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Facile, efficient and green phthalimide synthesis in supercritical carbon dioxide

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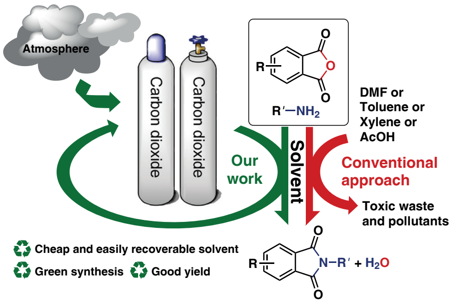
The reactions between phthalic anhydrides and primary amines in supercritical CO_2 (80–110 bar) to afford the corresponding phthalimides proceed at temperatures of 120–130 °C (aliphatic amines) or 260–275 °C (aromatic amines). The developed procedure fully complies with the principles of green chemistry and allows one to obtain target phthalimides in 65–85% isolated yields, without additional purification and extraction.



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Substituted phthalimides are popular building blocks in organic synthesis. A phthalate moiety serves as a reliable protection for amino-groups. Substituted phthalimides display diverse biological activities such as anthelminthic (Amphotalide), anti-inflammatory (Apremilast) and antifungal (Folpet) effects.[1–3] Recent studies show that phthalimide derivatives are potential anti-diabetic agents.[4] Polyimides such as poly(4,4′-oxydiphenylene-pyromellitimide) (Kapton) display outstanding properties and are applied in aerospace engineering or aerogel and membrane research (see Online Supplementary Materials, Figure S1).[5]

Commonly applied methods for the preparation of imides proceed *via* alkylation of imide salt with the corresponding alkyl halide or condensation of primary amines with the corresponding anhydrides (Figure 1). The use of alkyl halides offers excellent yields; however, some starting alkyl halides are not always easily available. Aryl halides are also used in synthesis of *N*-arylphthalimides *via* the Ullmann-type C–N coupling or Chan–Evans–Lam coupling reaction.[6] Another approach is the condensation of amines with phthalic anhydrides. The advantage of this approach is the possibility to take into reactions a broad scope of primary amine precursors such as amino acids,[7,8] amino alcohols,[9] alkylamines[10,11] and even arylamines.[12] The downside of this approach lies in the stepwise nature of this reaction. The amide intermediate formed in the first stage requires elevated temperatures for subsequent imide ring closure. For this purpose, known synthetic methods make use of various solvents with relatively high boiling points including ionic liquids,[13,14] which complicates the purification procedure. For example, preparation of Kapton-family polymers involves the use of *N*-methyl-2-pyrrolidone as a solvent.[15] The isolation of the product from the high-boiling solvent is a separate synthetic task; in addition, the solvent cannot be reused without purification from water, the secondary product of this reaction. It can thus be surmised that a considerable proportion of the toxic waste and industrial pollutants generated during phthalimide synthesis originate from a variety of solvents. The detrimental impact of these industrial pollutants on both human health and the environment is widely acknowledged.[16,17]

Taking into account the aforementioned issues of phthalimide synthesis, we carry out the condensation of phthalic anhydride using supercritical CO_2 ($scCO_2$) as a green alternative to conventional solvents. The reliability of supercritical carbon

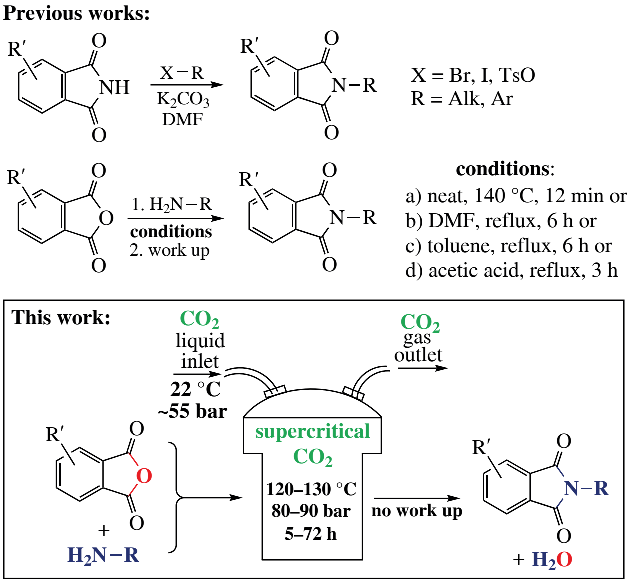


Figure 1 Comparison of the synthesis of phthalimides using literature methods and those developed in this work.

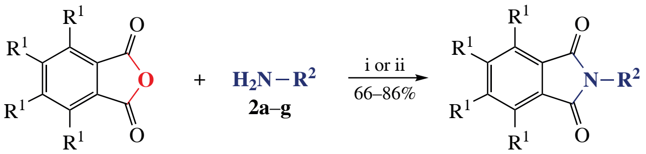
dioxide as a solvent has already been demonstrated in laboratory settings.[18,19] Supercritical CO_2 is stable and chemically inert towards different reagents in a wide range of reaction conditions. In addition, we anticipated that at sufficiently elevated pressures, carbon dioxide would bind water formed in the process of synthesis, thereby protecting the anhydride from hydrolysis. Moreover, the utilization of $scCO_2$ is regarded as a means of adhering to the principles of green chemistry.[19] The only disadvantage of using CO_2 as a solvent is the need for special equipment designed to operate at high pressures, because CO_2 has supercritical fluid properties above its critical temperature of 304 K (31 °C) and critical pressure of 73 bar.

In the first stage of the work, we synthesized *N*-phthaloylglycine using phthalic anhydride **1a** and glycine **2a** as precursors (Scheme 1) in $scCO_2$ under relatively mild conditions (80 bar, 70 °C). The reaction was stirred for 3 h in a sealed reactor (Table 1, entry 1). After cooling the setup down to room temperature (23 °C), carbon dioxide was pumped out/released, and the reactor was opened. Using ^1H NMR spectroscopy, we detected only traces of the target product **3a** with the reactants remaining largely intact. Raising the temperature above 120 °C, with a pressure being lower than the critical point (60 bar), resulted in the formation of product **3a**, although the conversion and purity of the product were lower than those anticipated: only 46% of initial anhydride **1a** was converted into *N*-phthaloylglycine **3a**, while the rest underwent a hydrolysis with water formed as the secondary product. Over the course of optimization, we discovered that the most appropriate conditions for phthalimide synthesis are 80–90 bar at 120–130 °C (see Table 1, entry 5). These conditions enable the use of anhydride and amine in a 1 : 1 ratio providing a good yield of the target product. It must also be emphasized that after the pressure in the reactor is set above 80 bar, hydrolysis of initial anhydrides does not occur, which is proven by the absence of the phthalic acid by-product (^1H NMR). Therefore, we affirmed that at a high pressure, $scCO_2$ completely removes water from the reaction medium, supposedly by forming carbonic acid.

Next, we carried out a series of reactions of phthalic and tetrachlorophthalic anhydrides **1a**,**b** with various amines **2a–g**, including amino acids, propargylamine and anilines, to determine the scope of application of the methodology (see Scheme 1). The syntheses were carried out under the optimal conditions found for compound **3a** and resulted in the formation of phthalimides **3b–j** with high yields and purities. Note that no by-products are formed in the reaction mixture, and the non-quantitative yield in all cases is the result of mechanical losses during the unsealing of the reaction chamber and the product take-out.

Table 1 Optimization of reaction conditions for phthalimide **3a** synthesis.

Entry	*P*/bar	*T*/°C	**1a**/**2a** ratio	NMR yield (%)
1	80	70	1 : 1	traces
2	60	120	1 : 1	46
3	60	120	2 : 1	75
4	90	120	2 : 1	97
5	90	120	1 : 1	98



1a R^1 = H
1b R^1 = Cl

2a, **3a** R^2 = $HOC(O)CH_2$
2b, **3b**, **3h** R^2 = $HOC(O)CH(Pr^i)$
2c, **3c** R^2 = HOC(O)CH(Bn)
2d, **3d**, **3i** R^2 = $HC{\equiv}CCH_2$
2e, **3e** R^2 = $4\text{-}MeOC_6H_4$
2f, **3f** R^2 = $4\text{-}BrC_6H_4$
2g, **3g** R^2 = $4\text{-}HOC_6H_4$

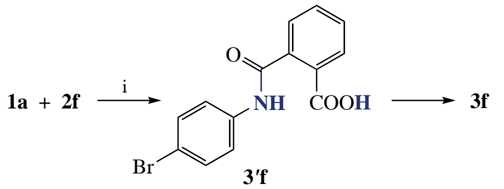
3a–g R^1 = H
3h,**i** R^1 = Cl

Scheme 1 *Reagents and conditions*: i, $scCO_2$, (80–100 bar), 120–135 °C (for **3a–d**,**i**); ii, $scCO_2$ (80–110 bar), 260–275 °C, 6 h (for **3e–h**).

We noticed that the substituents in the initial reactants **1** and **2** impact the reaction rate due to two-step nature of the phthalimide formation process. At the first step, the reaction of amine with phthalic anhydride results in the formation of 2-carbamoylbenzoic acid. Next, this amido carboxylic acid intermediate undergoes cyclization to final phthalimide. In case of phthalic anhydride **1a** and amino acids **2a–c** or propargylamine **2d**, the reactants are completely converted into the corresponding phthalimides after 3 h (shortest set reaction time in a sealed chamber), and the amide intermediates are not observed. However, for other reactants, the time needed to achieve full conversion may increase drastically. For example, our first attempt of synthesis of imide **3f** resulted in the formation of a mixture containing 92% of amide **3′f** and only 8% of title compound imide **3f** after 2 h (Scheme 2, Table S1 of Online Supplementary Materials). This can be attributed to lower nucleophilicity of arylamides compared to alkylamides, and this reaction can be a convenient method for obtaining 2-carbamoyl benzoic acids from phthalic anhydrides. However, extending the reaction time to 18.5 h provided the content of imide product **3f** of 94% (see Table S1). This experiment also demonstrates the applicability of the condensation of amines with phthalic anhydride in $scCO_2$ to the synthesis of 2-carbamoyl benzoic acids by adjusting the reaction time. Similar trend was observed in reactions of tetrachlorophthalic anhydride **1b** (see Scheme 1), although the rate of imide formation is lower even for derivatives of amino acids supposedly due to decreased nucleophilicity of tetrachlorobenzoylamide compared to benzoylamides.

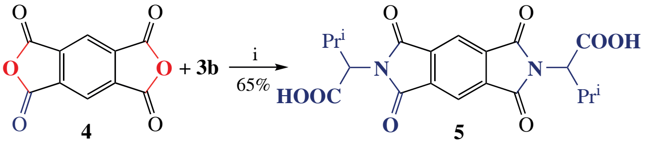
For highly deactivated pyromellitic dianhydride **4**, the time required for a complete conversion into the imide product may exceed 48 h. So we also tried to obtain product **5** by carrying the reaction at higher temperatures. At temperatures above 300 °C, the reactants underwent thermal decomposition regardless of the set pressure and thus the product could not be isolated. Luckily, by adjusting the temperature to 260 °C (108 bar), we managed to achieve a complete conversion of dianhydride **4** into diimide **5** in 7 h (Scheme 3). This finding allowed us to prepare imides **3e–h** through processing at 265–275 °C, with a complete conversion of initial anhydrides within 6 hours (see Scheme 1).

In conclusion, we have developed an efficient approach to phthalimide synthesis by carrying out the reactions of phthalic anhydrides with amines in the supercritical carbon dioxide as a reaction medium. This method requires little to no workup and purification of final products. In addition, the dehydrating ability of $scCO_2$ allows the use of an equimolar ratio of reactants with a complete conversion into the phthalimide derivative. In this



3′f

Scheme 2 *Reagents and conditions*: i, supercritical CO_2 (90 bar), 120 °C, 2–18.5 h.



Scheme 3 *Reagents and conditions*: i, $scCO_2$ (108 bar), 260 °C, 7 h.

study, we broadened the range of applications for $scCO_2$ as a solvent, thereby confirming its suitability as an alternative to traditional solvents in organic synthesis.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7646.

References

1 J. A. Clegg and M. A. Smith, *Adv. Parasitol.*, 1978, **16**, 165; https://doi.org/10.1016/S0065-308X(08)60574-6.

2 H. Abdulrahim, S. Thistleton, A. O. Adebajo, T. Shaw, C. Edwards and A. Wells, *Expert Opin. Pharmacother.*, 2015, **16**, 1099; https://doi.org/10.1517/14656566.2015.1034107.

3 X. Zang, J. Wang, O. Wang, M. Wang, J. Ma, G. Xi and Z. Wang, *Anal. Bioanal. Chem.*, 2008, **392**, 749; https://doi.org/10.1007/s00216-008-2296-1.

4 M. Emadi, M. Halimi, A. Moazzam, S. Hosseini, S. Mojtabavi, M. A. Faramarzi, R. Ghadimi, A. A. Moghadamnia, E. Nasli-Esfahani, M. Mohammadi-Khanaposhtani and M. Mahdavi, *Sci. Rep.*, 2023, **13**, 10030; https://doi.org/10.1038/s41598-023-36890-y.

5 Y. Gong, H. Tian, B. Niu, Y. Xing, X. Liang, Y. Zhang and D. Long, *Polym. Degrad. Stab.*, 2024, **220**, 110645; https://doi.org/10.1016/j.polymdegradstab.2023.110645.

6 K. K. Gurjar and R. K. Sharma, *ChemCatChem*, 2017, **9**, 862; https://doi.org/10.1002/cctc.201601174.

7 T.-T. H. Nguyen, A. Navarro, J. C. Ruble and H. M. L. Davies, *Org. Lett.*, 2024, **26**, 2832; https://doi.org/10.1021/acs.orglett.3c03652.

8 D. Fu, X. Wang and B. Liu, *Spectrochim. Acta, Part A*, 2024, **309**, 123808; https://doi.org/10.1016/j.saa.2023.123808.

9 R. Laskar, S. Dutta, J. C. Spies, P. Mukherjee, Á. Rentería-Gómez, R. E. Thielemann, C. G. Daniliuc, O. Gutierrez and F. Glorius, *J. Am. Chem. Soc.*, 2024, **146**, 10899; https://doi.org/10.1021/jacs.4c01667.

10 S. Zhang, X. Shi, J. Li, Z. Hou, Z. Song, X. Su, D. Peng, F. Wang, Y. Yu and G. Zhao, *ACS Omega*, 2019, **4**, 19420; https://doi.org/10.1021/acsomega.9b02853.

11 H. N. Nguyen, V. J. Cee, H. L. Deak, B. Du, K. P. Faber, H. Gunaydin, B. L. Hodous, S. L. Hollis, P. H. Krolikowski, P. R. Olivieri, V. F. Patel, K. Romero, L. B. Schenkel and S. D. Geuns-Meyer, *J. Org. Chem.*, 2012, **77**, 3887; https://doi.org/10.1021/jo3000628.

12 J.-C. Li, B.-X. Yan, G. Wang and Z.-S. Ye, *Org. Lett.*, 2023, **25**, 5890; https://doi.org/10.1021/acs.orglett.3c02180.

13 H. Liao, M. Chen, Y. Ma, Q. Peng, X. Wei and Z. Hou, *Ind. Eng. Chem. Res.*, 2022, **61**, 15156; https://doi.org/10.1021/acs.iecr.2c02480.

14 S. Kim, S. L. Song, J. Zhang, D. Kim, S. Hong and S. Chang, *J. Am. Chem. Soc.*, 2023, **145**, 16238; https://doi.org/10.1021/jacs.3c05258.

15 W. Tan, Z. Li, J. Dong, Q. Wang, Y. Cheng, X. Zhao and Q. Zhang, *J. Appl. Polym. Sci.*, 2017, **134**, 45497; https://doi.org/10.1002/app.45497.

16 A. K. Sharma, M. Sharma, A. K. Sharma and M. Sharma, *J. Geochem. Explor.*, 2023, **255**, 107325; https://doi.org/10.1016/j.gexplo.2023.107325.

17 F. Tarrass and M. Benjelloun, *Nefrologia (Engl. Ed.)*, 2022, **42**, 122; https://doi.org/10.1016/j.nefroe.2021.05.006.

18 A. V. Budkova, V. G. Merkulov, R. E. Ivanov, M. N. Zharkov, I. V. Kuchurov and S. G. Zlotin, *Mendeleev Commun.*, 2023, **33**, 461; https://doi.org/10.1016/j.mencom.2023.06.006.

19 S. G. Zlotin, K. S. Egorova, V. P. Ananikov, A. A. Akulov, M. V. Varaksin, O. N. Chupakhin, V. N. Charushin, K. P. Bryliakov, A. D. Averin, I. P. Beletskaya, E. L. Dolengovski, Y. H. Budnikova, O. G. Sinyashin, Z. N. Gafurov, A. O. Kantyukov, D. G. Yakhvarov, A. V. Aksenov, M. N. Elinson, V. G. Nenajdenko, A. M. Chibiryaev, N. S. Nesterov, E. A. Kozlova, O. N. Martyanov, I. A. Balova, V. N. Sorokoumov, D. A. Guk, E. K. Beloglazkina, D. A. Lemenovskii, I. Y. Chukicheva, L. L. Frolova, E. S. Izmest'ev, I. A. Dvornikova, A. V. Popov, A. V. Kutchin, D. M. Borisova, A. A. Kalinina, A. M. Muzafarov, I. V. Kuchurov, A. L. Maximov and A. V. Zolotukhina, *Russ. Chem. Rev.*, 2023, **92**, RCR5104; https://doi.org/10.59761/RCR5104.

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