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DAST-Mediated Cyclization of α,α-Disubstituted-α-acylaminoketones: Efficient and Divergent Synthesis of Unprecedented Heterocycles

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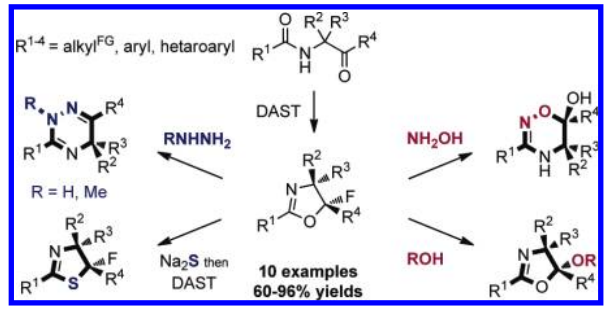
ABSTRACT



The design of a new potent nonsteroidal ecdysone agonist led to the discovery of a diethylaminosulfur trifluoride (DAST)-mediated cyclization of α,α-disubstituted-α-acylaminoketones. The resulting fluorooxazolines can be ring-opened or selectively substituted by a range of nucleophiles to provide in high yields a diverse array of unprecedented heterocyclic frameworks.

The constant need for small molecules able to disrupt biological pathways continues to drive efforts toward efficient sequences leading to diverse scaffolds.[1] A particularly relevant chemotype is represented by nitrogen-containing heterocycles since they are ubiquitous in biologically active compounds.[2] Therefore the development of general methods to access original N-heterocycles with unexplored properties from simple common intermediates is of great interest for pharmaceutical and agrochemical purposes. We report herein a diethylaminosulfur trifluoride (DAST)-mediated two-step sequence from readily available acylaminoketones affording highly functionalized and unprecedented heterocycles in an efficient and divergent fashion.

As part of a program directed toward the discovery of new insecticide leads, we became interested in the recently reported α,α-disubstituted-α-acylaminoketone chemotype[3] as a central scaffold to design new bioisosters. This class of ligands has been identified as potent analogues of the

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(1) (a) Strausberg, R. L.; Schreiber, S. L. *Science* **2003**, *300*, 294. (b) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48.

(2) (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell: Oxford, 2000. (b) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, 2003. (c) Katrizky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon: Amsterdam, 2000.

(3) (a) Tice, C. M.; Michelotti, E. L.; Mata, E. G.; Nicolas, E.; Garcia, J.; Albericio, F. *Tetrahedron Lett.* **2002**, *43*, 7491. (b) Garcia, J.; Nicolas, E.; Albericio, F.; Michelotti, E. L.; Tice, C. M. *Tetrahedron Lett.* **2002**, *43*, 7495. (c) Tice, C. M.; Hormann, R. E.; Thompson, C. S.; Friz, J. L.; Cavanaugh, C. K.; Saggers, J. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1883. (d) Tice, C. M.; Hormann, R. E.; Thompson, C. S.; Friz, J. L.; Cavanaugh, C. K.; Michelotti, E. L.; Garcia, J.; Nicolas, E.; Albericio, F. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 475. (e) Garcia, J.; Mata, E. G.; Tice, C. M.; Hormann, R. E.; Nicolas, E.; Albericio, F.; Michelotti, E. L. *J. Comb. Chem.* **2005**, *7*, 843, and references therein.

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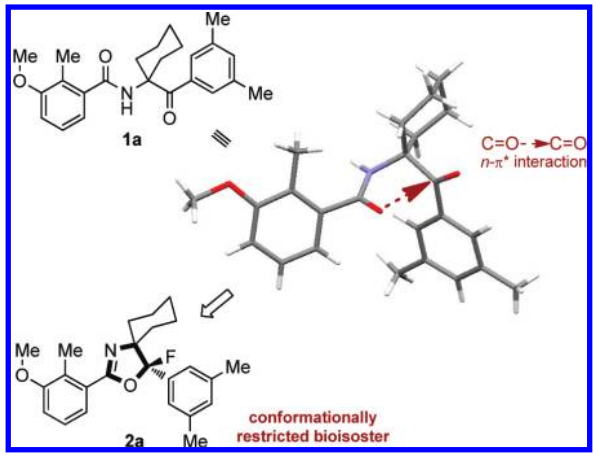
bisacylhydrazine family of commercial insecticides[4] and was used to control gene expression in systems based on engineered ecdysone receptors.[5] The generation of a small library[3e] allowed the identification of **1a** (Scheme 1),

Scheme 1. Design of a Conformationally Restricted Analogue Based on X-ray Structure of **1a**[a]



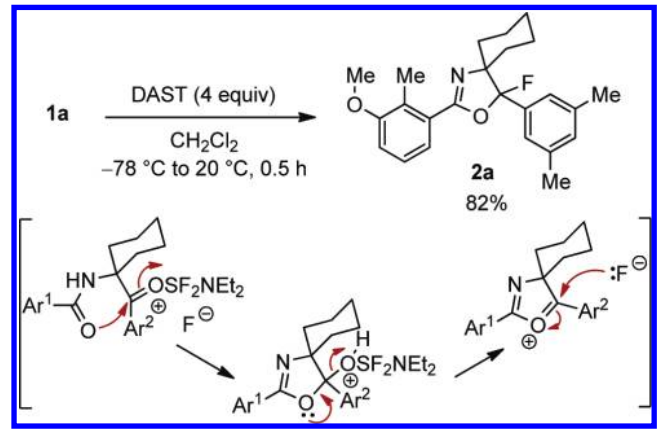
[a] X-ray structure from ref 3c.

synthetically derived from 1-aminocyclohexyl-1-carboxylic acid, displaying micromolar range affinity close to that of the commercial product Tebufenozide.[6]

The X-ray structure of **1a** displays a folded shape that particularly attracted our attention and was used as a starting point for our design. This conformation is induced to minimize steric clashes with the cyclohexyl substituent and is further stabilized by an additional carbonyl−carbonyl attractive interaction, recently thoroughly studied by Raines et al. and named $n-\pi^*$ interaction.[7,8] We assumed that this conformation was responsible for the biological activity, and conformationally restricted analogue oxazoline **2a** was designed to assess this hypothesis. Indeed **2a** mimics the X-ray structure of **1a** while displaying a similar electronic distribution. The (sp3)C−F bond is of particular importance, replacing the pyramidalized and elongated ketone of **1a** due to $n-\pi^*$ delocalization.

Surprisingly oxazolines bearing a heteroatom at C5 are scarcely found in the literature[9] despite the importance of the oxazoline scaffold[10] and the numerous methods of preparation.[11] We envisioned that **2a** could be directly synthesized from **1a** by the use of a deoxofluorinating agent such as DAST.[12] The cyclodehydration of β-hydroxyamide to 4,5-unsubstituted oxazolines is known;[11c] nevertheless this reagent was never applied to ketone counterparts. Gratifyingly the treatment of **1a** with an excess of DAST at low temperature promoted smoothly the desired cyclization affording **2a** in very good isolated yields (Scheme 2).

Scheme 2. DAST-Mediated Cyclization of **1a**



The cyclization is proposed to follow two S_N1 pathways involving prior activation of the carbonyl by DAST to allow intramolecular attack of the amide oxygen.[13] Subsequent formation of the stabilized benzylic α-oxycarbenium ion, which is trapped by a fluoride, provides the desired fluorooxazoline.

The biological evaluation of **2a** was performed on an ecdysone reporter gene assay.[14] It displayed a high potency similar to that of **1a** (EC_{30}(**2a**) = 1.21 μM; EC_{30}(**1a**) = 1.33 μM). Oxazoline **2a** represents therefore a potential new class of nonsteroidal ecdysone agonists based on a conformation analogue of **1a**.

Encouraged by these results we embarked on investigating the scope of the DAST-mediated cyclization process (Table 1). The substrates acylaminoketones **1b**−**j** were readily available in 2−3 steps from commercially available building

(4) Dhadialla, T. S.; Ross, R. *Modern Crop Protection Compounds*; Wiley-VCH: Weinheim, 2003; pp 773−797.

(5) (a) Laudet, V.; Gronemeyer, H. *The Nuclear Receptor Facts Book*; Academic Press: San Diego, CA, 2002; pp 181−191. (b) Dhadialla, T. S.; Carlson, G. R.; Le, D. P. *Annu. Rev. Entomol.* **1998**, *43*, 545.

(6) see the Supporting Information.

(7) (a) Choudhary, A.; Gandla, D.; Krow, G. R.; Raines, R. T. *J. Am. Chem. Soc.* **2009**, *131*, 7244. (b) Jakobsche, H. E.; Choudhary, A.; Miller, S. J.; Raines, R. T. *J. Am. Chem. Soc.* **2010**, *132*, 6651.

(8) The criteria for $n-\pi^*$ delocalization are fulfilled (see ref 7a): the distance between the oxygen of the amide and the carbon of the carbonyl is 2.62 Å which is less than the sum of their van der Waals radii ($r_S + r_C$ < 3.50 Å). The angle O−C═O is 104.9°, and the carbonyl presents a slight pyramidalization.

(9) (a) Hassner, A.; Burke, S. S.; Cheng-fan, I, J. *J. Am. Chem. Soc.* **1975**, *97*, 4692. (b) Morwick, T.; Hrapchak, M.; DeTuri, M.; campbell, S. *Org. Lett.* **2002**, *4*, 2665.

(10) For examples of naturally occuring oxazoline, see: (a) Portmann, C.; Blom, J. F.; Gademann, K.; Jttner, F. *J. Nat. Prod.* **2008**, *71*, 1193. (b) Wipf, P.; Fritch, P. C.; Geib, S. J.; Sefler, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 16758. For a review on insecticidal oxazolines, see: Stevenson, T. M.; Amoo, V. E.; Chiang, G. C.; Keskeny, E.; Long, J. K.; Crouse, B. A.; Sharpe, P.; Hillegass, K.; Jones, L.; Yatsko, C. *Synthesis and Chemistry of Agrochemicals VI*; ACS Symposium Series 800; American Chemical Society: Washington, DC, 2001; pp 188−198. For a review on recent applications of oxazoline-containing ligands, see: Hargaden, G. C.; Guiry, P. J. *Chem. Rev.* **2009**, *109*, 2505.

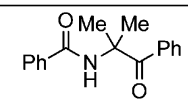
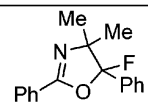
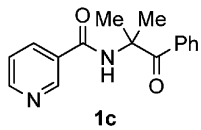
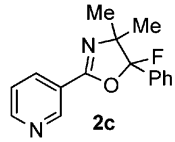
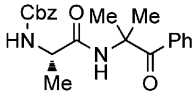
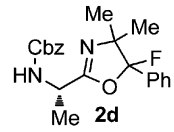
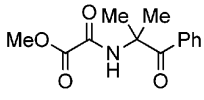
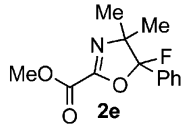
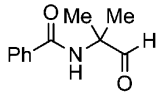
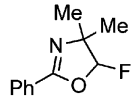
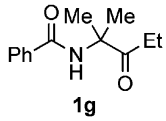
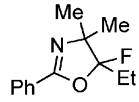
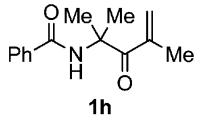
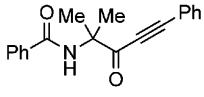
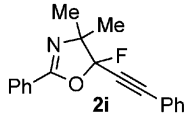
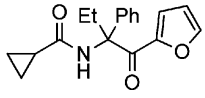
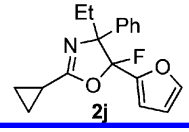
(11) For recent exemples, see: (a) Fan, L.; Lobkovsky, E.; Ganem, B. *Org. Lett.* **2007**, *9*, 2015. (b) Schwekendiek, K.; Glorius, F. *Synthesis* **2006**, 2996. (c) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165.

(12) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

(13) The $n-\pi^*$ delocalization increases the negative charge on the ketone oxygen, which possibly becomes more prone to react with DAST.

(14) See Supporting Information.

Table 1. Scope of the Reaction

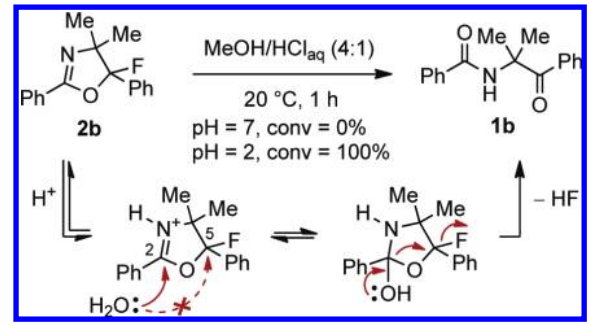
entry	substrate	product	conditions/ yield[a]
1	 **1b**	 **2b**	DAST (1.2 equiv), CH_2Cl_2, −10 °C, 10 min 96% yield
2	 **1c**	 **2c**	DAST (1.5 equiv), CH_2Cl_2, −10 °C to 20 °C, 2 h 92% yield
3	 **1d**	 **2d**	DAST (2.5 equiv), CH_2Cl_2, −10 °C to 20 °C, 1.5 h 81% yield[b]
4	 **1e**	 **2e**	DAST (2.5 equiv), CH_2Cl_2, 60 °C[c], 2 h 54% yield
5	 **1f**	 **2f**	DAST (1.2 equiv), CH_2Cl_2, −10 °C, 10 min 79% yield
6	 **1g**	 **2g**	DAST (1.2 equiv), CH_2Cl_2, −10 °C to 20 °C, 1.5 h 81% yield
7	 **1h**	 **2h**	DAST (1.2 equiv), CH_2Cl_2, −10 °C, 30 min 87% yield
8	 **1i**	 **2i**	DAST (2.5 equiv), CH_2Cl_2, −10 °C to 20 °C, 2.5 h 87% yield
9	 **1j**	 **2j**	DAST (2.5 equiv), CH_2Cl_2, 60 °C, 2 h 75% yield[d]

[a] Isolated yields. [b] As a 1:1 mixture of diastereoisomers according to ^{1}H NMR. [c] Reaction performed in a sealed tube under microwave irradiation. [d] As a 85:15 mixture of diastereoisomers according to ^{1}H NMR.

blocks through modified known procedures.[15] Initially **1b** was chosen for optimization study and showed that only a slight excess of DAST (1.2 equiv) was required to promote the cyclization in almost quantitative yield.[16] The process proved tolerant of variation of the amide with heteroaryl, ester, or alkyl substituents (Table 1, entries 2−4). Amide **1c** bearing an electron-withdrawing group required an excess of DAST to afford **2c** in high yields, and higher temperature was necessary to provide **2d** in moderate yields. The reaction proceeded smoothly in the presence of an aldehyde or a variety of ketone substituents such as alkyl, alkene, and alkyne (Table 1, entries 5−8). Heteroaryls were also tolerated together with variations at the *gem*-disubstituted position (Table 1, entry 9). All oxazolines **2b**−**j** were purified by column chromatography and proved to be stable over several weeks upon storage at 4 °C.

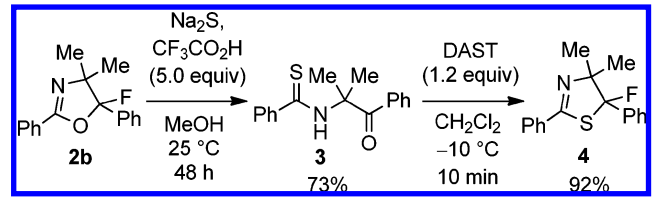
With the aim to further fonctionalize the fluorooxazolines **2**, we subsequently studied their chemical stability performing hydrolysis experiments with **2b** at several pH values (Scheme 3). As expected **2b** proved to be almost unaltered after a week at pH = 7, but complete hydrolysis to **1b** was observed after 1 h at pH = 2. The hydrolysis is assumed to be triggered by activation through protonation of the nitrogen with subsequent attack of the water at C2 rather than at the congested yet potentially reactive C5 bearing the fluorine. Subsequent ring opening with extrusion of HF provides acylaminoketone **1b**.

Scheme 3. Hydrolysis of **2b**



Thus we envisioned that addition of other nucleophiles could selectively lead to a derivatization of the amide functionality of acylaminoketones **1** through a DAST-mediated cyclization/ring-opening sequence. At first **2b** was subjected to an excess of sodium sulfide in acidic methanol (Scheme 4). As expected, thioamide **3** was isolated as the sole sulfur-containing isomer in 73% yield after 48 h. Subsequent treatment with DAST afforded smoothly the fluorothiazoline **4** in excellent yield.

Scheme 4. Ring Opening of **2b** with Na_2S and Subsequent Cyclization

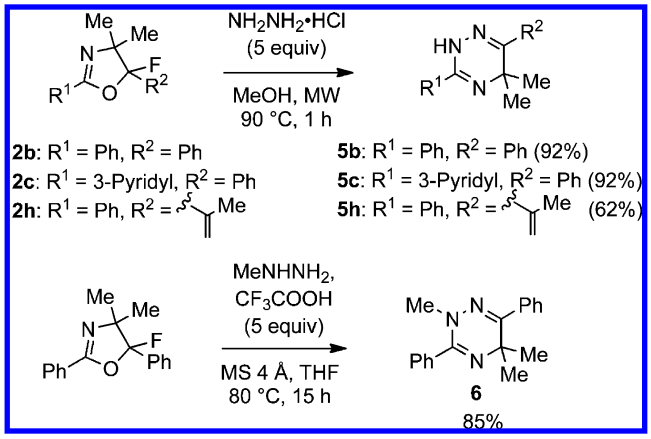


(15) See Supporting Information.
(16) The addition of a catalytic amount of an alcohol is usually required for the difluorination of ketones with DAST but was unnecessary in this case.

The versatility of this process was further investigated by reacting **2b** with hydrazine. We anticipated that upon opening of the ring, the formed hydrazonamide would condense onto the ketone to form cyclic triazines.

To our delight we found after some optimization that heating **2b** in the microwave for 1 h at 90 °C in methanol in the presence of excess hydrazine hydrochloride provided **5b** in excellent yield (Scheme 5).[17] The same conditions were

Scheme 5. Synthesis of 5,5-Disubstituted-1,2,4-triazines **5** and **6**



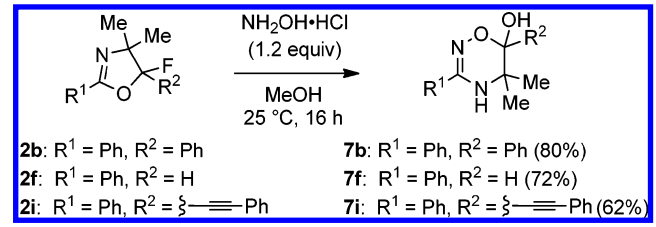
applied to oxazolines **2c/h**, affording the corresponding triazines in good to excellent yields. Addition of methyl hydrazine furnished under optimized conditions *N*-methyl-triazine **6** in high yield as the sole isomer. To our knowledge, this represents the first general synthesis of this rare class of 5,5-disubstituted-1,2,4-triazines[18] accessible in two steps from α,α-disubstituted-α-acylaminoketones of type **1**. It is noteworthy that the direct condensation of hydrazine to **1b** failed to give triazine **5b** even at high temperature for extended reaction time.

The addition of another simple binucleophile was next envisaged, and we found that addition of a slight excess of hydroxylamine hydrochloride to **2b/f/i** afforded the corresponding unprecedented oxadiazinols **7b/f/i** in good yields (Scheme 6).[19]

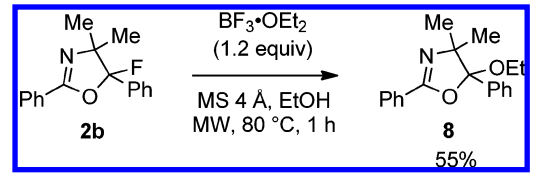
Finally the regioselective functionalization of fluorooxazolines **2** at C5 was addressed. We have found that Brønsted acids catalyze the nucleophilic ring opening of the oxazoline with regioselective attack at C2. We then speculated that fluorophilic Lewis acids could possibly lead to the formation of a transient carbocation at C5 allowing the direct substitution of the fluorine atom by nucleophiles.

Gratifyingly, microwave irradiation of **2b** in EtOH in the presence of BF_3•OEt_2 allowed the formation of **8** in 55% isolated yields. This result opens the door for further regioselective functionalization at C5.

Scheme 6. Synthesis of 5,5-Disubstituted-1,2,4-oxadiazinols **7**



Scheme 7. Regioselective Functionalization of **2b** at C5



In summary, an efficient two-step process was developed to afford a series of structurally distinct and unprecedented heterocyclic frameworks in a divergent fashion. Further investigations toward the use of other nucleophiles in order to expand the scope of this process together with the generation of a library for biological evaluation is currently underway and will be reported in due course.

Acknowledgment. We thank Dr. L. Hagman and M. Hellstern (Syngenta) for analytical support and technical assistance. P. Drayton and H. Gates (Syngenta) are acknowledged for the maintenance and supply of the mammalian cell line for the ecdysone assay. We are also grateful to Dr. J. Cassayre, Dr. A. De Mesmaeker, Dr. R. Dumeunier, Dr. E. Godineau, Dr. D. Stierli, Dr. S. Sulzer-Mosse and Dr. S. Wendeborn (Syngenta) for fruitful scientific discussions.

Supporting Information Available: Experimental procedures, compound characterization data, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The structure of **5b** was undoubtedly assigned by X-ray analysis. See Supporting Information.

(18) Rare exemples are found through addition to aromatic triazines under harsh conditions: (a) Konno, S.; Ohba, S.; Sagi, M.; Yamanaka, H. *Hererocycles* **1986**, *2*, 1243. (b) Benson, S. C.; Gross, J. L.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 3257.

(19) The structure of **7b** was undoubtedly assigned by X-ray analysis. See Supporting Information.