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Unexpected formal [4 + 2]-cycloaddition of chalcone imines and homophthalic anhydrides: preparation of dihydropyridin-2(1*H*)-ones†

Natalia Guranova, Pavel Golubev, Olga Bakulina, * Dmitry Dar'in, Grigory Kantin and Mikhail Krasavin

A series of medicinally important dihydropyridin-2(1*H*)-ones have been prepared *via* a novel [4 + 2]-formal cycloaddition reaction of chalcone imines and homophthalic anhydrides, which is a rare example of lactam construction from an imine acting as a four-atom building block. In contrast to previous studies on the reactivity of homophthalic anhydrides towards similar substrates, *N*-tosyl chalcone imines, we found the possibility of switching chemoselectivity by changing substituents at the nitrogen atom, which leads to the formation of heterocycles instead of the expected carbocycles. This reaction is very similar in appearance to the classic 1,2-addition of cyclic anhydrides to imines, often referred to as the Castagnoli–Cushman reaction, but differs in mechanistic details (representing a 1,4-reaction of imine). The developed atom-economical, stereoselective and catalyst- and chromatography-free protocol provided facile access to 28 structurally diverse heterocyclic products (in up to 88% yield) including synthetically challenging annelated tricyclic and previously unreported pentaaryl-substituted dihydropyridin-2(1*H*)-ones.

Introduction

1-Aza-1,3-dienes (Fig. 1a) have a long and fruitful history of application in organic synthesis[1] and have been recognized as useful and multifunctional building blocks for the construction of different carbo- and heterocyclic systems *via* pericyclic reactions,[2–5] condensations[6,7] or Michael addition reaction.[8,9] These transformations may involve different combinations of azadiene atoms, namely, 1,2/1,4 or 3,4. The interaction of azadienes with cyclic anhydrides of dicarboxylic acids has also been studied. Cinnamic aldehyde derivatives (*N*-alkyl/aryl/sulfonyl imines[10–13] and oximes[14]) reacted with homophthalic (HPA), succinic, glutaric and diglycolic anhydrides *via* the Castagnoli–Cushman reaction (CCR) pathway, giving vinyl substituted γ- or δ-lactams (Fig. 1b). This is an example of the "1,2"-reaction of azadienes, where a heterocyclic core is formed with the incorporation of an N(1)–C(2) fragment (the C=N double bond reacts). Introduction of a bulky trityl group (Trt) to the nitrogen atom switched the reaction chemoselectivity – azadiene atoms 3 and 4 were involved (C=C bond) in this case, giving α-tetralone-derived carbocyclic products, thus representing a Tamura-type reaction[15] (Fig. 1c). The same effect was achieved *via* introducing an aryl group to the C-2 atom of *N*-sulfonylazadienes (making them chalcone imines) as reported in ref. 16 (Fig. 1d).

In this work, we have expanded the scope of chalcone imines studied by using *N*-aryl/alkyl/OH/NHPh derivatives and discovered that in this case the reaction chemoselectivity is switched again to a rare Castagnoli–Cushman-type reaction (Fig. 1e). An unusual type of lactam cycle formation, where imine acts as a four-atom building block (atoms 1 and 4 are involved), differentiates it from the classic CCR. Herein, we report the first preparative procedure for the synthesis of dihydropyridin-2(1*H*)-ones based on this transformation. Such compounds have been reported previously in Castagnoli–Cushamn reactions only as minor impurities (2.2% yield)[17] or unstable reaction intermediates.[16]

Noteworthily, the 2-piperidone (δ-lactam) moiety belongs to highly relevant cores for medicinal chemistry design. In particular, dihydropyridin-2(1*H*)-ones have been reported as lead molecules in more than twenty patents aimed at the development of therapeutic agents for the treatment of heart diseases (human neutrophil elastase (HNE) inhibitors, Rho-kinase inhibitors),[18,19] pulmonary diseases (HNE inhibitors),[20] prostatic hyperplasia (α-**1a**-adrenoceptor antagonists)[21] and inflammatory diseases[22] (*S*-nitrosoglutathione reductase inhibitors and neurokinin-3 receptor antagonists). This aspect makes the development of a methodology giving access to

Saint Petersburg State University, Saint Petersburg, 199034 Russian Federation. E-mail: o.bakulina@spbu.ru; Tel: +7 904 618 15 09; Fax: +7 812 428 6939

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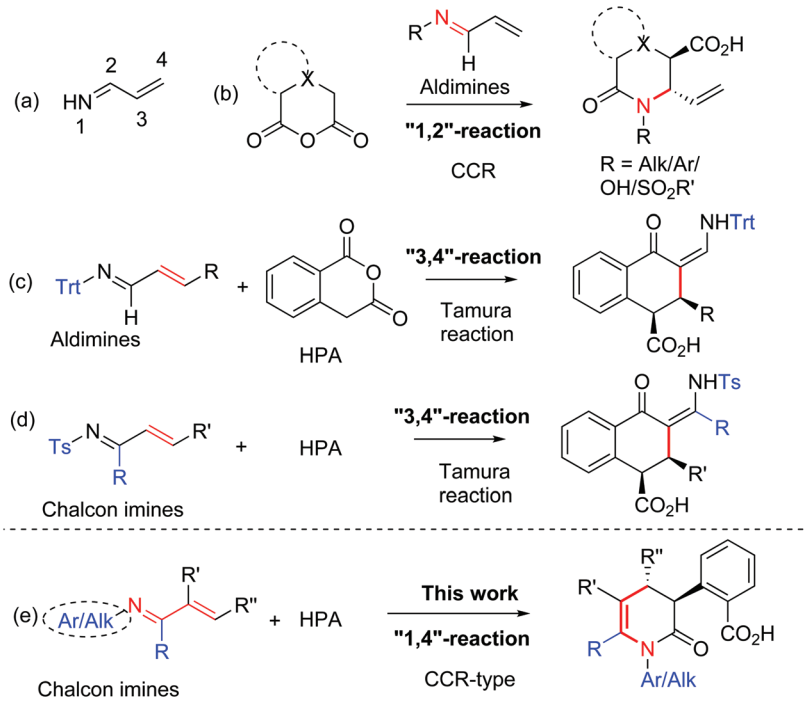


Fig. 1 (a) 1-Aza-1,3-dienes, general formula with numbering; (b) the CCR of 2-unsubstituted azadienes; (c) the Tamura reaction of 2-unsubstituted azadienes; (d) the Tamura reaction of 2-R azadienes; (e) Castagnoli-Cushman-type 1,4-reaction of 2R-azadienes developed in this work.

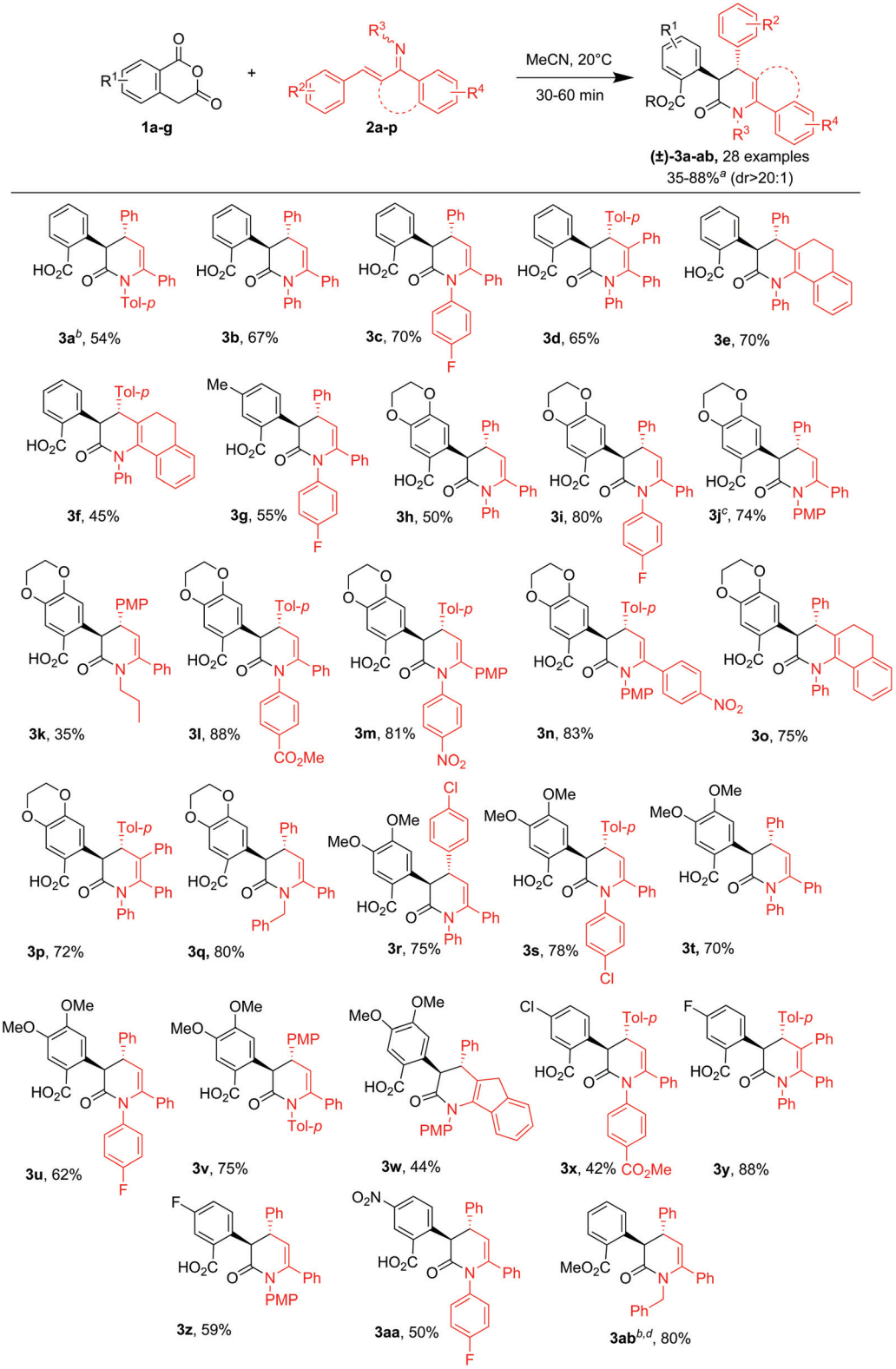
novel types of polysubstituted dihydropyridin-2(1*H*)-ones highly desirable.

Results and discussion

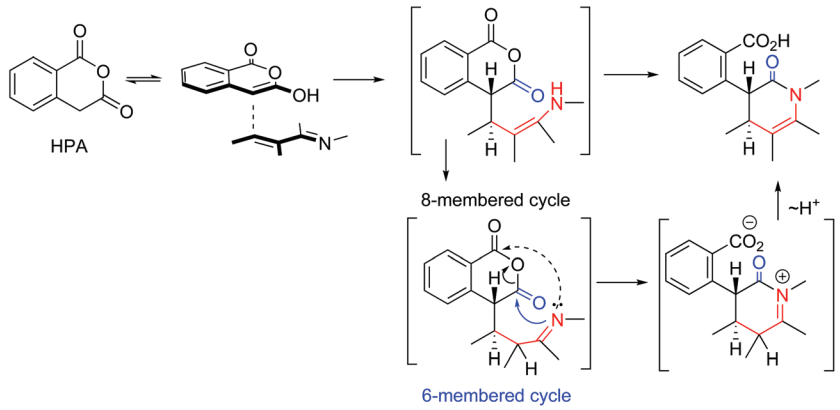
Having in mind that the nature of the substituent at the nitrogen atom of the 1-azadiene system affects its reactivity and selectivity drastically and that chalcone imines remain almost uninvestigated (except for *N*-tosyl derivatives) in reactions with cyclic anhydrides, in this work, we aimed at studying the behaviour of the corresponding *N*-aryl/alkyl/OH/NHR derivatives. Homophthalic anhydride was chosen as the second substrate due to its availability and high reactivity, both in the CCR and Tamura reaction.

A brief screening of the reaction conditions (temperature: 20–110 °C, solvent: toluene, MeCN, $CHCl_3$, acetone, THF) revealed that full conversion, a small amount of by-products (according to ^{1}H NMR of crude reaction mixtures) and simple isolation can be achieved when chalcone imines **2** were reacted with HPA, **1a**, at room temperature using a minimum amount of dry MeCN (0.25 mmol/0.5 mL) (Scheme 1). A thorough analysis of the NMR spectra also showed that dihydropyridin-2(1*H*)-ones were formed, involving atoms 1 and 4 of the azadiene system, instead of the expected carbocyclic Tamura reaction products reported in ref. 16 by J. Shaw and co-authors ("3,4-reaction" of azadienes). High concentrations of reactants provided both short reaction times (less than 1 h) and convenient product isolation – all compounds except **3ab** were isolated by centrifugation of precipitates. This protocol allowed the preparation of a series of 27 structurally diverse polysubstituted dihydropyridin-2(1*H*)-ones **3a–aa** in good to high yields (up to 88%, up to 1 mmol loading) as single *trans*-diastereomers (dr > 20 : 1). When the product did not precipitate from the reaction mixture (compound **3ab**), successful isolation was achieved by flash chromatography on silica after esterification with diazomethane. The structure and relative configuration of compounds **3a** and **3ab** were confirmed by X-ray crystallography (see the ESI† for details).

We introduced seven anhydrides **1a–g** into the reaction with sixteen chalcone imines **2a–p** and found no significant dependence of the reaction yields on the substitution patterns in both reactants. EDG (Me, alkoxy) as well as EWG (Hal, CO_2Me, NO_2) substituents were well tolerated in the anhydride molecule or aryl component of imine (all possible positions 1–4 were screened). The diminished yield of the *N*-propyl substituted compound **3k** is most likely caused by its better solubility and, consequently, by increased losses during isolation. Noteworthily, even tetraaryl-substituted imines were successfully involved in this reaction giving products **3d,p,y**, which are, to the best of our knowledge, the first reported examples of the preparation of pentaaryl dihydropyridines. Using cyclic imines derived from tetralone or indanone allowed the isolation of annelated tricyclic products **3e,f,o,w**. The latter represent at the same time quite a rare example of 3-alkyl (not aryl or H) substituted chalcone imine employed. Unfortunately, N-OH or N-NHR lactams could not be prepared under the same conditions due to the low reactivity of the



Scheme 1 Preparation and structures of dihydropyridin-2(1*H*)-ones **3**. Reaction conditions: anhydride (0.25 mmol), imine (0.25 mmol), concentration 0.5 M. [a] Isolated yields. [b] X-ray crystallographic data: **3a** – CCDC 2067829,† **3ab** – CCDC 2067830.† [c] PMP = 4-OMeC$_6$H$_4$. [d] Yield for two steps, including esterification.



Scheme 2 Proposed reaction mechanism.

corresponding oximes and hydrazones derived from chalcones and hydroxylamine or phenyl hydrazine.

Remarkably, all products were isolated as single *trans*-isomers without any additional purification, which is quite rare for formal cycloaddition reactions of HPA performed at room temperature. In most cases, a mixture with a predominant content of the kinetically favored *cis*-isomer is formed. The preparation of the thermodynamically preferred *trans*-isomer usually requires performing an additional isomerisation step with heating[23–25] or deprotonation,[26] often after esterification.[13,27]

Presumably, the reaction mechanism involves nucleophilic addition of HPA enolate to the C-4 atom of the azadiene system, followed by intramolecular *N*-acylation, thus presenting an example of imine acting as a four-atom building block (Scheme 2). Additionally, another difference from the classic Castagnoli–Cushman reaction is acylation occurring with the "acetic", not "benzoic", carbonyl group of HPA due to the preferred formation of six-membered cycles over eight-membered ones. It is also possible to describe this process as formal [4 + 2]-cycloaddition with inverted roles of HPA (normally diene and dienophile here) and imine (normally dienophile and diene here). Since the studied reaction involves the same types of reactants (anhydride + imine) and gives the same type of product (lactam with a carboxylic group) but differs in mechanistic details, we refer to it as the Castagnoli–Cushman-type reaction.

Interestingly, the closest structural analogs, *N*-tosyl derivatives, were described as unstable reaction intermediates[16] only detected by NMR in reaction mixtures at low temperatures (−20 °C), quickly transforming into the Tamura product at 25 °C and therefore not isolated. In contrast, our *N*-aryl/alkyl products **3** were found to be thermally stable even at 130 °C when heated in DMSO-d_6 with NMR monitoring.

Conclusion

The reactivity of *N*-aryl/alkyl/OH/NHPh chalcone imines towards a series of substituted homophthalic anhydrides has been investigated. Surprisingly, dihydropyridin-2(1*H*)-ones were formed *via* the rare Castagnoli–Cushman-type reaction of imine acting as a four-atom building block – we observed the "1,4"-reaction instead of the expected "3,4"-Tamura reaction. Based on this new transformation, we have developed a convenient and efficient protocol, which was used for the preparation of a series of 28 structurally diverse δ-lactams (fully characterized including X-ray analysis). Variation of the substitution pattern in both reactants showed no significant effect on the reaction yield, allowing the introduction of both EWG and EDG into the anhydride and/or imine component of the lactam product. The reaction proved to be general, chemo- and stereoselective and high-yielding.

Author contributions

N.G. – investigation, data curation, validation; P.G. – investigation, methodology; O.B. – investigation, supervision, writing – original draft, funding acquisition; D.D. – investigation, conceptualization, writing – review & editing; G.K. – investigation, validation; M.K. – conceptualization, project administration, writing – review & editing.

Conflicts of interest

The authors declare no competing financial interest.

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References

1 S. Jayakumar, M. P. S. Ishar and M. P. Mahajan, *Tetrahedron*, 2002, **58**, 379–471.
2 J. M. Neely and T. Rovis, *Org. Chem. Front.*, 2014, **1**, 1010–1015.
3 Y. S. Cheng, A. T. Lupo and F. W. Fowler, *J. Am. Chem. Soc.*, 2002, **105**, 7696–7703.
4 M. Komatsu, H. Ogawa, M. Mohri and Y. Ohshiro, *Tetrahedron Lett.*, 1990, **31**, 3627–3630.
5 R. Robles-Machin, A. Lopez-Perez, M. Gonzalez-Esguevillas, J. Adrio and J. C. Carretero, *Chemistry*, 2010, **16**, 9864–9873.
6 J. Barluenga, V. Kouznetsov, E. Rubio and M. Tomás, *Tetrahedron Lett.*, 1993, **34**, 1981–1984.
7 J. Barluenga, M. Tomás, A. Ballesteros and J.-S. Kong, *Tetrahedron*, 1996, **52**, 3095–3106.
8 D. Hu, Y. Gao, X. Song, W. Du and Y.-C. Chen, *Eur. J. Org. Chem.*, 2020, **2020**, 514–518.
9 W. Lin, C. Zhang, W. Xu, Y. Cheng, P. Li and W. Li, *Adv. Synth. Catal.*, 2018, **361**, 476–480.
10 H. Braunstein, S. Langevin, M. Khim, J. Adamson, K. Hovenkotter, L. Kotlarz, B. Mansker and T. K. Beng, *Org. Biomol. Chem.*, 2016, **14**, 8864–8872.
11 S. A. Cronin, A. Gutiérrez Collar, S. Gundala, C. Cornaggia, E. Torrente, F. Manoni, A. Botte, B. Twamley and S. J. Connon, *Org. Biomol. Chem.*, 2016, **14**, 6955–6959.
12 M. J. Di Maso, K. M. Snyder, F. De Souza Fernandes, O. Pattawong, D. Q. Tan, J. C. Fettinger, P. H. Cheong and J. T. Shaw, *Chemistry*, 2016, **22**, 4794–4801.
13 S. W. Laws, L. C. Moore, M. J. Di Maso, Q. N. N. Nguyen, D. J. Tantillo and J. T. Shaw, *Org. Lett.*, 2017, **19**, 2466–2469.
14 O. Bakulina, A. Bannykh, D. Dar'in and M. Krasavin, *Chemistry*, 2017, **23**, 17667–17673.
15 A. G. Collar, C. Trujillo and S. J. Connon, *Chemistry*, 2019, **25**, 7270–7274.
16 N. P. Burlow, S. Y. Howard, C. M. Saunders, J. C. Fettinger, D. J. Tantillo and J. T. Shaw, *Org. Lett.*, 2019, **21**, 1046–1049.
17 A. Georgieva, E. Stanoeva, S. Spassov, M. Haimova, N. De Kimpe, M. Boelens, M. Keppens, A. Kemme and A. Mishnev, *Tetrahedron*, 1995, **51**, 6099–6114.
18 H. Gielen, V. M.-J. Li, U. Rosentreter, K.-H. Schlemmer, S. Allerheiligen, L. Telan, L. Baerfacker, J. Keldenich, M. F. Fitzgerald, K. Nash, B. Albrecht and D. Meurer, WO2004020410, 2004.
19 D. Lee and K. B. Goodman, WO2005082890, 2005.
20 H. Gielen-Haertwig, B. Albrecht, M. Bauser, J. Keldenich, V. Li, J. Pernerstorfer, K.-H. Schlemmer and L. Telan, WO2005080372, 2005.
21 J. Barrow, H. G. Selnick and P. G. Nanterment, WO2000025782, 2000.
22 X. Sun and J. Qiu, WO2012009227, 2012.
23 M. I. Adamovskyi, M. M. Avramenko, D. M. Volochnyuk and S. V. Ryabukhin, *ACS Omega*, 2020, **5**, 20932–20942.
24 D. M. Floyd, P. Stein, Z. Wang, J. Liu, S. Castro, J. A. Clark, M. Connelly, F. Zhu, G. Holbrook, A. Matheny, M. S. Sigal, J. Min, R. Dhinakaran, S. Krishnan, S. Bashyum, S. Knapp and R. K. Guy, *J. Med. Chem.*, 2016, **59**, 7950–7962.
25 A. Mikheyev, G. Kantin and M. Krasavin, *Synthesis*, 2018, 2076–2086.
26 M. Krasavin, A. Safrygin, O. Bakulina and D. Dar'in, *Synthesis*, 2020, 2190–2195.
27 C. L. Jarvis, J. S. Hirschi, M. J. Vetticatt and D. Seidel, *Angew. Chem., Int. Ed.*, 2017, **56**, 2670–2674.