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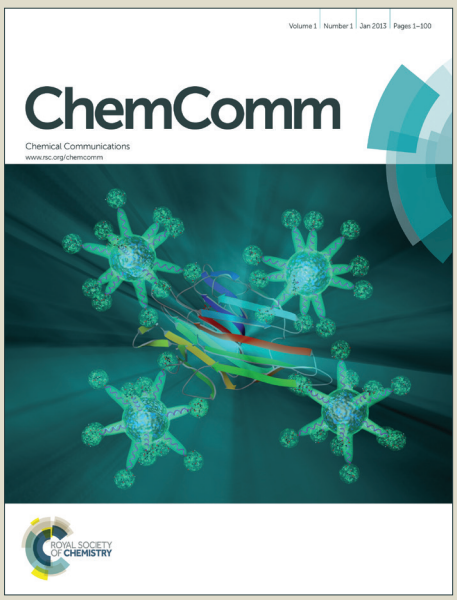

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DAST-Promoted Beckmann Rearrangement/Intramolecular Cyclization of Acyclic Ketoximes: Access to 2-Oxazolines, Benzimidazoles and Benzoxazoles

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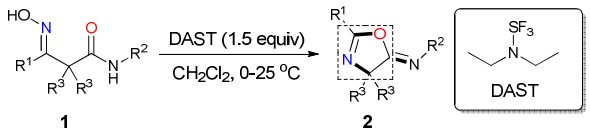
The first example of DAST-promoted Beckmann rearrangement/intramolecular cyclization of acyclic ketoximes is described. This unique protocol represents a direct and effective pathway to 2-oxazolines, benzimidazoles and benzoxazoles in moderate to good yields.

Diethylaminosulfur trifluoride (DAST) is the organo sulphur compound, popularly known as fluorinating reagent and has been reported frequently, used particularly for the fluorination of alcohols into the corresponding alkyl fluorides via dehydroxy-fluorination,[1] conversion of aldehydes and ketones into *gem*-difluorides by deoxy-fluorination,[2] and selective mono-fluorination of carboxylic acids into acyl fluorides.[3] In addition to fluorination reactions alone, DAST has been used successfully as the reagent for tandem reactions involving both fluorination and other reactions, such as intramolecular cyclization reactions for the conversion of β-hydroxy amides into oxazolines[4] and ring opening of cyclic ketoximes into fluorinated acyclic carbonitriles via sp^2-sp^3 C-C bond cleavage followed by fluorination or unstable fluorinated cyclic imines which further led to a complex mixture.[5] In addition to these, DAST has also been applied to induce rearrangement reactions.[6]

In the context of developing DAST-promoted reactions, we here described a novel protocol involving unprecedented DAST-promoted Beckmann rearrangement/intramolecular cyclization in a tandem manner for the effective conversion of acyclic ketoximes **1** into 2-oxazolines **2** (Scheme 1). To the best of our knowledge, this is the first example of DAST-promoted Beckmann rearrangement/intramolecular cyclization reaction. The methodology has provided an efficient route to 2-oxazolines, further extended to the synthesis of other most popular benzo-fused heterocyclic compounds such as benzimidazoles and benzoxazoles, which exist as core moieties in many medicinally active and pharmaceutically significant analogues.[7-9]

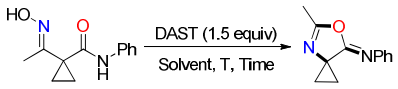


Scheme 1. DAST-Promoted Beckmann Rearrangement/Intramolecular Cyclization of Acyclic Ketoximes

Initially, in order to check feasibility of this DAST-promoted Beckmann rearrangement/intramolecular cyclization of acyclic ketoximes, a series of α,α-disubstituted-α-carbamoylketoximes **1a-o** with different R^1, R^2 and R^3 moieties, which has been demonstrated as a useful building block for construction of 1H-pyrazoles,[10a] spiro-fused pyrazolin-5-one *N*-oxides,[10b] isoxazoles[10a,10c] and spiro-fused pyrazolin-5-ones,[10c] were synthesized according to previously reported literature.[10b] (*E*)-1-(1-(hydroxyimino)ethyl)-*N*-phenyl-cyclopropane-carboxamide **1a** was selected and allowed to react with 1.5 equiv of DAST at different reaction temperatures in a series of solvents with varied reaction time (Table 1). Firstly, we relied on the literature reports of DAST-mediated reactions, and the reaction was carried out at -78 °C in CH_2Cl_2 for 5 h. The Beckmann rearrangement/intramolecular cyclization product *N*-(5-methyl-6-oxa-4-azaspiro[2.4]hept-4-en-7-ylidene) aniline **2a** was obtained in 81% isolated yield (entry 1). When reaction temperature was increased to 25 °C, the yield of desired product was slightly increased to 83% in 3.5 h (entry 2). Further screening of solvents showed that the reaction worked most effectively in CH_2Cl_2. Inferior results were observed when the reaction was performed in other solvents like THF, CH_3CN or DMF even for prolonged reaction time, up to 9 h (entries 3-5). Surprisingly, when reaction temperature was gradually

increased from 0 °C to 25 °C, the yield of **2a** was further increased to 87% (entry 6).

Table 1. Optimization of the Reaction Condition



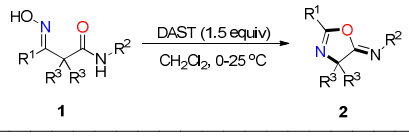
1a **2a**

entry	solvent	temp (°C)	time (h)	yield **2a** (%)[a]
1	CH_2Cl_2	-78	5	81
2	CH_2Cl_2	25	3.5	83
3	THF	25	9	74
4	CH_3CN	25	9	76
5	DMF	25	9	73
6	**CH_2Cl_2**	**0-25**	**3.5**	**87**

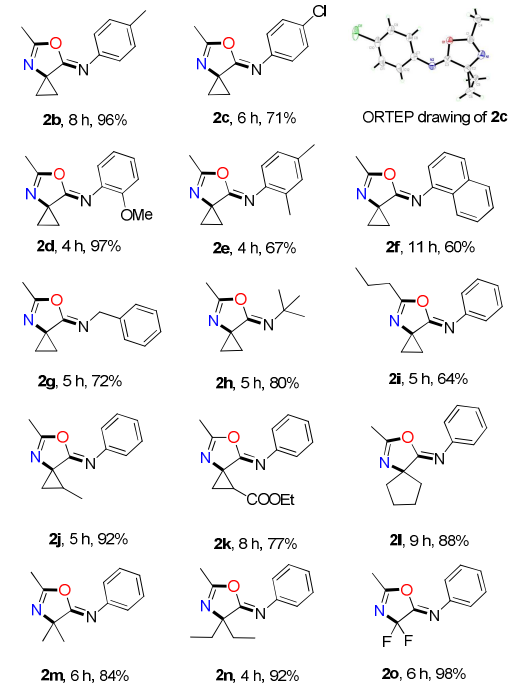
[a] Isolated yields of the product **2a**

With the optimized reaction conditions in hand (Table 1, entry 6), the substrate scope of this protocol was examined. All the prepared acyclic ketoximes **1a-o** underwent Beckmann rearrangement/intramolecular cyclization reaction smoothly in a tandem manner to afford fully substituted 2-oxazolines **2a-o** in 60-98% isolated yields (Table 2).

Table 2. Substrate Scope for the DAST-Promoted Synthesis of 2-Oxazolines

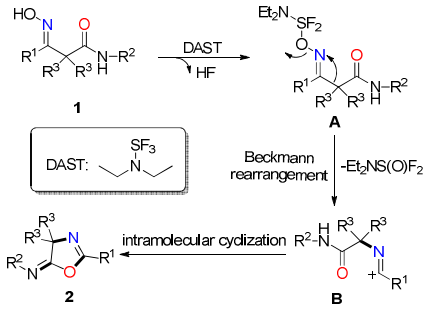


1 **2**



The α,α-disubstituted-α-carbamoylketoximes **1b-e** with R^2 = *p*-tolyl, *p*-chlorophenyl, *o*-anisole and *m*-xylene moiety respectively and **1f** with R^2 = naphthyl group were well tolerated in the reaction to afford corresponding fully substituted 2-oxazolines **2b-f** with varied isolated yield from 60% to 97%, which clearly indicates that the presence of electron rich aryl group at R^2 position increases the product yield, while the presence of electron deficient or hindered aryl group reduces the yield. The α,α-disubstituted-α-carbamoylketoximes **1g-h** with R^2 = benzyl or 3°-butyl group were well tolerated and afforded the corresponding 2-oxazolines **2g-h** in 72% and 80% yield. Later we checked the effect of the R^1 group. When R^1 is an ethyl group instead of methyl group, the yield of 2-oxazoline is diminished, **2i** is formed in 64% yield. Finally the effect of substituents at R^3 position was examined. α,α-Disubstituted-α-carbamoylketoximes **1j-o** with a variety of R^3 substituents such as methyl, ethyl, cyclopropyl, cyclopentyl group or fluorine atoms participated in Beckmann rearrangement/intramolecular cyclization reactions to afford 2-oxazolines **2j-o** in 77-98% isolated yield. The structure of 2-oxazoline **2c** was unambiguously confirmed by single crystal X-ray diffraction study (CCDC 942577). It is worth mentioning that compounds bearing cyclopropyl group (**2a-k**) might serve as a potential spirocyclopropanated analogue of Imidacloprid which is currently the most widely used insecticide in the world.[11]

On the basis of these experimental results and related precedents,[4c,5] a plausible reaction mechanism is depicted in scheme 2. The first step is the nucleophilic displacement of a fluorine in DAST by the oxygen of the oximino substrate **1** with elimination of hydrogen fluoride. Next, the reaction proceeds through Beckmann rearrangement. The carbon–carbon bond anti to the oximino leaving group in the intermediate **A** migrates to the nitrogen atom to afford the carbocation **B**, followed by intramolecular cyclization to form fully substituted 2-oxazolines **2**.

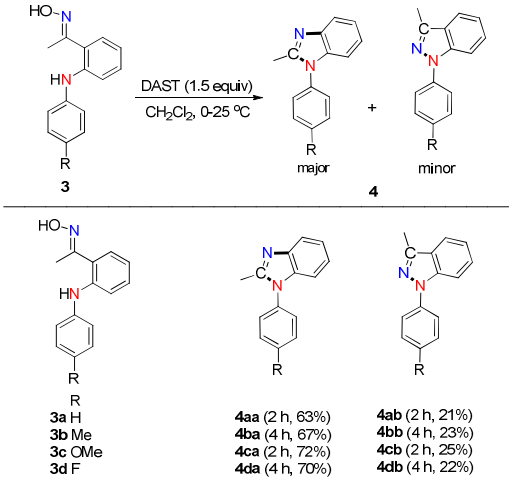


Scheme 2. Plausible Reaction Mechanism

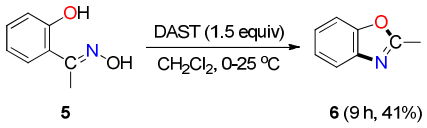
Building on the above results we wished to expand this novel protocol to the synthesis of most popular benzo-fused heterocylcles such as *N*-arylbenzimidazoles. Changing the substrates to *o*-arylamino-acetophenone-oximes **3** in the place of α,α-disubstituted-α-carbamoyl ketoximes **1**, the target 2-methyl-1-aryl-1*H*-benzo[*d*]imidazoles **4aa-da** were afforded as major products along with 3-methyl-1-aryl-1*H*-indazoles **4ab-db** as minor products (Table 3). Although Stambuli et al. reported the formation of *N*-arylbenzimidazoles and *N*-Arylindazolesfrom from *o*-arylamino-acetophenone-oximes and addressed the correct isomers of these compounds,[12] lower

yield was obtained for electron-rich arenes, such as **4ca** (36%). The current protocol provides the higher yield of **4ca** (72%).

Table 3. Reaction of *o*-Arylamino-Acetophenone-oximes with DAST



The scope of the protocol was further expanded towards the synthesis of 2-substituted benzoxazoles (Scheme 3). When (*E*)-1-(2-hydroxyphenyl)ethanone oxime **5** was allowed to react with DAST under standard reaction conditions, 2-methylbenzoxazole **6** is formed as the sole product in 41% isolated yield.



Scheme 3. DAST-Promoted Synthesis of 2-Methylbenzoxazole

In conclusion, we have developed a novel protocol as the first example of DAST-promoted Beckmann rearrangement/intramolecular cyclization reaction of acyclic ketoximes, which represents a facile and efficient route to 2-oxazolines, benzimidazoles and benzoxazoles. Efforts toward the utilization of this protocol for syntheses of other heterocyclic compounds are also underway and will be reported in due course.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedure, ^{1}H and ^{13}C NMR spectra for all compounds and CCDC 942577. See DOI: 10.1039/c000000x/.

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