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Application of Bis-acetylenic Ketones in Synthesis: One-Pot Preparation of the 1,2,4-Triazepine and Oxatriazaindenone Cores

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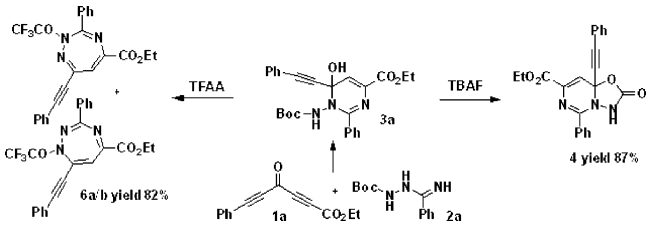


Bis-acetylenic ketones were used to generate two heterocyclic templates. Two efficient one-pot procedures for the preparation of the triazepine and oxa-triazaindenone cores are described.

Contemporary chemistry faces the challenge of supplying the research community with versatile and modular methodologies that allow the rapid assembly of molecules with potential medicinal activity. In this regard, multicomponent reactions and one-pot procedures play a pivotal role. Our approach toward the development of new multicomponent procedures involves the use of building blocks that contain a number of chemically distinct functionalities, which could be selectively reacted to generate diversity.[1,2] For example, we have designed the bis-acetylenic ketones **1a**−**c** (Figure 1) in which two carbonyl groups and two alkynyl moieties are present, that could be independently reacted.[1] Therefore, compounds **1a/c** represent a class of poly-electrophilic scaffolds, which could be used conveniently for the preparation of alkynylpyrazoles, alkynylpyrimidines, and alkynylpyridines.[1] In these syntheses regiochemical control was observed due to the presence of the carbethoxy group, which governs the relative reactivity of the two triple bonds.

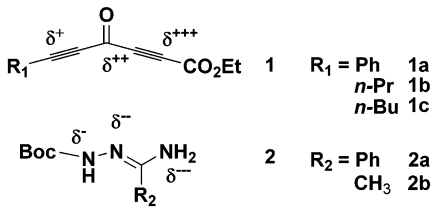
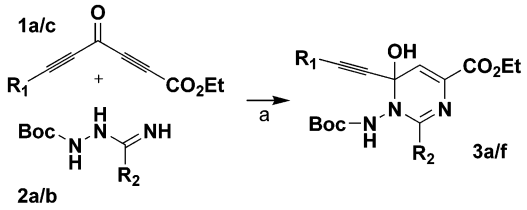


FIGURE 1. Polyelectrophiles **1** and polynucleophiles **2**.

To expand the range of applications of **1a**−**c** in synthesis, we decided to investigate the reactivity of **1a**−**c** with compounds containing three nucleophilic centers.

Amidrazones are compounds containing three nitrogen nucleophiles which are very popular templates in drug discovery,[3] the NNCN group being an essential part of molecules bearing high biological activities such as Lamotrigine and Sildenafil. We anticipated that compounds **1a/c** would react with NCNN nucleophiles in a regiocontrolled fashion only when the relative reactivity of the three N-nucleophiles was differentiated. In a test experiment, **1a** was reacted with phenylamidrazone to yield a complex mixture of products. However, when **1a** was reacted with *N*-Boc phenylamidrazone **2a** the corresponding adduct **3a** was obtained as the exclusive compound (Scheme 1). As anticipated, the presence of an electron-withdrawing group on the amidrazone moiety imparted a discrete order of reactivity to the three N-nucleophiles, resulting in a regiocontrolled reaction.

SCHEME 1[a]



[a] Key: (a) 1 mmol of **1a/c**, 1.1 mmol **of 2a/b**, solvent.

In this fashion, bis-acetylenic ketones **1a**−**c** reacted with Boc-amidrazones **2a**,**b** (1.1 equiv) under mild neutral conditions to afford the corresponding adducts **3a**−**f** in high yields (Scheme 1, Table 1). The reaction could be run under a wide variety of experimental conditions: it proceeded equally well at low (−78 °C) and room temperature (25 °C) and in a variety of different solvents such as THF, DCM, hexane, EtOH, and MeOH. The reaction times were surprisingly short, and typically, no starting materials could be detected just after 5−10 min. The reactions in Table 1 afforded only one product. For all these reasons, the reaction between **1a**−**c** and **2a**,**b** constitutes an example of "click chemistry"[4] in which compounds **1a**−**c** are spring loaded toward multiple nucleophilic additions.

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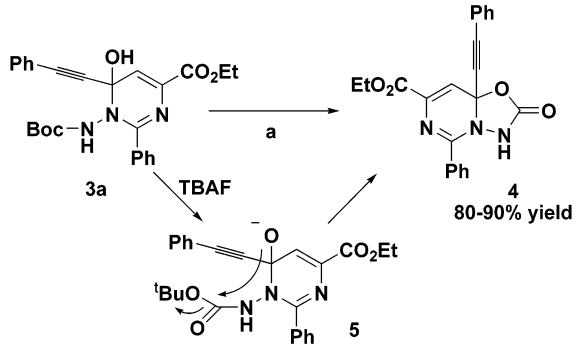
TABLE 1. Isolated Yields of Adducts 3

entry	compd	R_1	R_2	yield (%)
1	**3a**	Ph	Ph	91
2	**3b**	*n*-Pr	Ph	86
3	**3c**	*n*-Bu	Ph	87
4	**3d**	Ph	CH_3	88
5	**3e**	*n*-Pr	CH_3	82
6	**3f**	*n*-Bu	CH_3	88

Compounds **3a**−**f** proved useful intermediates to access two diverse heterocyclic cores such as the oxatriazaindenone **4** and triazepine **6** (Schemes 2 and 3). A few methods for the preparation of the 1,2,4-triazepine nucleus have been reported: these include synthetic strategies based on a nucleophile electrophile coupling[5] and methodologies relying on the thermal cycloaddition of 1-azirines to *sym*-tetrazines.[6] Our synthesis enhances the existing methodology by allowing the efficient preparation of the 1,2,4-triazepine core with a novel substitution pattern. To the best of our knowledge, the oxatriazaindenone core **4** is unprecedented.

SCHEME 2[a]



[a] Key: (a) 1 mmol of **3a**, THF or DCM (0.2 mmol/mL), TBAF (5 equiv), rReflux, 2 h.

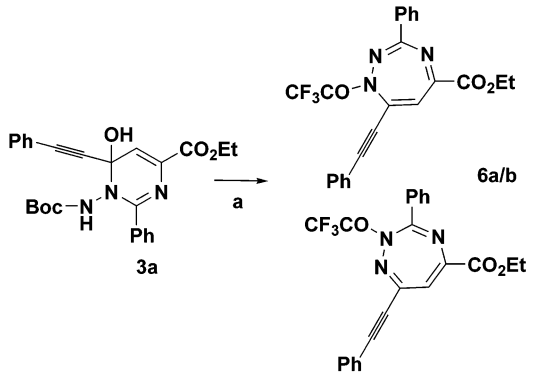
During a set of experiments aimed at promoting the cyclization of the Boc amino group onto the alkyne moiety present in **3a**, we found that upon treatment of **3a** with TBAF[7] the oxatriazaindenone **4** was obtained in 90% (Scheme 2). In this reaction, TBAF acted as the base forming the oxy anion **5**, which rapidly cyclizes to **4** (Scheme 2).

Importantly, the preparation of **3a** and its subsequent transformation to **4** could be run in a one-pot fashion. Therefore after reacting **1a** and **2a** (1.1 equiv) in DCM, addition of an excess of TBAF (5 equiv) gave **4** in 87% isolated yield.

We also found that **3a** could be used to access *N*-trifluoroacetyltriazepine **6a/b** in high yields when reacted with refluxing TFAA (Scheme 3).

It was anticipated and confirmed that the preparation of **6a/b** could be carried out directly from **1a** and **2a**

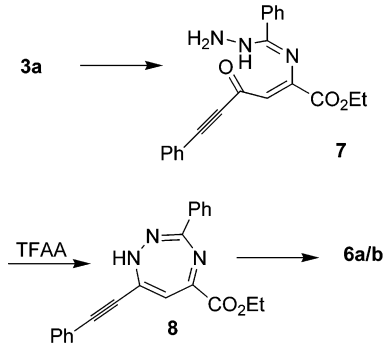
SCHEME 3[a]



[a] Key: (a) 1 mmol of **3a**, DCM (5 mL), TFAA (5 mL), reflux, 3 h.

through a one-pot procedure. Therefore by coupling of **1a** and **2a** and following addition of TFAA, trifluoroacetyltriazepine **6** was isolated in 82% yield as a 4:1 mixture of regioisomers **a/b**. The mechanism of conversion of **3a** to **6** most likely involves ring opening and deprotection of **3a** to the corresponding ketone **7** which undergoes ring closure to the triazepine ring system **8** before acylation to **6a/b** (Scheme 4).

SCHEME 4. Proposed Mechanism for the Formation of 6a/b



In conclusion we have confirmed that bis-acetylenic ketones **1a/c** are efficient building blocks, which could be used for the preparation of complex, diverse, and densely functionalized heterocycles such as **3a/f**, **4** and **6**. We also have established two one-pot procedures for the synthesis of the oxatriazaindenone **4** and the triazepine **6**. These reactions are facile, high yielding, and modular; therefore, they constitute useful tools for those studies in which the rapid generation of families of compounds is required.

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Supporting Information Available: Spectroscopic data for compounds **3a**−**f**, **4**, and **6a/b**; ^{1}H NMR and ^{13}C NMR spectra for compounds **3a**, **4**, and **6**. Experimental procedures for the syntheses highlighted in Schemes 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

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