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Library Synthesis

2,2,2-Trifluoroethyl Oxalates in the One-Pot Parallel Synthesis of Hindered Aliphatic Oxamides

Andrey V. Bogolubsky,[a] Yurii S. Moroz,*[b] Pavel K. Mykhailiuk,*[a,c] Sergey E. Pipko,[b,d] Alexander V. Grishchenko,[d] Anton V. Zhemera,[a] Anzhelika I. Konovets,[a,e] Roman A. Doroschuk,[c] Yurii V. Dmytriv,[a] Olga A. Zaporozhets,[c] and Andrey Tolmachev[a,b]

Dedicated to the 25th anniversary of Enamine Ltd.

Abstract: A simple parallel synthesis approach to unsymmetrical N^1,N^2-substituted aliphatic oxamides using methyl (2,2,2-trifluoroethyl) oxalate and bis(2,2,2-trifluoroethyl) oxalate was developed. The method was validated on a 52-membered set of the oxamides, derived mainly from hindered primary and secondary aliphatic amines, and gave the products with a high overall success rate in moderate yields.

Introduction

The "Escape from Flatland" concept has become an important part of modern drug discovery, as recent publications have placed complexity and three-dimensionality among the major descriptors for predicting the success of drug-candidate molecules.[1–3] The concept involves the substitution of a "flat" aromatic moiety in a molecule with a saturated fragment, rich in sp^3-hybridized carbon atoms, to positively influence important drug-related properties:[4–7] such a change decreases lipophilicity and toxicity, and increases solubility, permeability, and oral absorption. The development of suitable methods for the assembly of molecules from "saturated" fragments is an important goal within this context. We have contributed to this task by designing parallel synthesis approaches to aliphatic derivatives of sulfonamides,[8] ureas,[9] secondary amines,[10,11] sulfides, sulfoxides, sulfones,[12] and N^1-aryl-N^2-aliphatic-substituted oxamides.[13] A logical continuation of the last project would be the development of a method for the creation of unsymmetrical N^1,N^2-substituted aliphatic oxamide motifs bearing diverse substituents. Such motifs are found in medicinal[14–18] and synthetic organic chemistry[19–30] (Figure 1), but quick access to sized libraries of N^1,N^2-substituted aliphatic oxamides remains unknown.

Our typical strategy in achieving the synthesis of diverse sets of compounds is based on a parallel synthesis. The criteria for the parallel synthesis are as follows: i) a one-pot experimental design with simple set-up and work-up steps; ii) use of readily available substrates to give diversity to compound libraries; and iii) applicability of the method to various substrates.

The usual approach to unsymmetrical N^1,N^2-substituted aliphatic oxamides has been a stepwise aminolysis of ethyl chlorooxoacetate[26,29,31,32] (**1a**) or diethyl oxalate (**1b**) (Figure 2).[33,34] The procedure satisfies our criteria, but closer examination reveals that reagents **1a** and **1b** are incompatible with the parallel synthesis. The aminolysis of **1a** occurs vigorously with aliphatic amines, and requires a dropwise addition of the reactants, maintaining a low temperature, to give pure ester monoamides. The aminolysis of **1b** was successfully achieved with reactive amines, but it failed with sterically hindered amine substrates.[35] The solution to the "too reactive – too inert" dilemma could involve the use of a moderately reactive reagent.

Our previous experience with unsymmetrical aliphatic ureas[9] revealed that switching from ethyl chloroformate and diethyl carbonate to the bis(2,2,2-trifluoroethyl) analog resulted in a high chemoselectivity in the stepwise aminolysis, and thus enabled a one-pot parallel synthesis. Indeed, the moderately reactive bis(2,2,2-trifluoroethyl) carbonate has proved its efficiency with different aliphatic amines, affording ureas in 30–

[a] *Enamine Ltd., 78 Chervonotkatska Street, Kyiv 02094, Ukraine E-mail: Pavel.Mykhailiuk@mail.enamine.net Pavel.Mykhailiuk@gmail.com http://www.enamine.net/*
[b] *ChemBioCenter, Kyiv National Taras Shevchenko University, 61 Chervonotkatska Street, Kyiv 02094, Ukraine E-mail: ysmoroz@gmail.com*
[c] *Department of Chemistry, Kyiv National Taras Shevchenko University, 64 Volodymyrska Street, Kyiv 01601, Ukraine*
[d] *UkrOrgSyntez Ltd. (UORSY), 29 Schorsa Street, Kyiv 01133, Ukraine http://www.uorsy.net/*
[e] *The Institute of High Technologies, Kyiv National Taras Shevchenko University, 4 Glushkov Street, Building 5, Kyiv 03187, Ukraine*

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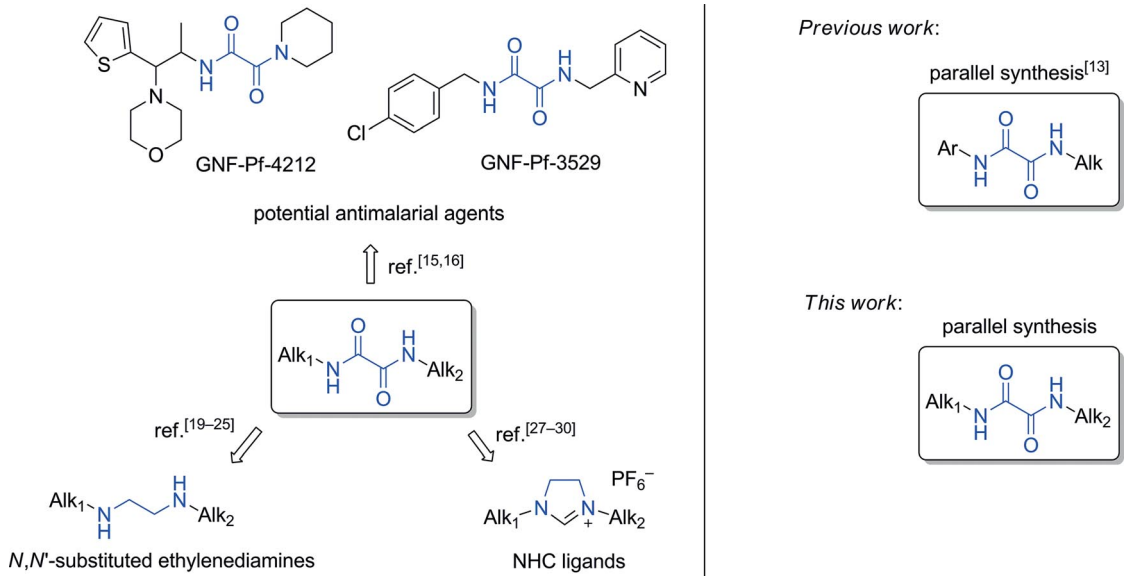


Figure 1. Aliphatic oxamides in medicinal and organic chemistry.

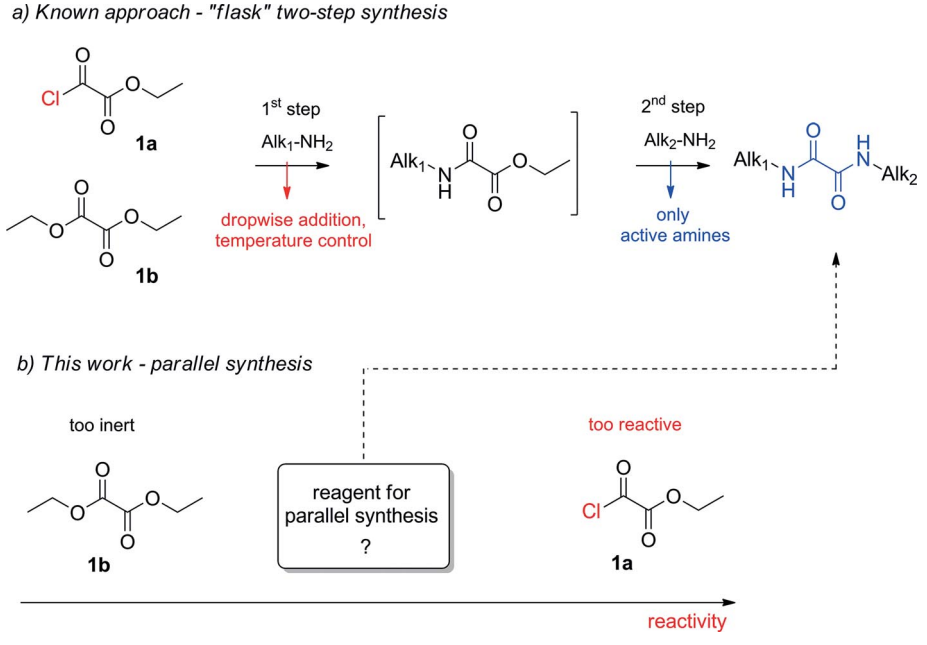


Figure 2. Comparison of reagents **1a** and **1b** in "flask" and parallel syntheses of aliphatic oxamides.

90 % isolated yield. We have now expanded this strategy to the synthesis of aliphatic oxamides, introducing 2,2,2-trifluoroethyl oxalate derivatives as valuable alternatives to the commonly used reagents. In this paper, we describe the development of a one-pot parallel synthesis procedure, and its application to the synthesis of a 52-membered set of unsymmetrical N^1,N^2-substituted oxamides.

Results and Discussion

The one-pot method we envisaged includes two types of reagents: amines and an oxalate, and we initially aimed to answer two questions: i) which 2,2,2-trifluoroethyl oxalate derivative should we use in the parallel synthesis? and ii) which aliphatic amines are we able to use with our approach? Consequently, in the first part of the study, we aimed to identify an optimal oxalate reagent, in the second part, we aimed to find the limits of the method. For the oxalate reagents, we chose three available 2,2,2-trifluoroethyl derivatives for testing: ethyl (2,2,2-trifluoroethyl) oxalate (**1c**), methyl (2,2,2-trifluoroethyl) oxalate (**1d**), and bis(2,2,2-trifluoroethyl) oxalate (**1e**), with **1b** as a reference (Figure 3). The effectiveness of the aminolysis increases with a decrease of the pK_a value of the alcohol leaving group (the pK_a values for ethanol, methanol, and 2,2,2-trifluoroethanol are 16, 15.5, and 12.5, respectively).[36–38] The reactivity of these reagents, therefore, should increase from **1b** to **1e**. For the

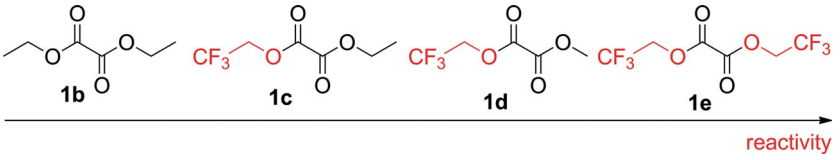


Figure 3. Tested reagents **1b**–**1e**.

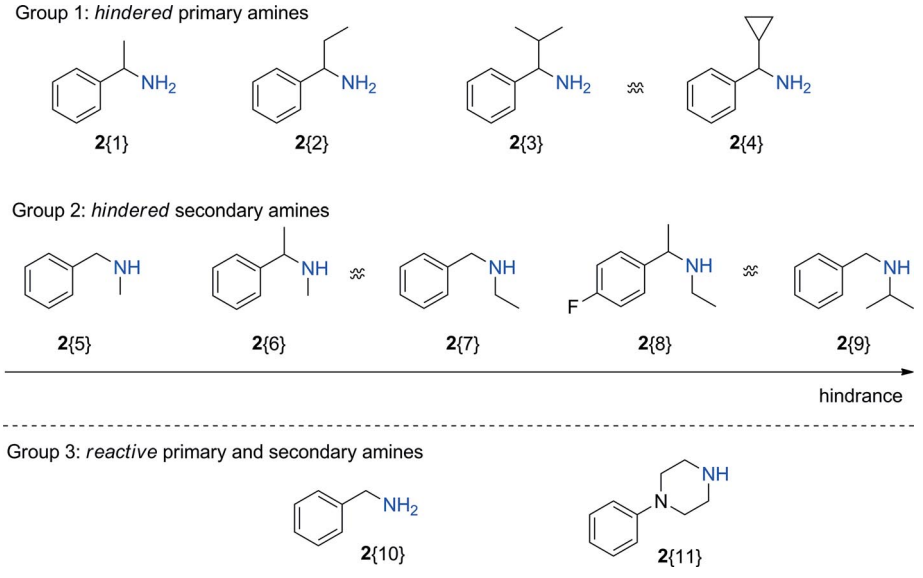


Figure 4. Diversity reagents **2** selected for the optimization of the reaction conditions.

amines, we chose 36 aliphatic amines from our internal database, and utilized 11 of these for optimization of the reaction conditions (chemset **2**, Figure 4, Figure S1 in the Supporting Information). In the optimization study, we focused on sterically hindered amines, because they have been major contributors to failed aminolysis experiments.[39] We divided the amine substrates into hindered primary (group 1, **2**{1–4}) and hindered secondary amines (group 2, **2**{5–9}), but also included two unhindered or reactive amines (group 3, **2**{10–11}) to test more combinations. Phenyl-containing amines were chosen for easy identification by LC–MS.

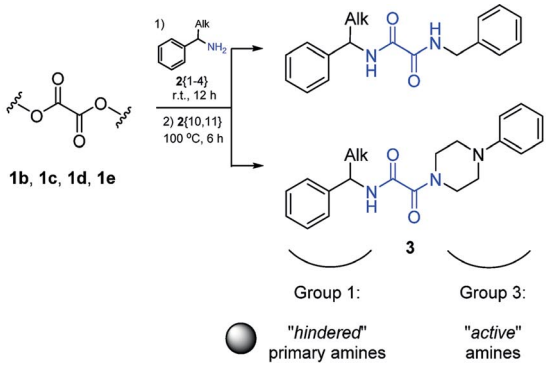
Optimization of the Reaction Conditions: When Hindered Meets Reactive

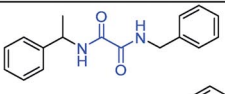
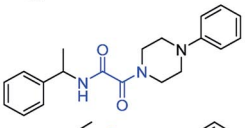
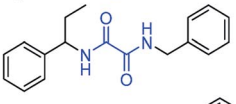
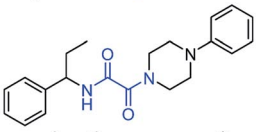
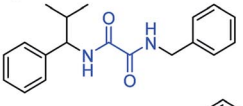
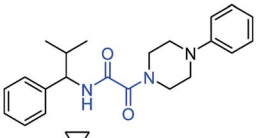
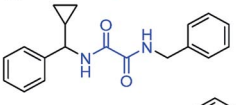
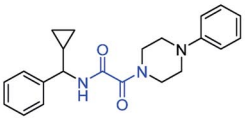
The oxalate reagent has to support: i) chemoselective formation of an ester monoamide but not symmetrical bisamide side-products in the first aminolysis; and ii) efficient conversion of the ester monoamide into the product in the second aminolysis. To identify the optimal oxalate derivative, we set up 72 reactions (18 per oxalate) on a millimolar scale, introducing hindered amines **2**{1–9} (i.e., groups 1 and 2) in the first aminolysis, and unhindered amines **2**{10–11} (i.e., group 3) in the second aminolysis (Table 1). We used a one-pot procedure similar to that reported for unsymmetrical aliphatic ureas.[9] Briefly, a sealed vial with an acetonitrile solution (1 mL) of the first amine **2** (1 equiv.) and the oxalate (1 equiv.) was kept at room temperature for 12 h with occasional shaking. Then, **2**{10} or **2**{11} (1 equiv.) was added, and the reaction mixture was heated at 100 °C for 6 h. We used two different work-up procedures, depending on the state of the reaction mixtures. If a precipitated product formed, it was collected by filtration, and dried in an oven. In other cases, extraction with $CHCl_3$ was carried out. The product content in the crude samples was determined by using LC–MS or ^{1}H NMR spectroscopy. Samples with purities below 90 % were subjected to flash chromatography. All synthesized compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy and LC–MS to confirm their identity and purity.

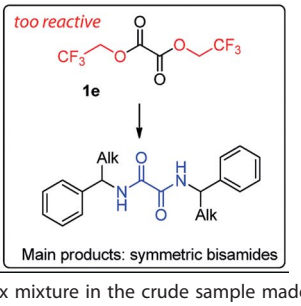
A combinatorial approach often gives compounds in low isolated yields, despite a high product content in the crude samples after the reaction. The low yields are a result of the use of a single method of purification that is optimal for most of the compounds, but not for the whole set. Thus, analysis based on isolated yields might result in incorrect conclusions about the effectiveness of a studied reaction. Therefore, we used product content in the crude samples as the main parameter in analyzing our data.

The experiments revealed two scenarios depending on the type of amine used. Reactions involving hindered primary aliphatic amines (Table 1, Figures S1–S32) were successful with unsymmetrical reagents **1c** and **1d**, resulting in a 70–96 % product content. Reagent **1b** was less efficient than **1c** and **1d** under the same conditions, and the experiments with **1e** failed, and gave mainly symmetrical side-products. The isolated yields for oxamides **3**{1–4, 10–11} were higher in the reactions with rea-

Table 1. Identifying the optimal oxalate reagent. Case 1: group 1 and group 3 amines.



Entry		Synthesized oxamides, chemset **3**	Product[a] in crude sample (%) / isolated yield (%)			
			1b	**1c**	**1d**	**1e**
1	**3**{1,10}		65/38	**87/40**	**96/78**	*43/< 5*[b]
2	**3**{1,11}		49/17	**76/38**	**76/42**	*< 5*
3	**3**{2,10}		**74/53**	**92/79**	**95/78**	*35/< 5*
4	**3**{2,11}		51/35	**73/47**	**84/39**	*< 5*
5	**3**{3,10}		61/20	**81/61**	**96/78**	53/17
6	**3**{3,11}		42/< 5	**71/23**	**84/47**	*7/< 5*
7	**3**{4,10}		65/48	**89/73**	**85/35**	61/21
8	**3**{4,11}		48/10	**70/37**	**72/58**	**74/25**



[a] Product content was determined by LC–MS or ^{1}H NMR spectroscopy. [b] Low product content or complex mixture in the crude sample made purification impossible.

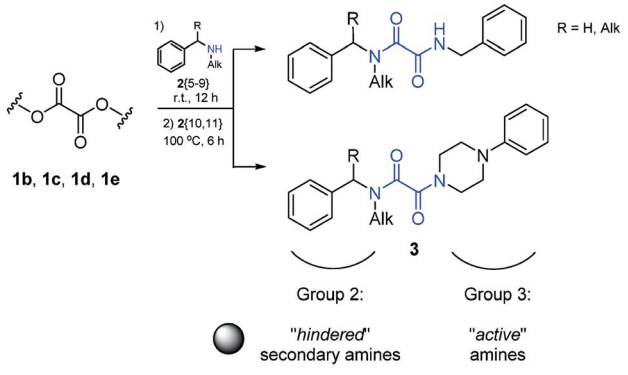
gents **1c** and **1d** than in the reactions with **1b**. We were not able to isolate compounds **3**{1, 10–11}, **3**{2, 10–11}, and **3**{3, 11} in the experiments with **1e**.

The formation of the ester monoamide is a critical step under the parallel synthesis conditions. This reaction requires the amine and the oxalate to have balanced reactivities to ensure complete reaction, and to avoid the formation of the symmetrical side-products. The electron-withdrawing 2,2,2-trifluoroethyl groups might tune the reactivity of the studied oxalates. This effect supported the chemoselective formation of the ester monoamides from reagents **1c** and **1d** with hindered primary aliphatic amines **2**{1–4}; while **1e** underwent complete aminolysis to give the symmetrical bisamides. Analysis of the crude product mixtures obtained in the synthesis of **3**{1–4, 10–11} clearly proved this conclusion. Also, the result of the following experiment supports our idea: substitution of an ethyl group with a 2,2,2-trifluoroethyl group positively affected the first aminolysis, and as a result the reactions with **1c** and **1d** gave higher isolated yields than those with **1b**. The combined data, therefore, allowed to identify oxalate **1c** or **1d** as the optimal reagent for the parallel synthesis of N^1,N^2-substituted aliphatic oxamides when a combination of primary and reactive amines is used (procedure A in the Experimental Section).

Reactions involving hindered secondary aliphatic amines (Table 2, entries 1–10) were successful with reagent **1e** and failed with **1b**, **1c**, and **1d**. LC–MS analysis showed a 54–97 % product content in the experiments with **1e**, which afforded isolated yields at least 2.5 times higher than those obtained with the other oxalate reagents. The reactions with **1b**, **1c**, and **1d** resulted mainly in the formation of the side-products including benzyl or 1-phenylpiperazenyl monoamide esters, bis-(benzyl) or bis(1-phenylpiperazenyl) oxamides, and the unreacted amines. The product content for most experiments with **1c** and **1d** was less than 20 %, and for **1b** it was less than 5 % (Figures S32–S67). This made purification of the products impractical.

Group 2 amines **2**{5–9} required a more reactive carbonyl substrate for the aminolysis to go to completion. Therefore, hindered secondary amines would react with **1e** more effectively than with **1b**–**1d** (which are too inert for these amines) to give the corresponding ester monoamides. The experimental data supported this conclusion, showing a 100 % success rate in the

Table 2. Identifying the optimal oxalate reagent. Case 1: group 2 and group 3 amines.



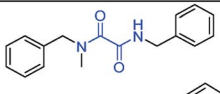
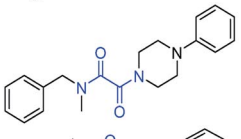
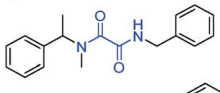
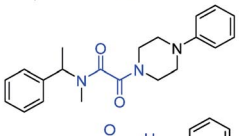
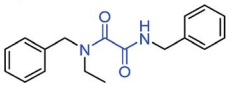
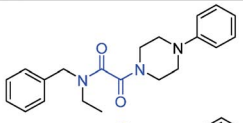
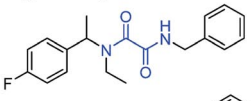
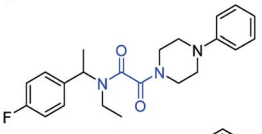
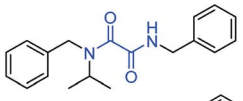
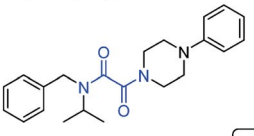
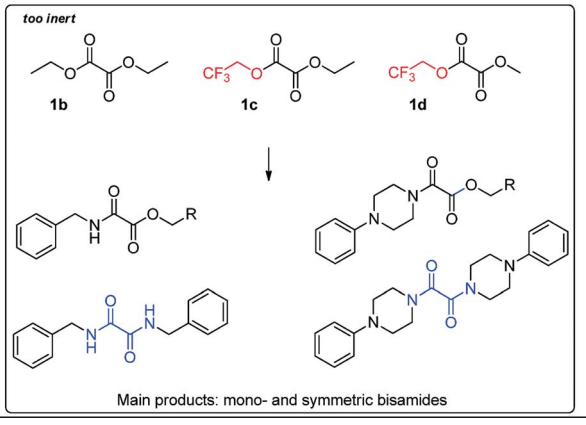
Entry		Synthesized oxamides, chemset **3**	Product[a] in crude sample (%) / isolated yield (%)			
			1b	**1c**	**1d**	**1e**
1	**3**{5,10}		*29/< 5*[b]	**68/18**	**74/12**	**93/75**
2	**3**{5,11}		*9/< 5*	*13/< 5*	*34/< 5*	**91/77**
3	**3**{6,10}		*< 5*	**73/20**	**60/15**	**99/79**
4	**3**{6,11}		*< 5*	*11/< 5*	*27/6*	**96/86**
5	**3**{7,10}		*< 5*	**70/18**	**61/20**	**97/74**

Table 2. *(Continued)*.

Entry		Synthesized oxamides, chemset **3**	Product[a] in crude sample (%) / isolated yield (%) **1b**	**1c**	**1d**	**1e**
6	**3**{7,11}		*< 5*	*8/< 5*	*24/< 5*	**90/66**
7	**3**{8,10}		*< 5*	*18/< 5*	**61/10**	**80/27**
8	**3**{8,11}		*< 5*	*10/< 5*	*28/< 5*	**54/15**
9	**3**{9,10}		*< 5*	*31/< 5*	*< 5/< 5*	**95/68**
10	**3**{9,11}		*< 5*	*14/< 5*	*25/< 5*	**87/72**



[a] Product content was determined by LC–MS or ^{1}H NMR spectroscopy. [b] Low product content or complex mixture in the crude sample made purification impossible.

reactions with **1e**, 33 % in the reactions with **1c** and **1d**, and less than 5 % in the reactions with **1b**. These data allowed us to identify oxalate **1e** as the optimal reagent for the parallel synthesis of N^1,N^2-substituted aliphatic oxamides when hindered secondary amines are used together with reactive amines (procedure B in the Experimental Section).

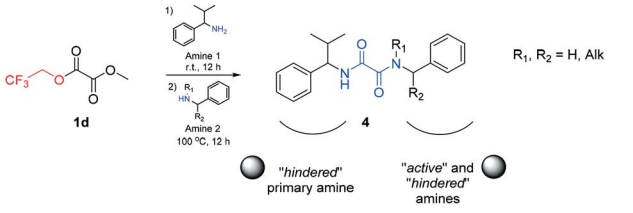
Evaluation of the Optimized Conditions

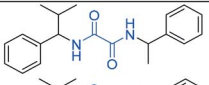
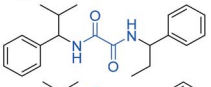
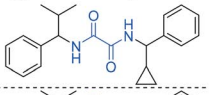
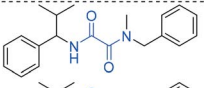
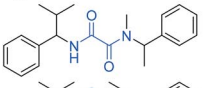
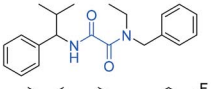
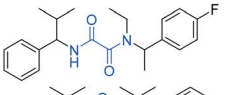
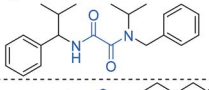
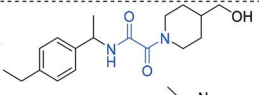
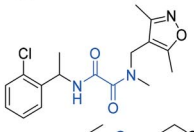
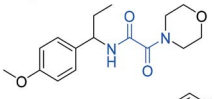
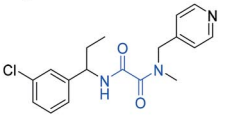
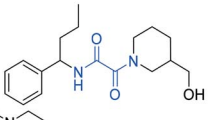
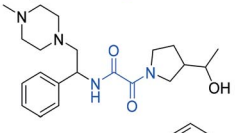
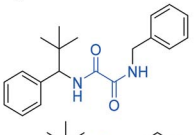
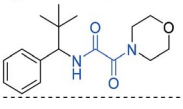
Encouraged by the outcome of the initial experiments, we went on to explore the limitations (if any) of our approach.

Case 1: When hindered meets hindered. As the low reactivity of the ester monoamides might result in low or no yield, we designed two series of experiments in which both the amine substrates were hindered (Table 3, entries 1–8, chemset **4.1**; Table 4, entries 1–8, chemset **5.1**). In chemset **4.1**, we utilized hindered primary amine **2**{3} as the first amine substrate, and a group 1 or group 2 amine as the second amine substrate. For chemset **4.1**, we ran the reactions with oxalate **1d** because it gave higher yields than the ethyl analog in the optimization experiments. In chemset **5.1**, we utilized hindered secondary amine **2**{8} as the first amine substrate, and a group 1 or group 2 amine as the second amine substrate. For chemset **5.1**, we ran the reactions with oxalate **1e** under the modified conditions for the second aminolysis to ensure full conversion of the ester monoamides into the products (vide infra).

LC–MS analysis of the crude mixtures of chemset **4.1** revealed high product content for the experiments with amines **2**{1–2} and **2**{4–5}, and these reactions gave moderate isolated yields. But the experiments with more hindered amines **2**{6–9} failed, and gave the methyl ester monoamides in most cases. Increasing the duration of the second aminolysis — heating for 12 h at 100 °C — had no effect on the efficacy of the conversion of the intermediate. A simple solution to resolve this issue was

Table 3. Identifying the limits of the parallel synthesis approach: hindered primary amine as the first amine substrate.



Entry		Synthesized oxamides, chemset **4**	Product[a] in crude sample (%) / isolated yield (%)
1	**4**{3,1}		**75/68**
2	**4**{3,2}		**91/66**
3	**4**{3,4}		**91/54**
4	**4**{3,5}		**74/34**
5	**4**{3,6}		*17/6*
6	**4**{3,7}		**30/10**
7	**4**{3,8}		*< 5*[b]
8	**4**{3,9}		*< 5*
9	**4**{12,27}		71/28
10	**4**{13,34}		58/34
11	**4**{14,29}		75/46
12	**4**{15,36}		42/22
13	**4**{16,28}		87/38
14	**4**{17,26}		85/38
15	**4**{18,10}		42/23
16	**4**{18,29}		58/35

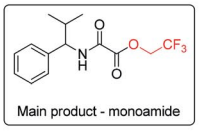


Table 3. *(Continued).*

Entry	Synthesized oxamides, chemset **4**	Product[a] in crude sample (%) / isolated yield (%)
17	**4**{20,27}	90/22
18	**4**{21,23}	95/45
19	**4**{21,32}	43/27
20	**4**{21,33}	43/15
21	**4**{22,24}	91/83
22	**4**{22,25}	95/65
23	**4**{22,30}	85/50
24	**4**{22,31}	61/47

[a] Product content was determined by LC–MS or ^{1}H NMR spectroscopy. The products of entries 1, 2, 3, 5, 7, 13, 14, 21 are mixtures of stereoisomers. [b] Low product content or complex mixture in the crude sample made purification impossible.

to switch to procedure B; the 2,2,2-trifluoroethyl ester monoamides are more reactive than their methyl analogs. Using the latter approach, we obtained the desired oxamides in moderate yields (Table 4, entries 3 and 9–12).

LC–MS analysis of the crude mixtures of chemset **5.1** revealed positive results in the reactions with the primary and less hindered secondary acyclic amine **2**{5} (Table 4, entries 1–5). Experiments with more hindered secondary amines failed, and afforded the corresponding ester monoamides (Table 4, entries 6–8). Increasing the duration of the second aminolysis to 36 h was unsuccessful.

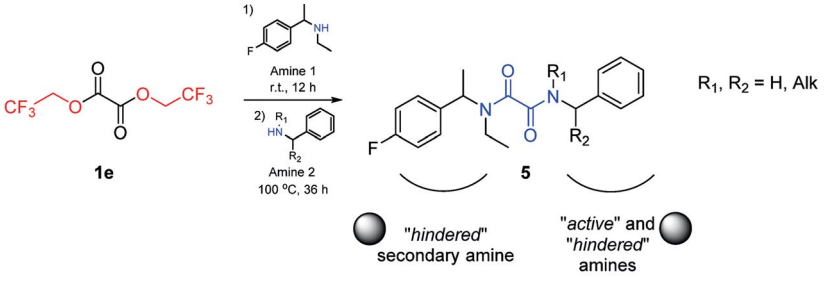
Case 2: When highly hindered meets reactive. We carried out reactions with two *t*Bu-containing amines **2**{18} and **2**{19} as the first amine substrate, and two "reactive" amines **2**{11} and **2**{29} as the second amine substrate. The experiments were successful with highly hindered primary amine **2**{18} (Table 3, entries 15 and 16), but failed with highly hindered secondary amine **2**{19}, which resulted in no reaction (Table 4, entries 13 and 14).

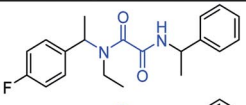
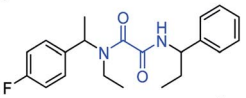
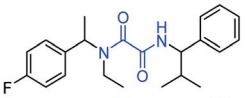
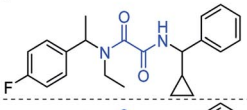
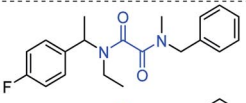
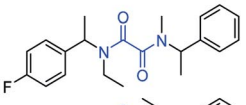
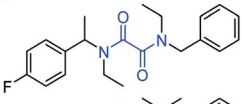
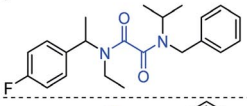
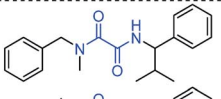
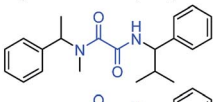
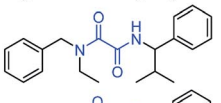
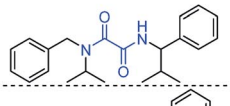
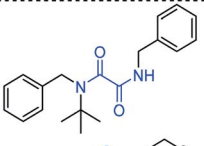
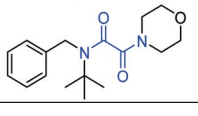
Therefore, a one-pot approach to N^1,N^2-substituted aliphatic oxamides involving poorly reactive aliphatic amines remains challenging,[40,41] and represents a potential limitation of our approach.

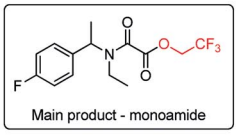
Case 3: When heteroaryl, substituted, or functionalized is involved. We evaluated our approach using aliphatic amines containing functionalities frequently used in medicinal chemistry: substituted phenyl rings (Table 3, entries 9–12, 19, and 20), five- and six-membered heterocycles (Table 3, entries 10, 12, and 17–24), hydroxyl groups (Table 3, entries 9, 13, and 14), and morpholine moieties (Table 3, entries 11, 16, 21, and 23). Positive results were obtained in all experiments, and this allowed us to conclude that: i) our method can be used with various phenyl- and heteroaryl-containing amine substrates; ii) the introduction of electron-withdrawing or electron-donating groups into the ring has no significant influence on the yields; and iii) our method tolerates amines containing additional functional groups.

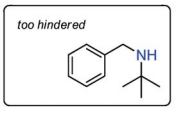
Our results allowed to establish the following guidelines (Figure 5) for the use of 2,2,2-trifluoroethyl oxalates for the one-pot parallel synthesis of N^1,N^2-substituted aliphatic oxamides: i) procedure A, based on ethyl (2,2,2-trifluoroethyl) oxalate (**1c**) or methyl (2,2,2-trifluoroethyl) oxalate (**1d**), is preferable if the first amine substrate is a primary amine, and the second amine substrate is not highly hindered; and ii) procedure B, based on bis(2,2,2-trifluoroethyl) oxalate (**1e**), is preferable if the first amine substrate is a hindered secondary amine.

Table 4. Identifying the limits of the parallel synthesis approach: hindered secondary amine as the first amine substrate.



Entry		Synthesized oxamides, chemset **5**	Product[a] in crude sample (%) / isolated yield (%)
1	**5**{8,1}		**78/50**
2	**5**{8,2}		**79/47**
3	**5**{8,3}		**49/30**
4	**5**{8,4}		**60/51**
5	**5**{8,5}		**85/42**
6	**5**{8,6}		*10/< 5*[b]
7	**5**{8,7}		*9/< 5*
8	**5**{8,9}		*44/< 5*
9	**5**{5,3}		**88/59**
10	**5**{6,3}		**75/44**
11	**5**{7,3}		**71/35**
12	**5**{9,3}		**85/53**
13	**5**{19,10}		*< 5*
14	**5**{19,29}		*< 5*





[a] Product content was determined by LC–MS or ^{1}H NMR spectroscopy. The products of entries 1, 2, 3, 4, 6, 10 are mixtures of stereoisomers. [b] Low product content or complex mixture in the crude sample made purification impossible.

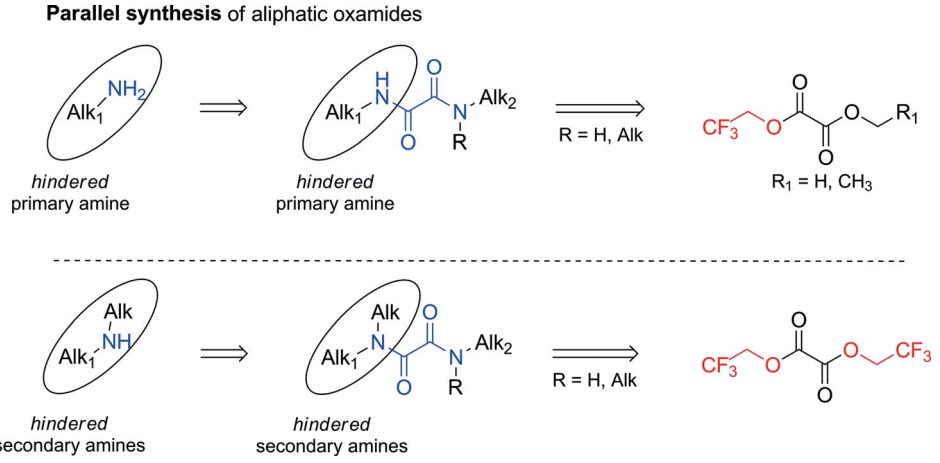


Figure 5. The choice of oxalate reagent depends on the first amine substrate.

Practical Application: When Reactive Meets Reactive

Can we use our approach if both the amine substrates are unhindered amines? We answered this question, carrying out four parallel reactions to prepare the known biologically active compound GNF-Pf-3529, the synthesis of which has not been reported before, under conditions identical to those used for the 18 member set. These experiments were successful, and revealed that the highest product content was obtained in the reaction with **1d**, which afforded GNF-Pf-3529 in 65 % isolated yield (Figure 6, Figures S68–S71).

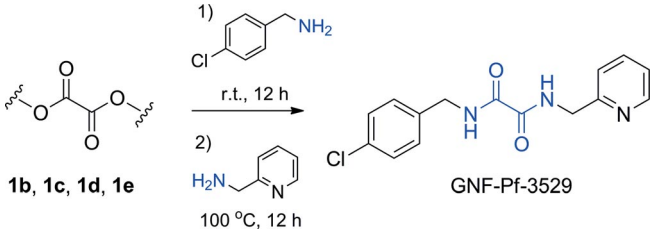


Figure 6. The parallel synthesis of GNF-Pf-3529.

Conclusions

We have developed a simple, one-pot parallel synthesis approach to N^1,N^2-substituted aliphatic oxamides. The approach uses a stepwise aminolysis of 2,2,2-trifluoroethyl oxalates: methyl (2,2,2-trifluoroethyl) oxalate and bis(2,2,2-trifluoroethyl) oxalate. The nature of first amine substrate determines the choice of oxalate reagent. We have established reaction conditions, and evaluated our method on a 52-membered set of new oxamides. The oxamides were prepared on multi-milligram scale from structurally varied aliphatic amines, including heteroaryl-containing and functionalized substrates. We believe that the developed approach will become a useful tool for synthetic and medicinal chemists, and will allow to expand the variety of aliphatic oxamides.

Experimental Section

General Remarks: All chemicals and solvents were obtained from Enamine, and were used without further purification. Ethyl (2,2,2-trifluoroethyl) oxalate, methyl (2,2,2-trifluoroethyl) oxalate, and bis(2,2,2-trifluoroethyl) oxalate were synthesized according to previously reported procedures.[42,43] ^{1}H and ^{13}C NMR spectra were acquired with Bruker Avance DRX 400 and Bruker Avance DRX 500 spectrometers, using [D$_6$]DMSO as a solvent, and tetramethylsilane (TMS) as an internal standard. IR spectra were recorded with a Perkin–Elmer Spectrum BX II instrument. Elemental analysis was carried out with a Vario MICRO Cube elemental microanalyzer (Elementar). Melting points were determined with a Buchi melting-point apparatus. LC–MS data were acquired with an Agilent 1100 HPLC system equipped with diode-array and mass-selective detectors, using a Zorbax SB-C18 column, 4.6 mm × 15 mm; eluent A: acetonitrile/water, 95:5, with 0.1 % TFA; eluent B: water with 0.1 % TFA. If the product content in the crude material was below 90 %, the samples were purified using a Companion Combi-Flash instrument with a UV detector and a reusable LukNova column (gradient elution; eluent A: $CHCl_3$; eluent B: $CHCl_3$/methanol, 7:3).

Optimized Procedures for the Parallel Synthesis of Unsymmetrical N^1,N^2-Substituted Aliphatic Oxamides

Procedure A: A sealed vial (8 mL) containing a mixture of methyl (2,2,2-trifluoroethyl) oxalate (1 mmol) and 2-methyl-1-phenylpropan-1-amine **2**{3} (1 mmol) in acetonitrile (1 mL) was shaken at room temperature for 12 h. Then, 1-phenylpropan-1-amine **2**{2} (1 mmol) was added, and the reaction vial was heated at 100 °C for 12 h to ensure full conversion of the ester monoamide. The product precipitated out upon cooling to room temperature. The precipitate was collected by filtration, then it was suspended in acetonitrile (1.5 mL), and the mixture was placed in an ultrasonic bath for 30 min. The product was collected by filtration, and dried in an oven to give N^1-(2-methyl-1-phenylpropyl)-N^2-(1-phenylpropyl)oxamide (223 mg, 66 %) as a whitish solid, m.p. 173–175 °C. IR (KBr): $\tilde{\nu}$ = 3299, 3035, 2970, 2930, 2872, 1650, 1510, 1213 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.63 (m, 3 H, CH$_3$), 0.79 (m, 3 H, CH$_3$), 0.91 (m, 3 H, CH$_3$), 1.79 (m, 2 H, CH$_2$), 2.17 (m, 1 H, CH), 4.38 (m, 1 H, CH), 4.68 (m, 1 H, CH), 7.15–7.40 (m, 10 H, Ar), 9.0 (m, 2 H, NH) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO): δ = 12.3, 20.0, 28.3, 31.9, 55.1, 60.3, 126.8, 126.9, 127.0 (2), 127.1, 127.5, 127.6, 128.2, 128.3, 128.4, 142.1, 142.2, 142.9, 143.0, 159.6, 159.7, 159.8 ppm. MS (APSI):

m/z = 361.3 $[M + Na]^+$. $C_{21}H_{26}N_2O_2$ (338.4): calcd. C 74.53, H 7.74, N 8.28; found C 74.68, H 7.89, N 8.11. The remaining compounds from chemset **4** were synthesized under essentially identical conditions.

Procedure B: An acetonitrile solution (1 mL) of bis(2,2,2-trifluoroethyl) oxalate (1 mmol) and *N*-ethyl-1-(4-fluorophenyl)ethan-1-amine **2**{8} (1 mmol) was kept at room temperature for 12 h in a sealed vial (8 mL). Then, *N*-methyl-1-phenylmethanamine **2**{5} (1 mmol) was added, and the resulting mixture was heated at 100 °C for 36 h to ensure full conversion of the ester monoamide. Then, the solvent was evaporated in vacuo. The crude mixture was dissolved in chloroform (3 mL), and the solution was washed with HCOOH (10 %), and water. The organic phase was evaporated. The crude product was purified by flash chromatography to give N^1-benzyl-N^2-ethyl-N^2-[1-(4-fluorophenyl)ethyl]-N^1-methyloxamide (144 mg, 42 %) as an oil. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 0.85 (m, 3 H, CH_3), 1.55 (m, 3 H, CH_3), 2.7–2.9 (m, 3 H, CH_3), 3.12 (m, 2 H, CH_2), 4.35–4.65 (m, 2 H, CH_2), 4.88, 5.54 (m, 1 H, CH), 7.15–7.55 (m, 9 H, Ar) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO): δ = 13.5 (2), 15.6, 15.7, 16.9 (2), 17.9, 30.8 (2), 34.4, 34.8, 35.7, 35.9, 48.5, 48.6, 50.7, 50.9, 52.6, 52.8, 55.2, 115.2 (2), 115.4 (2), 127.6, 127.8, 128 (m), 128.7 (m), 129.4 (m), 129.6 (m), 135.8 (m), 135.9 (m), 136.0, 136.6 (m), 160.6 (m), 162.6 (m), 164.3 (m), 164.9 (m), 165.1 ppm. MS (APSI): *m/z* = 359.2 $[M + OH]^-$. $C_{20}H_{23}FN_2O_2$ (342.4): calcd. C 70.15, H 6.77, N 8.18; found C 69.92, H 6.93, N 8.01. The remaining compounds from chemset **5** were synthesized under essentially identical conditions.

Supporting Information (see footnote on the first page of this article): Analytical data for selected synthesized compounds; LC–MS and NMR spectra.

Keywords: Synthetic methods · Combinatorial chemistry · Amides · Amines · Esters · Aminolysis · Steric hindrance

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