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Radical-Based Route to 2-(Trifluoromethyl)-1,3,4-oxadiazoles and Trifluoromethyl-Substituted Polycyclic 1,2,4-Triazoles and Dihydrofurans

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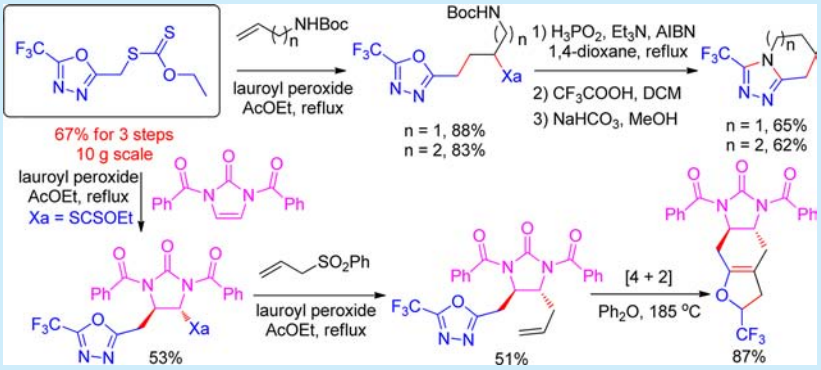
Supporting Information



ABSTRACT: *O*-Ethyl *S*-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]methyl xanthate was readily prepared on a large scale and shown to undergo very efficient intermolecular radical additions to unactivated alkenes. The products were further elaborated by exploiting both radical and ionic processes to provide a variety of trifluoromethyl-substituted derivatives, including medicinally relevant triazoles. In particular, the application of a radical allylation on the initial adducts leads to structures that are able to undergo intramolecular [4 + 2] cycloaddition reactions.

The introduction of fluorine-bearing groups into heteroaromatic structures has gained in intensity in recent years, in view of the importance of organofluorine compounds for the pharmaceutical and agrochemical industries as well as for material science.[1] The small atomic radius, high electronegativity, and low polarizability of the fluorine atom profoundly alters the properties of the molecules to which it is attached such as lipophilicity, permeability, and metabolic stability. The trifluoromethyl group, in particular, is the most widespread moiety present in the various building blocks and reagents that have so far been described.[2]

Owing to its metabolic profile and its ability to form hydrogen bonds, the 1,3,4-oxadiazole nucleus is a popular pharmacophore that is widely employed as a scaffold in medicinal chemistry[3] and present in marketed drugs such as tiodazosin[4] and nesapidil,[5] both antihypertensive agents, as well as furamizole,[6] an antibiotic (Figure 1). 1,3,4-Oxadiazoles are also well-known precursors of *N*-acylamidrazones and 1,2,4-triazoles, the latter being in their own right important heterocyclic building blocks for bioactive molecules.[7] Furthermore, 1,3,4-oxadiazoles can behave as electron-deficient azadienes in inverse-electron-demand Diels−Alder reactions and undergo tandem Diels−Alder/1,3-dipolar cycloaddition processes to furnish polycyclic structures, and they have therefore found application in several elegant total syntheses of natural products.[8]

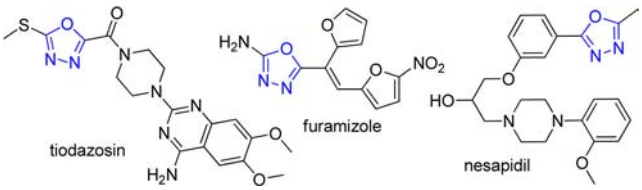


Figure 1. Marketed drugs containing a 1,3,4-oxadiazole.

In previous work, we described the synthesis of various fluorine-containing xanthates[9] and demonstrated their use for the generation and capture of the corresponding fluorine-containing radicals through the reversible addition−transfer process we discovered some years ago.[10] We now describe a simple, efficient route to *O*-ethyl *S*-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]methyl xanthate **4**, a convenient source of (trifluoromethyl)oxadiazolylmethyl radical. As far as we know, such a species (and 1,3,4-oxadiazolylmethyl radicals in general) has not been hitherto exploited for the introduction of this heteroaromatic moiety.

The desired xanthate **4** was readily prepared in three steps in 67% overall yield on up to 10-g scale (Scheme 1). Thus, following the procedure of Balsells and co-workers,[11] hydrazine

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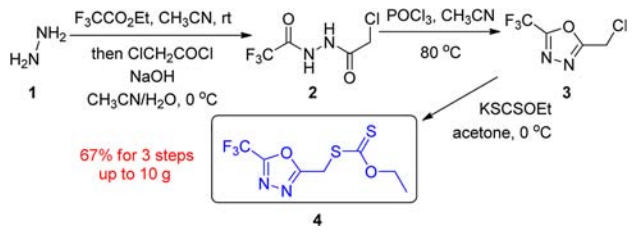
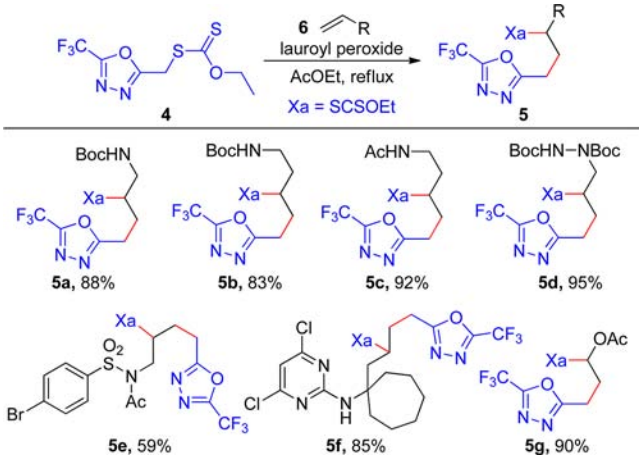
Scheme 1. Efficient Route to *O*-Ethyl *S*-[5-(Trifluoromethyl)-1,3,4-oxadiazolyl-2-methyl] Xanthate



1 was converted into bishydrazide **2** via a one-pot reaction with ethyl trifluoroacetate in acetonitrile and followed by simultaneous addition of chloroacetyl chloride and sodium hydroxide. This compound was further dehydrated by treatment with phosphorus oxychloride in acetonitrile to give (chloromethyl)-oxadiazole **3**. Finally, treatment with potassium *O*-ethyl xanthate in acetone at 0 °C afforded the desired *S*-(trifluoromethyl)oxadiazolylmethyl xanthate **4** as light yellow solid (mp 51−52 °C).

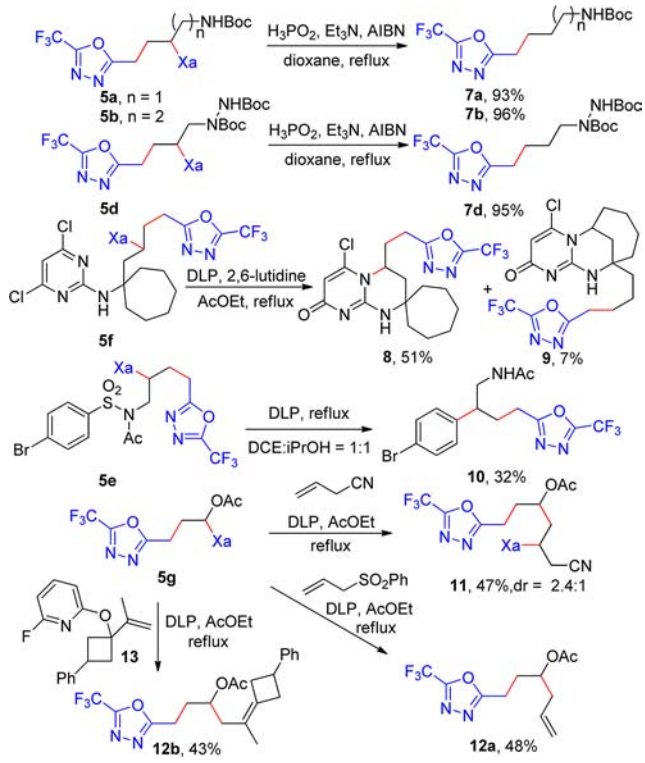
Generally, aryl- and heteroarylmethyl radicals are poorly reactive toward simple alkenes, unless the aromatic nucleus is itself electron withdrawing or is substituted by electron-withdrawing groups. This is because the resonance stabilization decreases the reactivity of the radical, and this effect has to be compensated by favorable polar factors, i.e., a matching between the mildly electron-donating nature of the simple alkene and a certain electrophilic character in the radical. Our hope that the trifluoromethyl group would impart sufficient electrophilicity to the radical to make its addition to the alkene synthetically useful was realized in practice, as shown by the examples in Scheme 2.

Scheme 2. Radical Additions of Xanthate 4 to Olefins



The mildness of the experimental conditions typical of the xanthate transfer translates into a tolerance for numerous useful functional groups (e.g., the hydrazide in compound **5d**). Furthermore, the addition products can be simply reductively dexanthylated by the Barton reagent system[12] (examples **7a**, **7b**, and **7d** in Scheme 3) or modified and further enriched by a number of transformations we have previously devised. For instance, further treatment of adduct **5f** with stoichiometric quantities of lauroyl peroxide results in ring closure on the nitrogen of the pyrimidine nitrogen (but interestingly not on the oxadiazole nitrogen) to give spiro derivative **8** accompanied

Scheme 3. Further Transformations of the Adducts



by a small amount of **9**, which arises from a 1,5-hydrogen translocation, prior to the cyclization step.[13] Acetamide **10** is the result of a radical Smiles rearrangement triggered by regeneration of the radical from xanthate **5e**,[14] whereas the formation compound **11** illustrates the possibility under certain conditions of performing a second radical addition. The complexity may also be further increased by allylation using an allyl phenyl sulfone, as in the case of **12a**,[15] or by reaction with derivative **13** to give alkylidenecyclobutane **12b**. The latter is an example of the use of fluoropyridyl derivatives of allylic alcohols as radical allylating agents.[16] In general, C−O bonds are very difficult to cleave homolytically, and this recently discovered process opens vast synthetic possibilities.

The purpose of the allylation leading to **12a** and **12b** was to set up an arrangement that was capable of undergoing an intramolecular cycloaddition.[8] Indeed, upon heating in diphenyl ether at 185 °C, the former was smoothly converted into bicyclic dihydrofuran **14** (Scheme 4). Unfortunately, the intermediate dipole could not be captured by vinyl acetate to give **15** (see Scheme 5 for the mechanism), nor could a similar cycloaddition leading logically to **16** be accomplished starting with compound **12b**, presumably because of the congested nature of the alkene.

In contrast, oxadiazole **19**, prepared by addition of xanthate **4** to imidazoledione **17** followed by radical allylation of adduct **18**, was effectively converted into (trifluoromethyl)-dihydrofuran **20**. The *trans* fusion between the imidazolininone and the cyclohexene rings is worthy of note.[17] In a similar fashion, unsaturated ester **22**, obtained by radical addition and 1,2-aryl migration with concomitant elimination of a sulfonyl radical, underwent cycloaddition to afford bicyclic tetrahydrofuran **23** in 63% yield (or 71% brsm). No dehydration of the hemiketal took place in this case, despite the harsh reaction conditions. The elimination of water is in all likelihood

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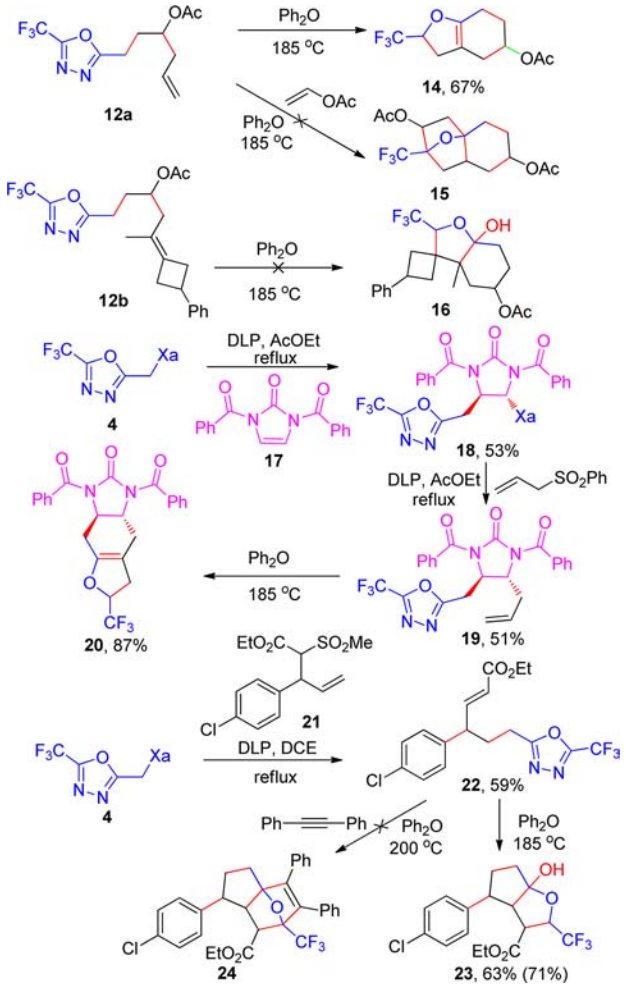
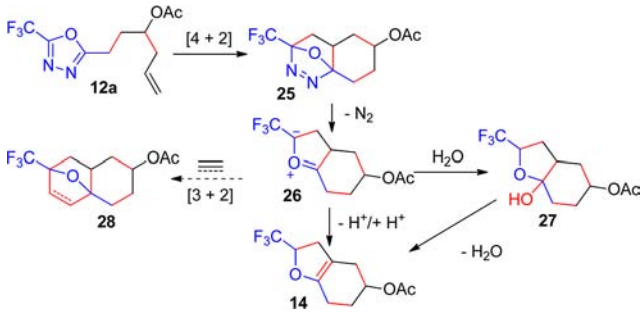
Scheme 4. Synthesis of Trifluoromethyldihydrofurans



Scheme 5. Mechanistic Rationale

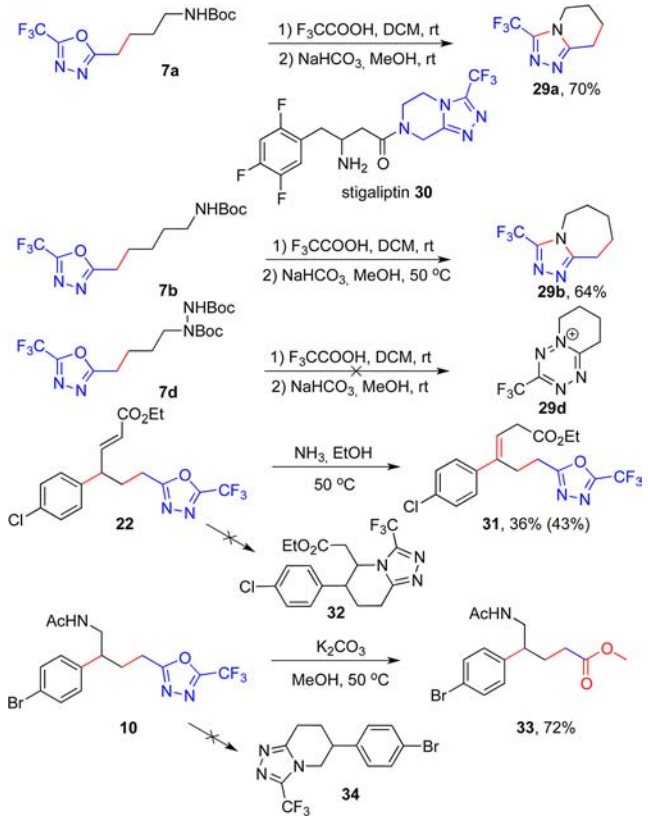


prevented by the strain that would be generated in the fused oxa-[3.3.0] structure. An attempt to capture the intermediate dipole with diphenylacetylene also failed in this case. Instead of the expected tricyclic compound **24**, and despite the higher reaction temperature, we only isolated compound **23**, albeit in somewhat lower yield than when it was heated alone.

A mechanistic rationale for these transformations, using oxadiazole **12a** as a typical substrate, is outlined in Scheme 5. A [4 + 2] cycloaddition furnishes diazo intermediate **25**, which rapidly loses nitrogen at the high reaction temperature to give dipole **26**. In our limited study, this dipole failed to provide structures of type **28** by a [3 + 2] cycloaddition with an external dipolarophile. Instead, it was converted into dihydrofuran **14** either by protonation/deprotonation or, perhaps more likely, via hemiketal **27** through loss of water.

The trifluoromethyl-substituted oxadiazole ring is fairly electron-deficient and readily undergoes attack by various nucleophiles. The most interesting is the reaction with internal amines.[11] Thus, reductively dexanthylated product **7a** was readily transformed into bicyclic (trifluoromethyl)triazole **29a** in good yield via deprotection of Boc group by trifluoroacetic acid in dichloromethane and neutralization by sodium bicarbonate in methanol at room temperature (Scheme 6).

Scheme 6. Synthesis of (Trifluoromethyl)triazoles



Compound **29a** bears some resemblance to the (trifluoromethyl)triazole portion of stigaliptin **30**, a promising antidiabetes drug. We could even prepare the seven-membered ring homologue **29b** by a similar sequence starting with **7b**, but a higher reaction temperature was needed in the last step to induce the more difficult formation of the azepine ring. In the case of derivative **7d**, we expected a structure such as tetrazine **29d** or a derivative thereof, but we were disappointed to find that deprotection of the hydrazine moiety and neutralization with bicarbonate gave rise to a complex mixture with no readily identifiable product.

Finally, we attempted to access the more substituted triazole **32** through conjugate addition of ammonia to the unsaturated ester in compound **22** followed by intramolecular reaction with the oxdiazole ring. Unfortunately, all we obtained was a modest yield of the simple oxadiazole **31**, where ammonia, acting as a base, caused the migration of the olefin into conjugation with the chlorophenyl ring. An attempt at the direct base-induced cyclization of acetamide**10** also failed to give the corresponding triazole **34**. Only methanolysis of the oxadiazole ring to give ester **33** was observed.

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In summary, we have shown the myriad trifluoromethyl-substituted structures that can be obtained through the exploitation of the 2-(trifluoromethyl)-1,3,4-oxadiazolyl-5-methyl radical. Such molecular architectures cannot be easily obtained through ionic chemistry in view of the sensitivity of the electrophilic oxadiazole ring to basic conditions and its susceptibility to nucleophilic attack. The ability to rapidly introduce alkenes or protected amines in positions suitable for subsequent [4 + 2] cycloadditions or nucleophilic condensations with the oxadiazole nucleus is particularly noteworthy.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This article is dedicated with respect and admiration to Professor Iwao Ojima (Stony Brook University) on the occasion of his 70th birthday.

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