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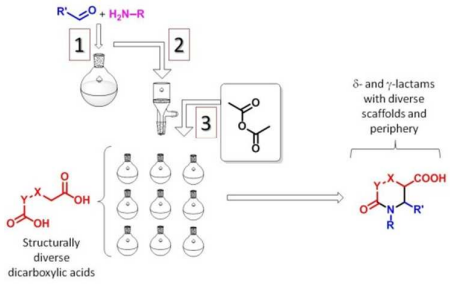


Skeletal Diversity in Combinatorial Fashion: A New Format for the Castagnoli-Cushman Reaction

Anastasia Lepikhina,[†] Dmitry Dar'in,[†] Olga Bakulina,[†] Evgeny Chupakhin,[‡] and Mikhail Krasavin[†,‡,*]

[†] Saint Petersburg State University, Saint Petersburg, 199034 Russian Federation

[‡] Immanuel Kant Baltic Federal University, Kaliningrad, 236016 Russian Federation

ABSTRACT: A new format for the Castagnoli-Cushman reaction of structurally diverse dicarboxylic acids, amines and aldehydes in the presence of acetic anhydride as dehydrating agent is described. The reaction is distinctly amenable to parallel format: the combinatorial array of 180 reactions delivered 157 products of >85% purity without chromatographic purification (of this number, 143 compounds had >94% purity). The new method offers a convenient preparation of the skeletally and peripherally diverse, lead- and druglike γ- and δ-lactam carboxylic acids with high diastereoselectivity in combinatorial fashion.

KEYWORDS: diversity-oriented synthesis, skeletal diversity, multicomponent reactions, Castagnoli-Cushman reaction, cyclodehydration, Schiff bases, phase separation.

INTRODUCTION

The ultimate goal of diversity-oriented synthesis (DOS)[1] is to be able to control the structural diversity of the resulting compounds at the skeletal (scaffold) level with the same degree as combinatorial chemistry allows controlling the diversity of periphery appendages on a given scaffold. This concept was reduced to practice for the first time over 10 years ago in the seminal works of Schreiber and Burke.[2-3] The principal strategy underpinning the realization of this revolutionary approach to sampling the chemical space was in the design of such a common precursor molecule which would act as a substrate toward numerous sets of reagents and conditions, delivering a unique molecular scaffold in each case.[4] Although the design of such pluripotent precursors remains the principal challenge, this does not seem to hinder the steady development of DOS into a routine compound collection enrichment and drug discovery technology.[5]

While offering a high degree of peripheral diversity and definitely amenable to parallel format,[6] multicomponent reactions tend to deliver redundant skeletons unless the variation in the reagent space also results in a variable scaffolds. The latter situation is nicely illustrated by the

employment of different oxocarboxylic acid bifunctional reagents **1** in the Ugi reaction, in which case a variety of lactam frameworks **2** can be harvested.[7] This approach to scaffold diversity, however, can be seldom exploited in the array format as the reaction conditions need to be tailored to each type of **1**.[8] Another multicomponent reaction leading to, primarily, δ- and γ-lactams **3** (recently also shown to deliver ε-lactams[9]) is the Castagnoli-Cushman reaction (CCR)[10] of imines **4** (preformed from the respective amines **5** and aldehydes **6**) with a variety of cyclic α-C-H anhydrides **7**. Compounds **3** are based on a saturated (high-F_{sp3}),[11] relatively hydrophilic scaffold and are distinctly stereodefined (and can be produced in either *trans*- or, less commonly, *cis*-configuration[12]), which makes them ideal[13] potential starting points (leads) for medicinal chemistry optimization, should an associated bioactivity be discovered. For a long time, the range of cyclic anhydrides **7** employable in the CCR[14] remained limited to succinic, glutaric and homophthalic anhydrides. These three have been reported to react under a unified array chemistry format with imines **4**.[15] Recently, we added various heteroatom-including analogs of glutaric anhydride to the arsenal of reagents for the CCR.[16] These, as any other cyclic anhydride, are prepared via the dehydration of respective dicarboxylic acids **8**. This, in principle, adds an additional chemical operation *en route* to **3** and an extra set of variables as to the reaction conditions. Moreover, cyclic anhydrides **7** are hydrolytically prone[17] and can convert back to **8** if not stored with care. Based on these considerations, we decided to investigate if the reagent space for the CCR could be altered to primary amines (**5**), carbonyl compounds (**6**) and α-C-H dicarboxylic acids (**8**). The latter are easier to prepare and handle and can be dehydrated *in situ*, which would make the reaction amenable to parallel format for a wider range of cyclic anhydride components and can potentially eliminate the need to maintain strictly anhydrous conditions while carrying out the reaction array (Figure 1). Herein, we report on a successful realization of this strategy.

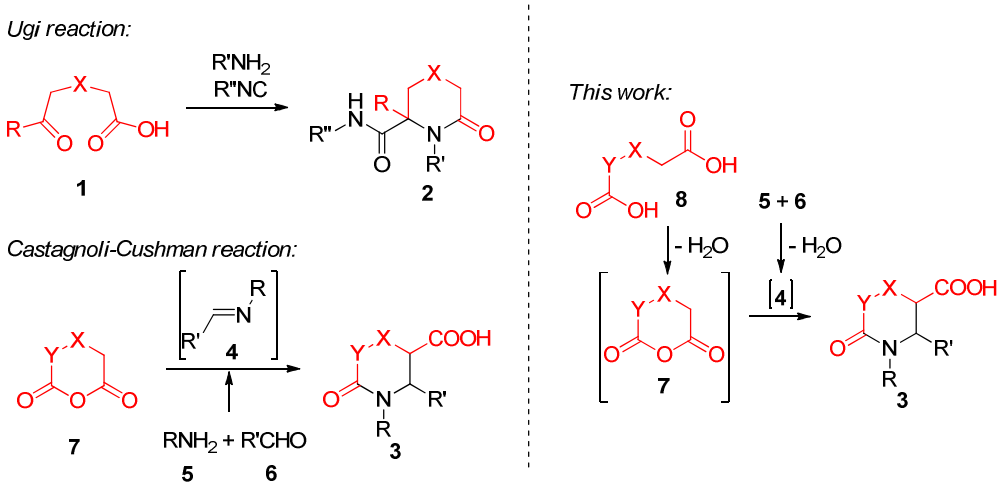
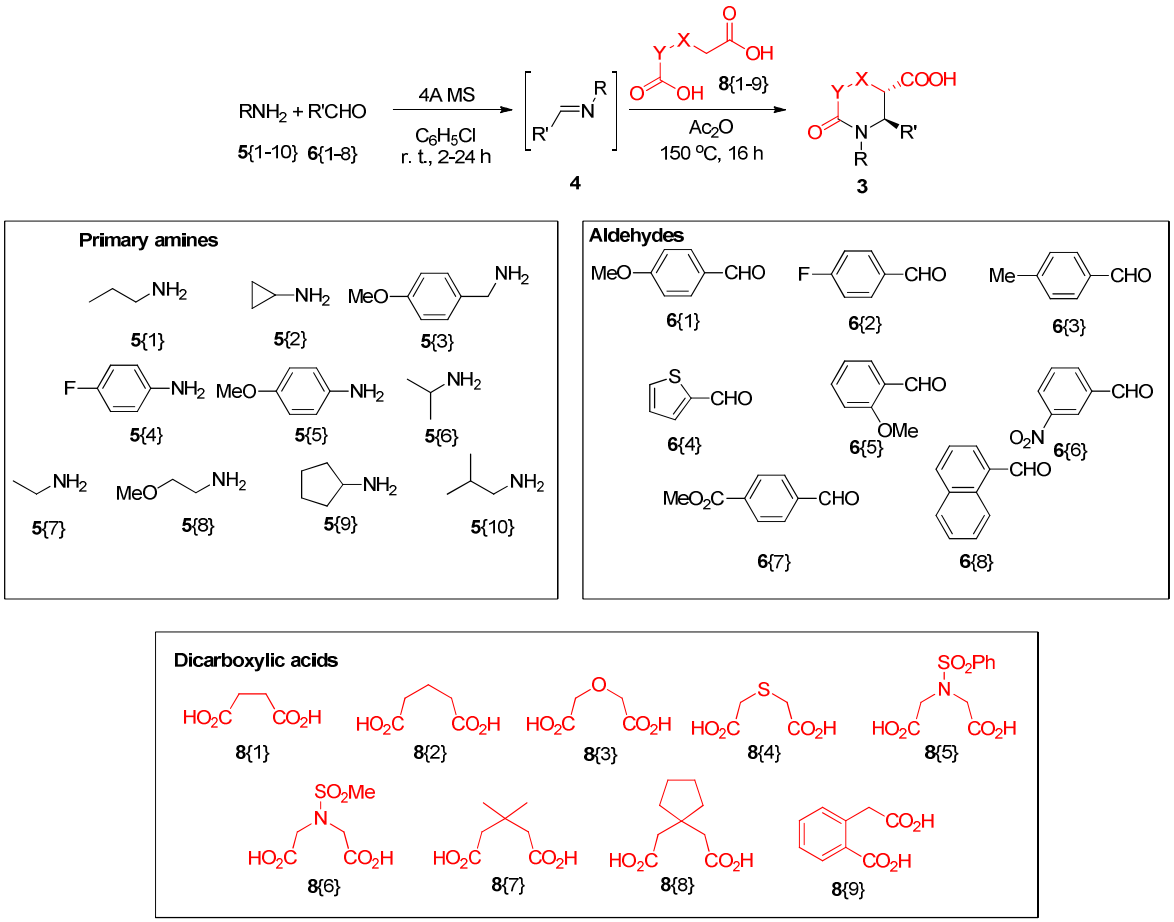


Figure 1. Multicomponent reactions generating skeletal product diversity.

RESULTS AND DISCUSSION

Cyclic anhydrides **7** are known to enter the CCR under a range of conditions – from room temperature in polar solvent such as acetonitrile to reflux in high-boiling hydrocarbon solvents such as toluene or xylenes.[14] In order to allow conducting combinatorial synthesis of lactams **3** with variety of anhydride precursors **8** (Figure 2), after preliminary experimentation, we selected high-boiling chlorobenzene as the solvent of choice both for the *in situ* formation of imine **4** from **5** and **6** and for the subsequent reaction of **4** with **8** under dehydrative conditions.

Table 1. Substrate scope for the new format of the CCR.



Our goal was to minimize the number of manipulations required to pre-form the imine **4** in situ and bring it in contact with dicarboxylic acid **8** in presence of an efficient dehydrating agent. To this end, we tested the formation of **4** in chlorobenzene in presence of 4Å molecular sieves and found it (by ^{1}H NMR monitoring of the reaction progress) to go to completion after 2 h for aliphatic amines and after 24 h for anilines. We then attempted adding **8** directly into the solution of **4** containing molecular sieves followed by addition of acetic anhydride as the dehydrating

agent. However, after reacting these components at 150 ºC for 16 h (i. e., the conditions we found previously to be sufficient to achieve full conversion in most of the CCRs) rather unsatisfactory results in terms of the product yield and purity were obtained. We reasoned that at higher temperature, molecular sieves could release water (absorbed in the course of formation of **4**) which may interfere with the course of the CCR. Simply removing the molecular sieves by filtration led to a marked improvement of the reaction outcome. Therefore, we adopted this procedure as the new general protocol (see Experimental Procedures) for the CCR and applied it to a wide range of substrates **5**, **6** and **8** (Table 1).

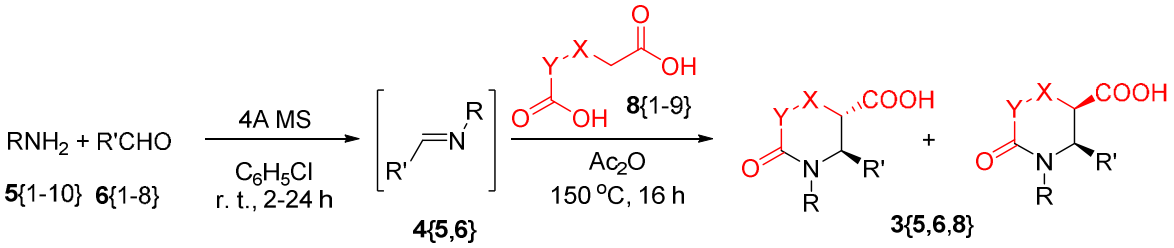
It should be noted that the use of acetic anhydride appears to be optimal for the successful outcome of the reaction. For instance, using thionyl chloride to achieve *in situ* dehydration of **8** in presence of **4** was found to deliver no CCR product whatsoever, presumably, due to the high concentration of HCl in the reaction mixture. The same could be the reason for the failed CCR when oxalyl chloride was tested as the dehydrating agent. The later was recently shown to bring about efficient cyclodehydration of a range of dicarboxylic acids.[18] However, its use in the one-pot CCR format discussed herein was ineffective.

After reacting imines **4** with dicarboxylic acids **8** in presence of a slight excess of acetic anhydride in chlorobenzene at 150 ºC for 16 h, aqueous potassium bicarbonate solution was added to neutralize the acetic acid produced in the course of the dehydration of **8** and to convert product carboxylic acids **3** into respective water-soluble potassium salts. This allowed extracting by-products into an organic solvent (DCM), after which the target products **3** simply precipitated from the neutralized aqueous phase. All reactions were performed in parallel format in screw-capped thick-walled tubes equipped with the stirrer; liquid-liquid and liquid-solid phase separation was performed with an aid of a centrifuge, in centrifuge tubes (see Experimental Procedures). Notably, no specific pre-cautions were taken to exclude air or moisture.

The results presented in Table 2 clearly show that this convenient synthesis and isolation protocol led to high purities and medium-to-high yields of target carboxylic acids **3** in the majority of cases among the 180 reactions performed. For some highly lipophilic (cLogP > 4) products derived from starting material **8**{5}, the isolated yields of **3** were initially rather poor, most likely due to low solubility of the respective carboxylate salts in the aqueous medium. Hence, an alternative isolation protocol was applied involving simple crystallization of the crude product mixture, which raised the yields and resulted in high product purities. Interestingly, the use of 3,3-*gem*-dialkyl-substituted dicarboxylic acids **8**{7} and **8**{8} resulted in markedly poorer results: in nearly half the cases, product purities were lower than 85% (in these as well as in

other similar cases we did not undertake chromatographic purification, considering the overall high success of this reaction array); in three cases, no product **3** formed at all and in all other cases when product **3** purity was satisfactory, the isolated yield was quite low. This result is in line with the previously observed[19] lower reactivity of the respective cyclic anhydrides **7**, most likely attributable to the sterically hindered character of the α-carbon atom in the latter which is a key player[14] in the formation of the target lactam framework.

Table 2. Results (isolated yield,[a] product purity,[b] diastereomeric ratio,[c] cLogP[d], isolation method[e]) obtained in the combinatorial array of 180 CCR-based syntheses of lactams **3**{**5**,**6**,**8**}.



4{5,6}	**8**{1}	**8**{2}	**8**{3}	**8**{4}	**8**{5}	**8**{6}	**8**{7}	**8**{8}	**8**{9}
4{1,1}	68% (6.6:1) [1.87]	89% (5:1) [2.22]	68% (7:1) [2.01]	67% (5:1) [2.49]	68% (6.6:1) [1.87]	82% (*trans*) [1.70]	49% (6:1) [3.25]	40% (7:1) [3.73]	72% (trans) [2.63]
4{2,1}	93% (*trans*) [1.18]	89% (6:1) [1.52]	60% (11:1) [1.31]	80% (7:1) [1.80]	75% (10:1) [3.08]	82% (*trans*) [1.00]	41% (4.5:1) [2.56]	42% (5:1) [3.04]	60% (*trans*) [1.94]
4{3,1}	73% (8:1) [2.41]	60% (5:1) [2.76]	46% (10:1) [2.62]	48% (5.5:1) [3.12]	88%[B] (*trans*) [4.45]	86% (*trans*) [2.34]			38% (*trans*) [3.31]
4{1,2}	66% (15:1) [2.01]	76% (*trans*) [2.36]	71% (*trans*) [2.14]	56% (7:1) [2.63]	71% (8:1) [3.91]	83% (*trans*) [1.84]	37% (4.5:1) [3.39]	32% (6.5:1) [3.39]	68% (*trans*) [2.77]
4{5,1}	53% (9:1) [2.42]	58% (3.3:1) [2.76]	47% (9:1) [2.30]	43% (13:1) [3.04]	91%[B] (*trans*) [4.32]	67% (*trans*) [2.24]	13% (4.3:1) [3.80]	17% (14:1) [4.28]	48% (4.3:1) [4.34]
4{2,2}	64% (8:1) [1.31]	63% (10:1) [1.66]	54% (*trans*) [1.45]	50% (9:1) [1.93]	40% (10:1) [2.65]	40% (10:1) [2.65]	8% (3.5:1) [2.69]	15% (3.8:1) [3.17]	78% (*trans*) [2.07]
4{4,1}	40% (10:1) [2.65]	63% (9:1) [3.00]	27% (13:1) [2.54]	26% (*trans*) [3.27]	63%[B] (*trans*) [4.56]	78% (*trans*) [2.48]			55% (*trans*) [4.57]
4{1,3}	85% (8:1) [2.42]	90% (5:1) [2.77]	62% (8:1) [2.55]	50% (*trans*) [3.04]	74% (*trans*) [4.32]	95% (*trans*) [2.24]	61% (5:1) [3.80]	44% (*trans*) [4.28]	64% (*trans*) [3.18]
4{2,3}	76% (8:1) [1.72]	75% (10:1) [2.07]	59% (14:1) [1.85]	63% (8:1) [2.34]	65% (*trans*) [3.36]	81% (*trans*) [1.55]	30% (4:1) [3.10]		69% (*trans*) [2.48]
4{5,3}	76%	86%	56%	76%	62%[B]	89%			55%

	(9:1) [2.96]	(8:1) [3.31]	(*trans*) [2.85]	(10:1) [3.58]	(5.5:1) [4.86]	(*trans*) [2.79]			(*trans*) [4.88]
4{4,3}	60% (8.5:1) [3.20]	32% (8:1) [3.54]	42% (10:1) [3.08]	74% (7:1) [3.82]	75%[B] (*trans*) [5.10]	86% (*trans*) [3.02]			63% (*trans*) [5.12]
4{3,3}	77% (7.5:1) [2.95]	33% (3.5:1) [3.30]	65% (7.5:1) [3.78]	52% (6:1) [3.67]	90%[B] (6:1) [4.99]	82% (*trans*) [2.89]			75% (*trans*) [3.31]
4{4,2}	15% (9:1) [2.79]	49% (9:1) [3.14]	31% (10:1) [2.68]	69% (10:1) [3.41]	89%[B] (*trans*) [4.69]	75% (*trans*) [2.62]			58% (*trans*) [4.71]
4{3,2}		89% (2:1) [2.89]	77% (4:1) [2.75]	44% (5.5:1) [3.26]	60%[B] (*trans*) [4.59]	80% (*trans*) [2.48]			58% (*trans*) [3.45]
4{5,2}	63% (7.5:1) [2.55]	67% (7.5:1) [2.90]	47% (4:1) [2.44]	67% (9:1) [3.17]	80%[B] (*trans*) [4.46]	75% (*trans*) [2.38]			65% (*trans*) [3.78]
4{6,4}	94% (11:1) [1.45]	52% (11:1) [1.80]	43% (*trans*) [1.58]	43% (9.3:1) [2.07]	66% (*trans*) [3.36]	66% (*trans*) [1.28]	18% (8:1) [2.83]	21% (6:1) [3.31]	
4{7,5}	50% (*trans*) [1.34]	59% (*trans*) [1.69]	56% (*trans*) [1.47]	45% (*trans*) [1.96]	81% (*trans*) [3.25]	81% (*trans*) [1.17]	29% (5.3:1) [2.72]	30% (5:1) [3.20]	74% (*trans*) [2.10]
4{8,6}	33% (*trans*) [0.69]	52% (*trans*) [1.04]	32% (*trans*) [0.82]	60% (6.5:1) [1.31]	75% (*trans*) [2.59]	79% (*trans*) [0.52]	8% (5:1) [2.07]	11% (4.3:1) [2.55]	77% (*trans*) [1.45]
4{9,7}	48% (5.5:1) [2.37]	48% (6.7:1) [2.72]	42% (5:1) [2.50]	78% (8.8:1) [2.99]	76%[B] (*trans*) [4.27]	81% (*trans*) [2.19]			75% (*trans*) [3.13]
4{10,8}	33% (16:1) [3.54]	35% (15:1) [3.88]	38% (6:1) [3.67]	37% (*trans*) [3.36]	75%[B] (*trans*) [5.44]	58% (*trans*) [3.36]			50% (*trans*) [4.30]

[a]Yield (%) of isolated and fully characterized (ESI) product (purity >85% only).
[b]Product purity range: >94%, 85–94%, <85% (not isolated), no product.
[c]Ratio of *trans*(major) : *cis*(minor)-configured lactams **3** according to integration of characteristic signals in the ^{1}H NMR spectrum (shown in round parentheses).
[d]Calculated using ACD Labs 10.0 software (shown in square parentheses).
[e]Method A – throughout unless noted (xx%[B]) otherwise.

The selection of product structures obtained in >94% purity using the approach described (Figure 2) clearly demonstrate the power of the CCR in controlling both the periphery and skeletal diversity of the respective lactams **3**, now in combinatorial fashion. As we did not set any conscious boundaries to the physicochemical properties of the reagents **5**, **6** and **8** utilized in the described array, we were also curious to see if the 157 products obtained in >85% purity from the 180 combinatorial reactions (87% success rate) conform to the rules of drug-[20] and lead-likeness.[21] As it can be seen from Figure 3, only three compounds lie outside of the rule-of-five (Ro5 of Lipinski's rules of druglikeness) boundaries and a good number of products **3** fall within rather strict limits of rule-of-three (or lead-likeness). At the same time, the highly hydrophilic area (cLogP<3) is quite substantially populated.

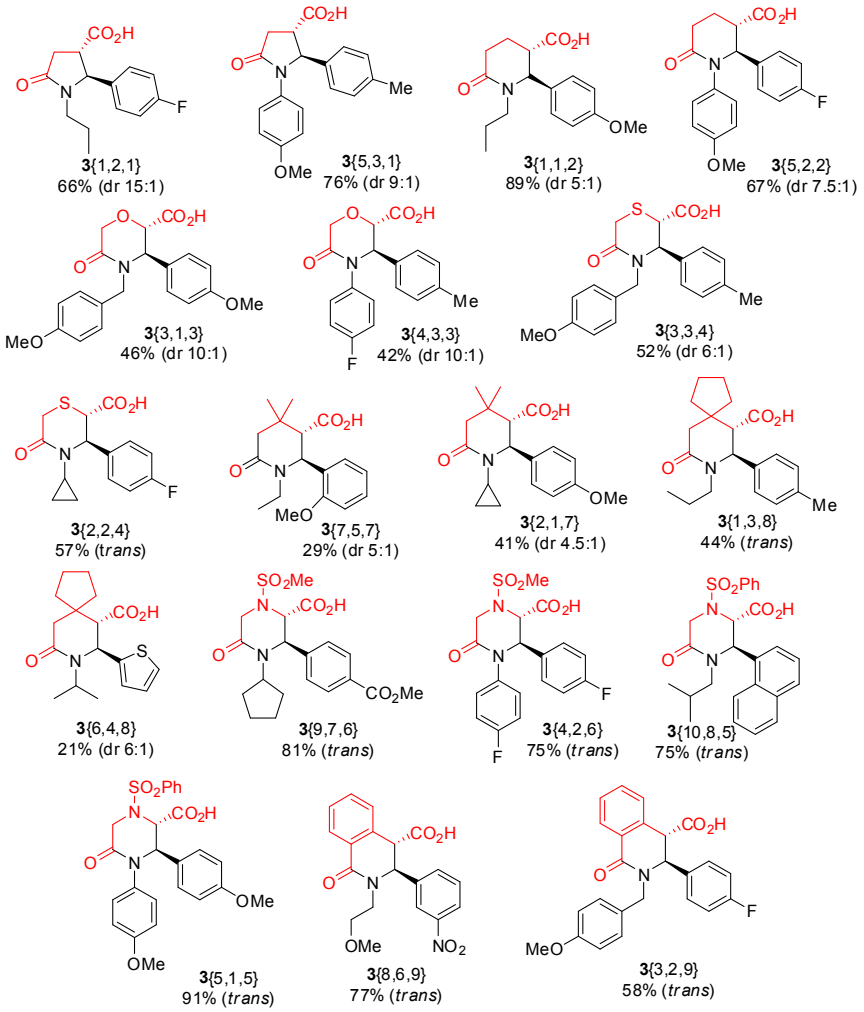


Figure 2. Representative lactams **3**{**5**,**6**,**8**} obtained in this work.

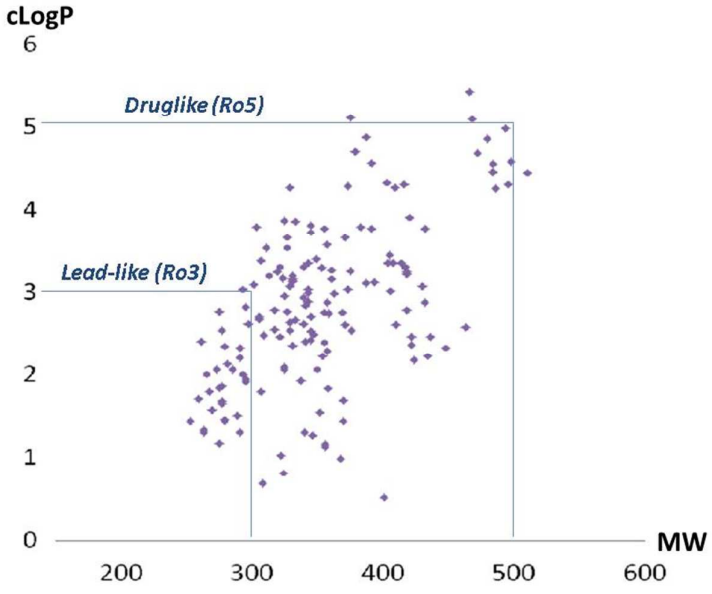


Figure 3. Drug- and lead-likeness (MW/cLogP) of the lactams **3** obtained in this work.

CONCLUSIONS

We have described a novel format for the Castagnoli-Cushman reaction which relies on the arsenal of structurally diverse dicarboxylic acids which is much more readily available compared to the respective cyclic anhydrides (the latter are also hydrolytically prone that limits their storage and mandates special handling). The reaction is distinctly amenable to parallel format and clearly offers a simultaneous control of over the periphery groups and the skeleton. The latter consideration aligns this method with the spirit of diversity-oriented synthesis. No chromatographic purification was employed to obtain the products and yet 157 compounds were obtained in >85% purify from 180 reactions, of which number 143 compounds had purity of >94%, clearly attesting to the high combinatorial efficiency of the method. The compounds obtained are within the limits of druglikeness and a large portion thereof – within the lead-like property space. This makes these compounds useful tools for the interrogation of biological targets, which would offer ample room for medicinal chemistry optimization should any promising biological activity be discovered.

EXPERIMENTAL PROCEDURES

General Procedure (Method A) for the Synthesis of Lactams 3. Amine **5** (10 mmol) and aldehyde **6** (10 mmol) were combined in chlorobenzene (20 mL). Activated 4Å molecular sieves (0.8 g) were added and the mixture was shaken for 2 h (for aliphatic amines) or 24 h (for aromatic amines) at room temperature. The molecular sieves were filtered off and equal volume (2 mL, 1 mmol) of the imine **4** solution thus obtained was added to thick-walled, screw-capped tubes equipped with a magnetic stirrer, containing dicarboxylic acids **8** (0.9 mmol). Acetic anhydride (1.1 mmol) was added to each reaction vessel. The latter were capped and heated under stirring at 150 ºC for 16 hours. Upon cooling of the reaction tubes to ambient temperature, 5% aqueous $KHCO_3$ solution (6 mL) was carefully added to each tube (gas evolution!). The reaction mixtures were transferred to 15 mL centrifuge tubes and the reaction vessels were additionally rinsed with dichloromethane (1 mL) and 5% aqueous $KHCO_3$ solution (2 mL). The vials were vigorously shaken for 30 min and then centrifuged at 4700 rpm for 5 min to ensure efficient phase separation. The lower (dichloromethane) layer was carefully removed by a pipette and the pH of the aqueous layer was carefully adjusted to 3.0 with concentrated HCl (gas evolution!). The mixtures containing thick product precipitates were centrifuged at 5 ºC and 4700 rpm for 20 min. The supernatant was decanted and the solid residue was washed with water (5 mL), separated by a repeat centrifugation and dried at 70 ºC. If oil-like residues were obtained

at this point, these were extracted with ethyl acetate, the extracts were dried over anhydrous $MgSO_4$ and evaporated to dryness.

General Procedure (Method B) for the Synthesis of Lactams 3. This method is identical to Method A except for the product isolation procedure. Reaction mixtures obtained were evaporated to dryness. Dichloromethane (5 mL) was added and the resulting solutions were chilled to 5 ºC overnight. The resulting precipitate was filtered off and air-dried. If the precipitate did not form, dichloromethane was evaporated and the residue was triturated with hexane (12 mL) and the solid thus formed was dried *in vacuo*.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.xxxxxxx. Characterization and full spectroscopic data (^{1}H, ^{13}C NMR, HRMS) of compounds **3** (PDF).

AUTHOR INFORMATION

Corresponding Author

* E-mail: m.krasavin@spbu.ru

ORCID

Olga Bakulina: 0000-0002-4930-0739
Dmitry Dar'in: 0000-0002-0413-7413
Mikhail Krasavin: 0000-0002-0200-4772

Notes

The authors declare no competing financial interest.

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