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Base-promoted direct amidation of esters: beyond the current scope and practical applications†

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The base-promoted direct amidation of unactivated esters is among the most useful reactions for amide bond formation in contemporary organic chemistry. The intensive research in this area has led to the development of a number of new methods to achieve this transformation. However, to date, the existing literature is more methodological and in many instances lacks practical directions. Therefore, the full potential of this transformation is yet to be revealed by broadening the substrate scope. In a search for new practical applications of the amidation reaction, herein we present a comprehensive study of a number of base-promoted direct amidations that encompass a wide range of amines and esters. Furthermore, we applied our findings in the synthesis of phosphoramidates and several industrially relevant products.

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Introduction

Due to its importance for organic synthesis and its ubiquity in nature, the amide bond is among the most fundamental functionalities in organic molecules. Therefore, new strategies are always needed to meet the contemporary synthetic challenges. Classical methods, using coupling agents,¹ metal catalysts² or harsh reaction conditions,³ have become less and less favored due to several issues, such as atom economy,⁴ energy efficiency, and poor green chemistry metrics.

Due to their availability, the direct amidation of esters⁵ is among the most attractive methods to achieve the synthesis of amides. Different methods have been developed (Scheme 1), utilizing different bases, solvents and reaction conditions (Scheme 1a–d),^{6–9} including settings for flow chemistry (Scheme 1e),¹⁰ and mixer mill (Scheme 1f).¹¹

However, despite their straightforwardness at first glance, these transformations are often challenging. Among the already developed methods, some limitations can be pointed out. In many instances the existing literature suffers from non-systematic approach, fractionalized data, lack of diversity in the used substrates and a complete overview of the reaction's

scope and limitations. Virtually there are no reports of unsuccessful experiments, which can create a misconception that the reaction is universal towards all esters and amines. To date, the practical application, *i.e.* the implementation of the new reaction setting for the synthesis of valuable synthetic products, has received less research focus, and thus needs additional diligence.

Phosphoramidates are another important class of compounds, which finds applications spanning agriculture,¹² organic synthesis,¹³ pharmaceutical and medicinal chemistry.^{14,15} To date, the synthesis of phosphoramidates mainly rely on oxidative cross-coupling or reduction routes. The preparation of these compounds by redox neutral methods remains rather unexplored and suffers from various drawbacks, such as the use of toxic and sensitive chlorophosphonates,¹⁷ laborious inorganic salt elimination methods^{18–20} or the use of harsh conditions²¹ and transition metal catalysis^{22,23} (Scheme 1).

Driven by these considerations, herein we report a detailed study of direct amidation of unactivated esters with amines, promoted by strong bases. Our work represents a systematic study of over 75 reactions that encompass large substrate scope, ranging from anilines and heterocyclic amines to aliphatic amines and guanidines, and stretching to the synthesis of phosphoramidates. We performed a thorough examination of the scope and the limitations of the reaction settings and applied them in the synthesis of several important derivatives.

Results and discussion

DMSO/*t*-BuOK promoted amidation of esters

The amidation of esters, promoted by potassium *tert*-butoxide has been reported in several instances.^{11,24,25} However, the

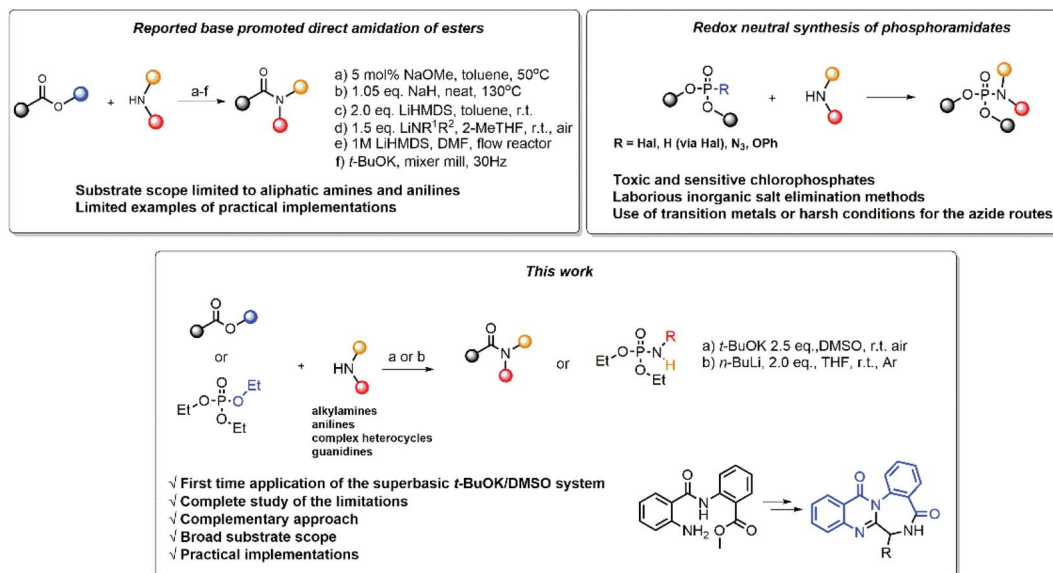
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Scheme 1 Synthesis of amides and phosphoramidates *via* direct amidation.

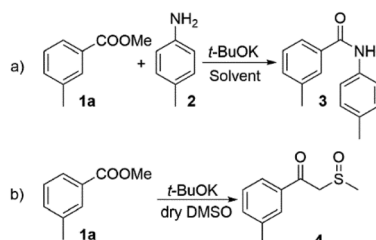
reactions outcome was found to largely depend on the nature of both ester and amine reaction partners. For instance, Kim *et al.*²⁴ reported a difference of approx. 30% higher yield for ethyl benzoate as compared to its methyl analogue. Similar differences could be found with respect to the amine counterparts.

We started our investigation by exploring the reaction between methyl 3-methyl benzoate (**1a**) and 4-methyl aniline (**2**) (Scheme 2a). Under similar conditions to those, reported by Kim *et al.* we observed moderate yield of compound **3** (62%, Table 1, entry 1), which is in accordance with the literature data. The use of DMF as a solvent did not provide any significant advantage (Table 1, entry 2). In an attempt to solve this issue we decided to increase the basicity by using DMSO/*t*-BuOK system, which is reported to behave as a superbase.²⁶ To the best of our knowledge DMSO/*t*-BuOK has never been reported as a reaction medium for the direct amidation of esters. A rational explanation of this observation is the possible competition between the amine nucleophile and the formed *in situ* sulphur ylide nucleophilic species²⁷ (Scheme 2b). To our delight we observed significant improvement of the reaction yield up to 94% (Table 1, entry 3), without the formation of the competitive side product **4** (Scheme 2b) and only hydrolysis of **1a** was observed in

trace amount as a side reaction. The attempt to decrease the required equivalents of *t*-BuOK resulted in a significant decrease of the yield (Table 1, entries 4 and 5).

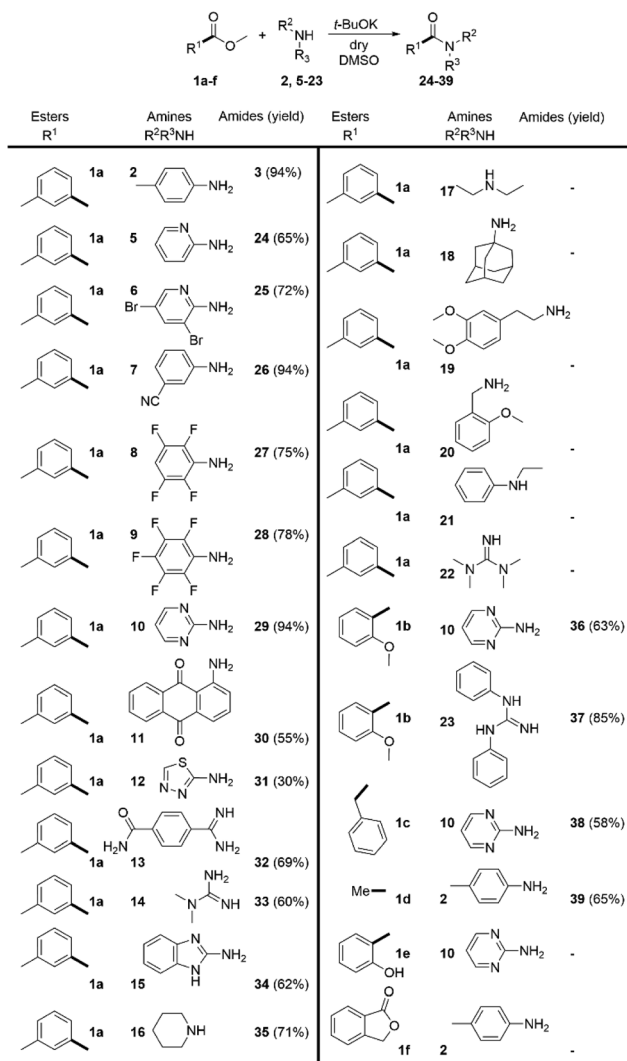
Having these reaction conditions in hand, we explored the amine scope by using methyl 3-methylbenzoate (**1a**) as a model compound (Scheme 3). The reaction proceeded smoothly with various substituted anilines (**2**, **5**–**7**). The presence of aliphatic, halogen or cyano-substituents at the aromatic ring was tolerated and the desired amides were isolated in moderate to excellent yields. The scope of the reaction was broadened by the acylation of two very weakly nucleophilic fluorinated anilines (**8** and **9**) in high yields. Notably, the challenging acylation of 2-aminopyrimidine (**10**) and the highly deactivated aminoanthraquinone (**11**) was achieved in 94% and 55% yield respectively. The heterocyclic amine **12** provided the desired product **31** in 30% yield. The reaction scope was extended with imidamide **13** and guanidine **14** and the heterocyclic aromatic amine **15** which were acylated in good yields. Nevertheless, the applicability of the method to aliphatic amines proved very limited. The only aliphatic amine that has been successfully acylated under these conditions was piperidine (**16**). Surprisingly, the use of tetramethylguanidine **22** was also unsuccessful.

We extended the scope of the method towards the acylation of methyl 2-methoxybenzoate (**1b**) with 2-aminopyrimidine (**10**)

Scheme 2 (a) *t*-BuOK promoted direct amidation; (b) possible side reaction under DMSO/*t*-BuOK conditions.Table 1 Optimization of the synthesis of amide **3**^a

	Solvent	Concentration (amine)	Eq. (ester)	Eq. (<i>t</i> -BuOK)	Yield
1	THF	1 mmol ml ⁻¹	1.3	2.0	62%
2	DMF	1 mmol ml ⁻¹	1.3	2.0	70%
3	DMSO	1 mmol ml ⁻¹	1.3	2.0	94%
4	DMSO	1 mmol ml ⁻¹	1.0	0.3	Traces
5	DMSO	1 mmol ml ⁻¹	1.0	1.5	84%

^a Reaction time 5 min.

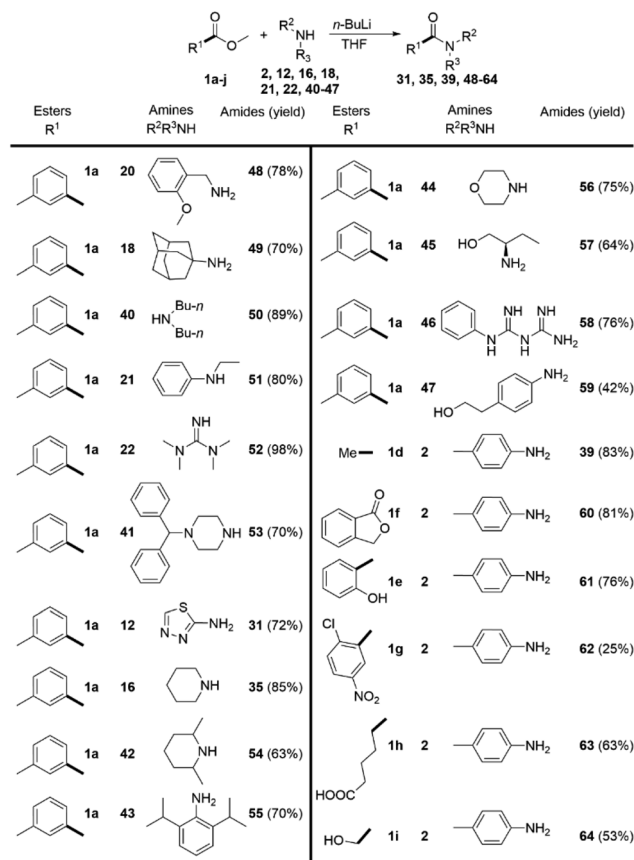


Scheme 3 Substrate scope of the DMSO/*t*-BuOK system. Reaction conditions: 1.0 eq. of amine and 2.0 eq. of ester were dissolved in dry DMSO, and then *t*-BuOK (2.5 eq.) was added slowly portionwise. Reaction time 5 min.

and *N,N'*-diphenylguanidine (**23**). The desired products **36** and **37** were formed in 63% and 85% yield respectively. CH-acidic esters methyl 2-phenylacetate (**1c**) and ethyl acetate (**1d**) were also successfully subjected to direct amidation with 2-aminopyrimidine (**10**) and 4-methylaniline (**2**) in moderate yields. However, the reaction of 2-aminopyrimidine with methyl 2-hydroxybenzoate (**1e**) and the attempt to amidate lactone **1f** with aniline **2** were unsuccessful.

n-BuLi promoted amidation of esters

In order to overcome the limitations of the DMSO/*t*-BuOK system, we decided to study a complimentary approach, which would allow us to comparably broaden the scope. Based on the data, reported in the literature²⁸ and common synthetic rationale, our choice fell on *n*-BuLi. The ester **1a** was again used as a model substrate.



Scheme 4 *n*-BuLi promoted direct amidation of esters. Reaction conditions: 1.0 eq. of the corresponding amine and 2.0 eq. ester; THF as solvent, and *n*-BuLi (2.0 eq.) as a base (at r.t. in inert atmosphere). Reaction time 5 min.

We methodically tested the classes of amine substrate (Scheme 4), which did not react or provided poor yields under the previous reaction conditions. In contrast with the DMSO/*t*-BuOK system benzyl amine (**20**), primary (**18**) and secondary (**40**) alkylamines, were successfully acylated, as well as alkylphenylamine (**21**), tetramethylguanidine (**22**), and *N*-mono-substituted piperazine (**41**). The products **31** and **35**, which were previously obtained in poor yields, were isolated in significantly improved yields, 72% and 85% (Scheme 4) *versus* 30% and 71% (Scheme 3), respectively. The substrate scope was extended to the sterically hindered amines **42** and **43**, morpholine **44**, aminoalcohol **45**, biguanide **46** and aniline **47**. Acetamide **39** was obtained in a higher yield compared to the DMSO/*t*-BuOK system. The opening of lactone **1f** and the amidation of 2-hydroxybenzoate **1e** were also successfully providing the desired products **60** and **61** in high yields. The amidation of 3-nitro-2-chloro benzoate **1g** with aniline **2** rendered product **62** in poor yield due to extensive formation of side products, showing that this reaction conditions do not tolerate nitro substituents. Esters containing carboxy (**1h**) and hydroxyl (**1i**) groups were also successfully amidated.

Despite the numerous methods to achieve the synthesis of phosphoramidates¹⁶ the direct reaction of amines with

triethylphosphate (65), without any catalyst, to the best of our knowledge, has never been reported before. Driven by these considerations, we decided to go beyond the carboxylic esters and apply our findings in the amidation of readily available 65. To our delight, this approach was successful and we were able to synthesize phosphoramidates 70–74. Both aromatic and aliphatic amines were applicable as substrates providing the desired products in very high yields (Scheme 5). Noteworthy, the synthesis of similar phosphoramidates was achieved by Tf₂O-promoted activating strategy. However, this approach provided only low to moderate yields.²⁹

Methods comparison

Based on the extensive investigation of the reaction scope of the two methods, we outlined some advantages and drawbacks. The DMSO/*t*-BuOK-promoted amidation of esters is simple and affordable. It requires a minimum amount of solvent and no heating or cooling. The reactions are practically instantaneous and no inert atmosphere is required. The substrate scope cover wide range of aromatic amines, and its ability to acylate unreactive amines like 2-aminopyrimidine and *N,N'*-diphenylguanidine is particularly valuable.

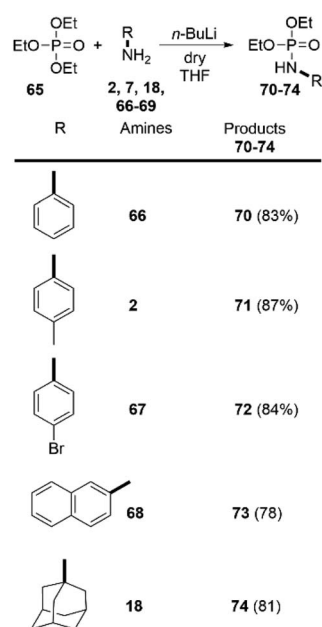
Despite its great potential this method suffers from several drawbacks. It is generally not applicable to important classes of substrates, such as aliphatic and benzylic amines. It's worth mentioning that in all the unsuccessful experiments, the competing reaction of the esters with the DMSO, derived sulfur ylide, leading to the formation of product 4 (Scheme 1). This observation hampers further optimization of the reaction conditions (time, temperatures, *etc.*), due to the fact that in the

case of slowly reacting amines, all the ester is predominantly consumed in the faster competitive reaction.

In contrast, the amidation of esters with THF/*n*-BuLi is applicable to a broader substrate scope. Various aliphatic and aromatic amines can be easily acylated with high to excellent yields. The reaction itself is clean and fast, with a straightforward work-up. The method is further applicable towards the synthesis of phosphoramidates. Nevertheless, the work with aggressive base such as *n*-BuLi that requires inert atmosphere is a major drawback. In several instances, the low solubility of some substrates in THF limited the scope of the reaction.

Amine substrates that were not applicable under both reaction condition are summarized in Fig. 1. Both reaction settings failed in the amidation of 1a with nitroanilines (75a–b) resulting in a complex mixture of products. No conversion was observed during our attempts to acylate aminophenol (75c), diphenylamines (75k–l) and primary amide (75h). Several amine substrates, containing sulfonamido group (75d–g) as well as some highly sterically hindered amines (75i) and heterocycles (75j, 75m–o) were also not applicable.

Having in hands this large amount of experimental data, we focused our attention towards some practical applications. Driven by the interesting selectivity of the DMSO/*t*-BuOK system that was found to effectively promote direct acylation of anilines, while not effective for alkyl and benzyl amines we attempted to selectively react 4-amino benzylamine (76) with 3-methyl methylbenzoate (1a) at the aniline nitrogen. Nevertheless, the reaction failed to provide the desired product 77. Surprisingly, when the same reaction was carried out in the presence of *n*-BuLi we observed remarkable selectivity at the aniline position, leading to the formation of 77 as a sole product in 70% yield (Scheme 6a). The structure of 77 was unambiguously confirmed by X-ray crystallography as hydrochloric acid salt, 77·HCl (See section X-ray and ESI†). This protocol represents a new way for protective group free functionalisation of anilines in a presence of competitive amino groups, which up to



Scheme 5 Synthesis of phosphoramidates by direct amidation of triethylphosphate. Reaction conditions: 1.0 eq. of the corresponding amine and 2.0 eq. triethylphosphate; THF as solvent, and *n*-BuLi (2.0 eq.) as a base (at r.t. in inert atmosphere). Reaction time 5 min.

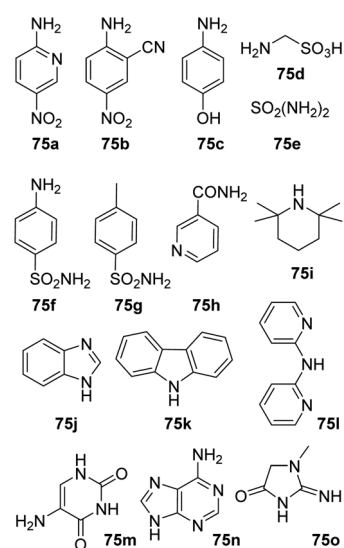
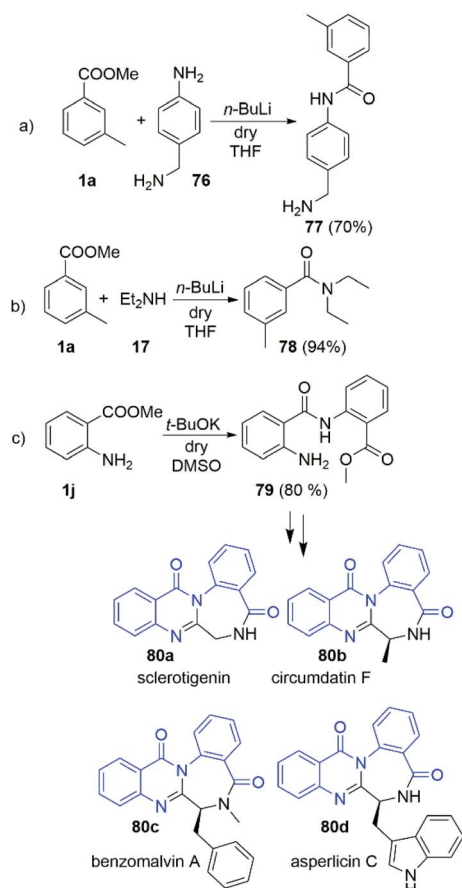


Fig. 1 Not applicable substrates.



Scheme 6 Practical implementations of the amidation reactions. Reaction conditions for (a) and (b): 1.0 eq. of the corresponding amine and 2.0 eq. ester; THF as solvent, and *n*-BuLi (2.0 eq.) as a base (at r.t. in inert atmosphere). Reaction conditions for (c): 1.0 eq. of methyl anthranilate was dissolved in dry DMSO, and then *t*-BuOK (2.5 eq.) was added slowly portionwise. Reaction time 5 min.

now has been achieved by protection/deprotection sequence,³⁰ or through much more laborious synthetic protocols.^{31–33}

We further demonstrated the potential of our findings in a *n*-BuLi promoted synthesis of *N,N*-diethyl-*meta*-toluamide (DEET) (**78**) (Scheme 6b). DEET is among the most common active ingredients in insect repellents. To date, it has been mostly prepared *via* classical amidation of the corresponding acylchloride³⁴ and amidation of 3-methyl benzoic acid in presence of coupling agents³⁵ Other methods based on transition metal catalysis^{36–39} and Grignard promoted amidation of 3-methyl benzonitrile⁴⁰ could be also found in the literature. Herein, we report its synthesis in nearly quantitative yield (94%) from the readily available methyl 3-methylbenzoate and diethylamine (**17**) at r.t. for 5 min.

The practical potential of the DMSO/*t*-BuOK system was demonstrated in the “auto-amidation” of anthranilic ester **1j** (Scheme 6c). The resulting compound **79** is a precursor in the synthesis of various natural compounds such as the alkaloids sclerotigenin (**80a**), circumdatin F (**80b**), benzomalvin A (**80c**), asperlicin C (**80d**) and others (Scheme 6). To date **79** was synthesized using a laborious two-step procedure, which includes

reflux in H₂SO₄/MeOH for 4–5 days.^{41,42} In contrast, our protocol provided **79** in 5 minutes with 80% yield.

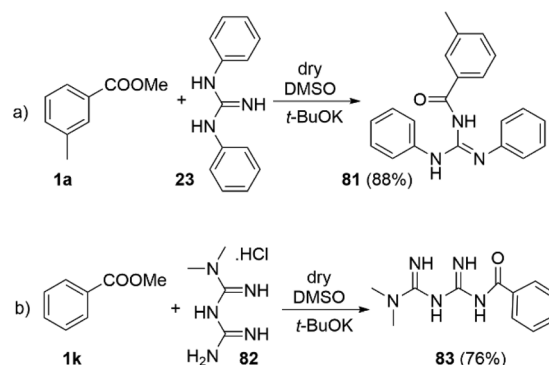
Traditionally the direct acylation of guanidines has been a challenging synthetic task. Therefore, we explored the utility of the DMSO/*t*-BuOK system for direct acylation of *N,N*-diphenylguanidine **23** (Scheme 7a). Although several methods to achieve the synthesis of acylated diphenylguanidines exist, they require laborious synthetic procedures and use of metal catalysts (Pd, Hg, *etc.*).^{43–46} None of them is direct and they mostly exploit substituted thioureas as starting materials. To the best of our knowledge, the direct acylation of diphenylguanidine is being reported here for the first time. Furthermore, the reaction itself is very straightforward, fast, catalyst-free and high yielding. The structure of **81** was confirmed by single crystal X-ray diffraction (See section X-ray and ESI†).

The antiplatelet thrombotic agent **83** (Scheme 7b) was originally synthesized by acylation of *N,N*-dimethyl biguanide with benzoic anhydride in acetone at r.t. for 5 hours, with 71% yield.⁴⁷ Our conditions provided its direct synthesis in 76% yield from *N,N*-dimethyl biguanide hydrochloride (**82**) and methyl benzoate at r.t. for 5 min.

X-ray

Suitable single crystals of key compounds **77**·HCl and **81** were prepared, in order to confirm their solid-state structures. Compound **77**·HCl was found to crystallise in the *P2*₁/*n* space group with a single molecule in the asymmetric unit cell. The packing included numerous intermolecular interactions, with the structure being observed as a hydrogen bonded dimer between a pair of (symmetry equivalent) bonds between the amide oxygen atom and the ammonium group (N···O = 2.832(4) Å). This network expanded three dimensionally *via* several N–H···Cl contacts from both the amide and ammonium groups present, with N···Cl distances of 3.544(3) Å and 3.084(3)/3.114(3) Å, respectively. These distances are all within the expected ranges for these types of intermolecular interactions.

The structure of **81** was found to crystallise in the *P2*₁/*c* space group, again with only a single molecule present in the asymmetric unit cell. Interestingly, despite the potential for



Scheme 7 Acylation of guanidines using DMSO/*t*-BuOK. Reaction conditions: 1.0 eq. of amine and 2.0 eq. of ester were dissolved in dry DMSO, and then *t*-BuOK (2.5 eq.) was added slowly portionwise. Reaction time 5 min.

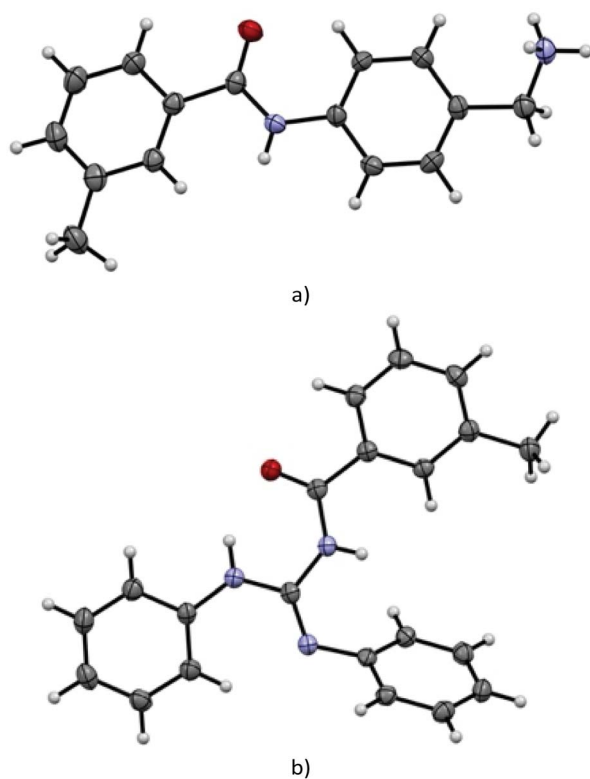


Fig. 2 View of the molecular structure obtained by single-crystal X-ray analysis and atom-numbering scheme of compounds (a) **77**·HCl (chloride anion omitted for clarity), (b) **81** (all thermal ellipsoids at 50% probability).

hydrogen bonding, only a single intramolecular interaction is present, with all intermolecular contacts consisting of weaker C–H \cdots O (C \cdots O = 3.314(2) Å) or C–H \cdots N (C \cdots N = 3.483(2) Å) interactions, or π – π interactions (centroid to centroid distances = 3.88 Å) between the aromatic rings (Fig. 2).

Conclusions

Herein we report a detailed study of base promoted direct amidation of unactivated esters. A new system (DMSO/*t*-BuOK) was employed and its scope and limitations were investigated. An alternative protocol (THF/*n*-BuLi) was developed in order to overcome its limitations. Our studies encompass a wide range of esters and amines that in full revealed the reaction scope and its limitations. Several practical applications of our findings were proposed. We have achieved straightforward synthesis of several important products, thus paving new ways for their preparation.

Author contributions

Conceptualization: Svilen Simeonov and Georgi Dobrikov. Experimental: Ivaylo Slavchev and Georgi Dobrikov, drafting: Ivaylo Slavchev and Svilen Simeonov. X-ray: Jas. S. Ward and Kari Rissanen. Review and editing the final manuscript: Svilen Simeonov.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 C. A. G. N. Montalbetti and V. Falque, Amide bond formation and peptide coupling, *Tetrahedron*, 2005, **61**, 10827–10852.
- 2 S. Roy, S. Roy and G. W. Gribble, Metal-catalyzed amidation, *Tetrahedron*, 2012, **68**, 9867–9923.
- 3 O. Rezazgui, B. Boëns, K. Teste, J. Vergnaud, P. Trouillas and R. Zerrouki, One-pot and catalyst-free amidation of ester: a matter of non-bonding interactions, *Tetrahedron Lett.*, 2011, **52**, 6796–6799.
- 4 R. A. Sheldon, Atom efficiency and catalysis in organic synthesis, *Pure Appl. Chem.*, 2000, **72**, 1233–1246.
- 5 C. W. Cheung, M. L. Ploeger and X. Hu, Direct amidation of esters with nitroarenes, *Nat. Commun.*, 2017, **8**, 14878–14888.
- 6 T. Ohshima, Y. Hayashi, K. Agura, Y. Fujii, A. Yoshiyama and K. Mashima, Sodium methoxide: a simple but highly efficient catalyst for the direct amidation of esters, *Chem. Commun.*, 2012, **48**, 5434–5436.
- 7 S. A. Rzhavskiy, A. A. Ageshina, G. A. Chesnokov, P. S. Gribov, M. A. Topchiy, M. S. Nechaev and A. F. Asachenko, Solvent- and transition metal-free amide synthesis from phenyl esters and aryl amines, *RSC Adv.*, 2019, **9**, 1536–1540.
- 8 G. Li, C.-L. Ji, X. Hong and M. Szostak, Highly chemoselective, transition-metal-free transamidation of unactivated amides and direct amidation of alkyl esters by N–C/O–C cleavage, *J. Am. Chem. Soc.*, 2019, **141**, 11161–11172.
- 9 M. Fairley, L. J. Bole, F. F. Mulks, L. Main, A. R. Kennedy, C. T. O’Hara, J. García-Alvarez and E. Hevia, Ultrafast amidation of esters using lithium amides under aerobic ambient temperature conditions in sustainable solvents, *Chem. Sci.*, 2020, **11**, 6500–6509.
- 10 J. L. Vrijdag, F. Delgado, N. Alonso, W. M. De Borggraeve, N. Pérez-Macias and J. Alcázar, Practical preparation of challenging amides from non-nucleophilic amines and esters under flow conditions, *Chem. Commun.*, 2014, **50**, 15094–15097.
- 11 W. I. Nicholson, F. Barreteau, J. A. Leitch, R. Payne, I. Priestley, E. Godineau, C. Battilocchio and D. L. Browne, Direct amidation of esters by ball milling, *Angew. Chem., Int. Ed.*, 2021, **60**, 21868–21874.
- 12 P. Jeschke, Pesticides and their use as agrochemicals, *Pest Manage. Sci.*, 2016, **72**, 210–225.

- 13 J. F. Teichert and B. L. Feringa, Phosphoramidites: Privileged Ligands in Asymmetric Catalysis, *Angew. Chem., Int. Ed.*, 2010, **49**, 2486–2528.
- 14 F. M. Oliveira, L. C. A. Barbosa and F. M. D. Ismail, The diverse pharmacology and medicinal chemistry of phosphoramidates – a review, *RSC Adv.*, 2014, **4**, 18998–19012.
- 15 E. J. Itumoh, S. Data and E. M. Leita, Opening up the toolbox: synthesis and mechanisms of phosphoramidates, *Molecules*, 2020, **25**, 3684–3721.
- 16 F. Bouchareb and M. Berredjem, Recent progress in the synthesis of phosphoramidate and phosphonamide derivatives: A review, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2021, 1–21.
- 17 L. F. Audrieth and A. D. F. Toy, The Aquo Ammono Phosphoric Acids. I. Preparation of Phenyl Esters of Amido- and Diamidophosphoric Acids, *J. Am. Chem. Soc.*, 1941, **63**, 2117–2119.
- 18 F. R. Atherton, H. T. Openshaw and A. R. Todd, Studies on phosphorylation. Part II. The reaction of dialkyl phosphites with polyhalogen compounds in presence of bases. A new method for the phosphorylation of amines, *J. Chem. Soc. (Resumed)*, 1945, 660–663.
- 19 J. Steinbach, E. Herrmann and L. Riesel, Zur Umsetzung des Zweikomponentensystems Trialkylphosphit/Tetrachlorkohlenstoff mit wasserstoffhaltigen Nucleophilen 2. Die Reaktion mit Ammoniak und Aminen, *Z. Anorg. Allg. Chem.*, 1985, **523**, 180–186.
- 20 A. Zwierzak and K. Osowska-Pacowicka, Direct conversion of diethyl hydrogen phosphate into diethyl phosphoramidates, *Monatsh. Chem.*, 1984, **115**, 117–120.
- 21 Q. Li, X. Sun, X. Yang, M. Wu, S. Sun and X. Chen, Transition-metal-free amination phosphoryl azide for the synthesis of phosphoramidates, *RSC Adv.*, 2019, **9**, 16040–16043.
- 22 H. Kim, J. Park, J. G. Kim and S. Chang, Synthesis of phosphoramidates: a facile approach based on the C–N bond formation via Ir-catalyzed direct C–H amidation, *Org. Lett.*, 2014, **16**, 5466–5469.
- 23 W. Xiao, C.-Y. Zhou and C.-M. Che, Ruthenium(IV) porphyrin catalyzed phosphoramidation of aldehydes with phosphoryl azides as a nitrene source, *Chem. Commun.*, 2012, **48**, 5871–5873.
- 24 B. R. Kim, H.-G. Lee, S.-B. Kang, G. H. Sung, J.-J. Kim, J. K. Park, S.-G. Lee and Y.-J. Yoon, tert-Butoxide-assisted amidation of esters under green conditions, *Synthesis*, 2012, **44**, 42–50.
- 25 F.-Z. Zradni, J. Hamelin and A. Derdour, Synthesis of amides from esters and amines under microwave irradiation, *Synth. Commun.*, 2002, **32**, 3525–3531.
- 26 D. Caine, Potassium *t*-Butoxide–Dimethyl Sulfoxide, *Encyclopedia of Reagents for Organic Synthesis (EROS)*, 2001.
- 27 P. J. Wagner and M. J. Lindstrom, Radical cleavage and competing photoreactions of phenacyl sulfides, *J. Am. Chem. Soc.*, 1987, **109**, 3062–3067.
- 28 D. C. Deka, B. Purkayastha and M. Paul, A facile conversion of aromatic esters to amides by using lithium amide under mild reaction condition, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2003, **42**(10), 2641–2642.
- 29 H. Huang, J. Ash and J. Y. Kang, TiF_4 -promoted activating strategy of phosphate analogues: synthesis of mixed phosphates and phosphinate, *Org. Lett.*, 2018, **20**, 4938–4941.
- 30 J. Lee, J. Lee, M. Kang, M. Shin, J.-M. Kim, S.-U. Kang, J.-O. Lim, H.-K. Choi, Y.-G. Suh, H.-G. Park, et al., *N*-(3-Acyloxy-2-benzylpropyl)-*N'*-[4-(methylsulfonylamino)benzyl] thiourea Analogues: Novel Potent and High Affinity Antagonists and Partial Antagonists of the Vanilloid Receptor, *J. Med. Chem.*, 2003, **46**, 3116–3126.
- 31 G. Hahn, P. Kunnas, N. de Jonge and R. Kempe, General synthesis of primary amines via reductive amination employing a reusable nickel catalyst, *Nat. Catal.*, 2019, **2**, 71–77.
- 32 D. C. Lenstra, P. E. Lenting and J. Mecnović, Sustainable organophosphorus-catalysed Staudinger reduction, *Green Chem.*, 2018, **20**, 4418–4422.
- 33 R. Labes, D. González-Calderón, C. Battilocchio, C. Mateos, G. R. Cumming, O. de Frutos, J. A. Rincón and S. V. Ley, Rapid continuous ruthenium-catalysed transfer hydrogenation of aromatic nitriles to primary amines, *Synlett*, 2017, **28**, 2855–2858.
- 34 L. K. Pandey, U. Pathak, A. Mazumder and S. Mathur, A convenient one-pot preparation of *N*-substituted thioamides, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2010, **49B**, 1225–1228.
- 35 T. T. Tung and J. Nielsen, Amide bond formation in aqueous solution: direct coupling of metal carboxylate salts with ammonium salts at room temperature, *Org. Biomol. Chem.*, 2021, **19**, 10073–10080.
- 36 B. Zoller, J. Zapp and P. H. Huy, Rapid organocatalytic formation of carbon monoxide: application towards carbonylative cross couplings, *Chem.–Eur. J.*, 2020, **26**, 9632–9638.
- 37 H. Mei, J. Hu, S. Xiao, Y. Lei and G. Li, Palladium-1,10-phenanthroline complex encaged in Y zeolite: An efficient and highly recyclable heterogeneous catalyst for aminocarbonylation, *Appl. Catal., A*, 2014, **475**, 40–47.
- 38 Z. Li, L. Liu, K. Xu, T. Huang, X. Li, B. Song and T. Chen, Palladium-catalyzed *N*-acylation of tertiary amines by carboxylic acids: a method for the synthesis of amides, *Org. Lett.*, 2020, **22**, 5517–5521.
- 39 S. Kar, Y. Xie, Q. Q. Zhou, Y. Diskin-Posner, Y. Ben-David and D. Milstein, Near-ambient-temperature dehydrogenative synthesis of the amide bond: mechanistic insight and applications, *ACS Catal.*, 2021, **11**, 7383–7393.
- 40 A. Bhattacharya, R. E. Plata, V. Villarreal, S. Muramulla and J. Wu, An efficient conversion of nitriles to amides: application in the synthesis of *N,N*-diethyl-*m*-toluamide (DEET™), *Tetrahedron Lett.*, 2006, **47**, 505–506.
- 41 M.-C. Tseng, C.-Y. Lai, Y.-W. Chu and Y.-H. Chu, Tin triflate-mediated total synthesis of circumdatin F, sclerotigenin, asperlicin C, and other quinazolino[3,2-*a*][1,4] benzodiazepines, *Chem. Commun.*, 2009, 445–447.

- 42 M.-C. Tseng, H.-Y. Yang and Y.-H. Chu, Total synthesis of asperlicin C, circumdatin F, demethylbenzomalvin A, demethoxycircumdatin H, sclerotigenin, and other fused quinazolinones, *Org. Biomol. Chem.*, 2010, **8**, 419–427.
- 43 H. Esteves, Â. de Fátima, R. d. P. Castro, J. R. Sabino, F. Macedo and T. O. Brito, A simple one-pot methodology for the synthesis of substituted benzoylguanidines from benzoylthioureas using *tert*-butyl hydroperoxide, *Tetrahedron Lett.*, 2015, **56**, 6872–6874.
- 44 G. Qiao, Z. Zhang, B. Huang, L. Zhu, F. Xiao and Z. Zhang, Palladium-catalyzed one-pot synthesis of *N*-sulfonyl, *N*-phosphoryl, and *N*-acyl guanidines, *Synthesis*, 2018, **50**, 330–340.
- 45 S. Cunha, B. R. de Lima and A. R. de Souza, Bismuth nitrate pentahydrate: a new and environmentally benign reagent for guanidylation of *N*-benzoylthioureas, *Tetrahedron Lett.*, 2002, **43**, 49–52.
- 46 P.-X. Li, X.-J. Meng, L. Yang, H.-T. Tang and Y.-M. Pan, Synthesis of multisubstituted guanidines through palladium-catalyzed insertion of isonitriles, *Synlett*, 2018, **29**, 2326–2330.
- 47 G. Xin, Y. Ming, C. Ji, Z. Wei, S. Li, S. L. Morris-Natschke, X. Zhang, K. Yu, Y. Li, B. Zhang, et al., Novel potent antiplatelet thrombotic agent derived from biguanide for ischemic stroke, *Eur. J. Med. Chem.*, 2020, **200**, 112462–112465.