene (10 mL) was heated at reflux during 48 h. After cooling the reaction mixture at room temperature, a solution of HCl 1M (3 mL) was added and the mixture was stirred for more 16 h at room temperature. The reaction mixture was partitioned between dichloromethane (20 mL) and H_2O (15 mL) and separated. The aqueous layer was re-extracted with dichloromethane (2 x 20 mL) and the combined

organic fractions were dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo obtaining the 1,4-butanediol, which was used for the synthesis of busulfan without further purification. 1,4-Butanediol was dissolved in dichloromethane (5 mL) and Et_3N (2.2-4.4 equiv.) was added and the solution was stirred at room temperature for 10 minutes. Then, MsCl (2.2-4.4 equiv.) was added and the reaction mixture was stirred at room temperature overnight. After concentration in vacuo, the residue was partitioned between dichloromethane (20 mL) and H_2O (15 mL) and separated. The aqueous layer was re-extracted with dichloromethane (2 x 20 mL) and the combined organic fractions were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. ^{1}H NMR (300 MHz, $CDCl_3$): 4.32-4.25 (m, 4H, 2 CH_2), 3.03 (s, 6H, 2 OMs), 1.97-1.86 (m, 4H, 2 CH_2) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): 68.8, 37.5, 25.5 ppm.

4 - Synthesis of aspirin derivative 1 from P4HB or PBS

A mixture of P4HB or PBS (2.0 mmol), $MoO_2Cl_2(H_2O)_2$ (5 mol%) and TMDS (3-6 equiv.) in toluene (10 mL) was heated at reflux during 24 h. After cooling the reaction mixture at room temperature, a solution of HCl 1M (3 mL) was added and the mixture was stirred for more 16 h at room temperature. The reaction mixture was partitioned between dichloromethane (20 mL) and H_2O (15 mL) and separated. The aqueous layer was re-extracted with dichloromethane (2 x 20 mL) and the combined organic fractions were dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo obtaining the 1,4-butanediol, which was used for the synthesis of aspirin derivative **1** without further purification. 1,4-Butanediol was dissolved in dichloromethane (5 mL) and Et_3N (2.2-4.4 equiv.) was added and the solution was stirred at room temperature for 10 minutes. Then, *O*-acetylsalicylic chloride (2.2-4.4 equiv.) was added and the reaction mixture was stirred at room temperature overnight. After concentration in vacuo, the residue was partitioned between dichloromethane (20 mL) and H_2O (15 mL) and separated. The aqueous layer was re-extracted with dichloromethane (2 x 20 mL) and the combined organic fractions were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The product was purified by preparative chromatography using a mixture of ethyl acetate and n-hexane (1:2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.00 (d, 2H, *J* = 7.83 Hz, H-arom), 7.55 (t, 2H, *J* = 7.59 Hz, 7.77 Hz, H-arom), 7.30 (t, 2H, *J* = 7.62 Hz, 7.53 Hz, H-arom), 4.33 (brs, 4H, $2CH_2$), 2.34 (s, 6H, $2CH_3$), 1.88 (brs, 4 H, $2CH_2$) ppm. ^{13}C NMR ($CDCl_3$, 300 MHz): δ 169.7, 164.4, 150.7, 133.9, 131.6, 126.0, 123.8, 123.2, 64.5, 25.4, 21.0 ppm.

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References

1- T. Thiounn, R. C. Smith, *J. Polym. Sci.*, 2020, 58, 1347-1364.

2- D. P. Martin, S. F. Williams, *Biochem. Eng. J.*, 2003, 16, 97-105.

3- G. W. Coates, Y. D. Y. L. Getzler, *Nat. Rev. Mater.*, 2020, 5, 501-516.

4- A. Chama, H. Moon, J. Zheng, Y. Qiu, T. Tabassum, J. H. Jang, M. Abu–Omar, S. L. Scott, S. Suh, *ACS Sustain. Chem. Eng.*, 2020, 8, 3494-3511.

5- R. Geyer, J. R. Jambeck, K. L. Law, *Sci. Adv.,* 2017, 3, e1700782

6- A. C. Fernandes, *Green Chem.*, 2021, *23*, 7330-7360.

7- L. Monsigny, J.-C. Berthet and T. Cantat, *ACS Sustain. Chem. Eng*., 2018, *6*, 10481-10488.

8- E. Feghali, T. Cantat, *ChemSusChem*, 2015, *8*, 980-984.

9- B. F. S. Nunes, M. C. Oliveira, A. C. Fernandes, *Green Chem.,* 2020, *22*, 2419-2425.

10- J. Sha, Z. Cao, Z. Huang, Y. Gong, Y. Wan, R. Sun, H. He, G. Jiang, Y. Li, T. Li, B. Ren, *J. Chem. Thermodyn.,* 2021, 154, 106328.

11- J. A. Fernández-Salas, S. Manzini, S. P. Nolan, *Chem. Commun.*, 2013, 4*9*, 9758-9760.