Vinyl Fluorides: Competent Olefinic Counterparts in the Intramolecular Pauson–Khand Reaction

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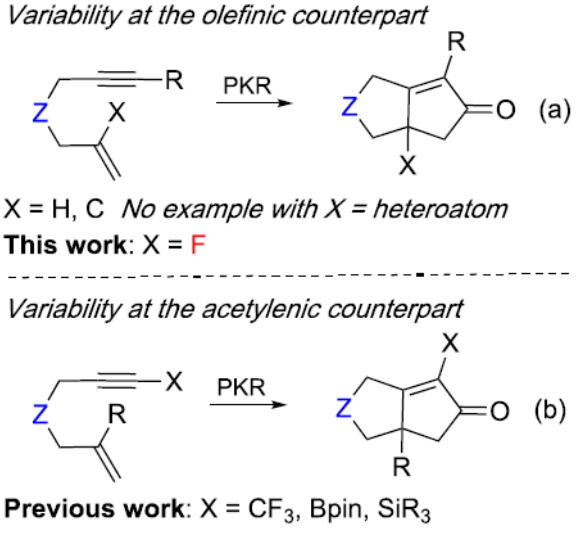
ABSTRACT: Despite the great advances achieved in the Pauson− Khand reaction and the ever-increasing demand for fluorinated compounds, the use of vinyl fluorides as olefinic counterparts in the above-mentioned transformation had been completely overlooked. Herein, we describe, for the first time, the intramolecular Pauson− Khand reaction of enynes containing a vinyl fluoride moiety.

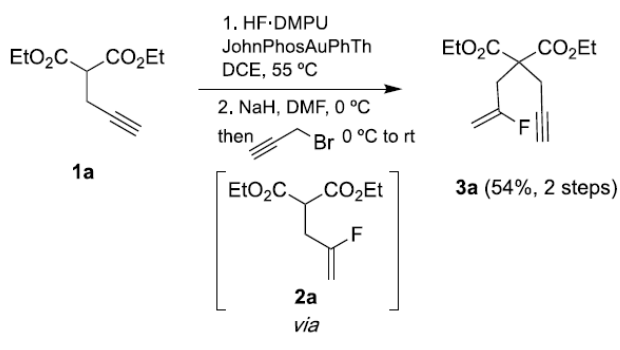
The ever-increasing demand for organofluorine compounds by key industrial fields such as the pharmaceutical, agrochemical, or materials is unquestionable.1 In recent years, following a general trend in drug discovery referred to as escape from flatland, the synthesis of new molecular entities bearing a fluorine atom or a fluorinated motif directly attached to an sp3 carbon atom has received renewed impetus.2 Within this trend, the installation of a fluorine atom in a quaternary stereocenter is of paramount importance.3 On the other hand, the Pauson−Khand reaction (PKR) has arguably become the methodology of choice for the preparation of the cyclo- pentenone core, especially for the synthesis of bicyclic scaffolds by means of the intramolecular version.4 In our continuous efforts to construct functionalized monofluorinated scaffolds, we envisioned the use of vinyl fluorides as olefinic counterparts in this emblematic transformation (Scheme 1, equation a).5 While we and others have achieved significant advances in broadening the scope with regard to the substitution at the triple bond (Scheme 1, eq b),6 we were astonished to find that the use of not only fluoro olefins but also heteroatom-substituted olefins had been overlooked in this area (Scheme 1, eq a).7,8

Scheme 1. Pauson−Khand Reactions with Heteroatom-Substituted Olefins and Alkynes



In view of the increasing availability of fluorinated building blocks and fluorination methodologies,[9] we set out to tackle this striking synthetic lack. A literature search revealed that the required fluorinated 1,n-enynes were hitherto unknown.[10] Our first challenge, then, was the synthesis of an appropriate model substrate (Scheme 2). Recently, Hammond disclosed the Markovnikov hydrofluorination of terminal alkynes using HF·DMPU and gold catalysis.[11] In that report, product 2a caught our attention since it could be transformed into model substrate 3a just by propargylation of the fluoroallylmalonate intermediate 2a. Hence, starting from commercially available diethyl propargyl malonate 1a, 3a was obtained in two steps in good overall yield (Scheme 2).

Scheme 2. Synthesis of Model Substrate 3a

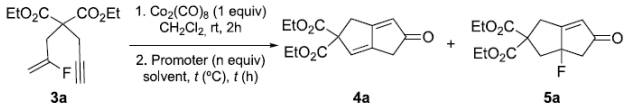


This model substrate was then used to assess suitable reaction conditions for the unprecedented fluoro Pauson−Khand reaction (Table 1). We started the optimization using the reaction conditions that had already proved successful by our group in several structurally diverse scenarios, namely, NMO (10 equiv, CH2Cl2, rt) (Scheme 3).6b,12 Under these reaction conditions, however, the only defined species formed was elimination product 4a. This substructure was reported to be formed by the palladium-catalyzed carbonylation of diynes 6 (Scheme 3).[13] Since *N*-methyl morpholine is the only base present in the reaction medium and the reaction conditions are very mild, the elimination of HF from 4a to form 6 or 6′ seemed unlikely.[13b] We anticipated that 4a may be formed instead by elimination of HF from 5a (Scheme 3).[14] The antiaromatic character of the corresponding cyclopentadienone would account for the complete regioselectivity observed in the elimination step. This possibility would mean that the fluoro- PKR takes place and that the desired product 5a could be afforded just by avoiding the elimination reaction.

Encouraged by this promising result, we decided to carry out an optimization of the reaction conditions avoiding the use of NMO as an oxidant, rather looking for an oxidizing promoter that would render a reduced neutral species. A pioneering study by Pauson showed that DMSO is also able to promote the PKR, albeit under somewhat more energetic reaction conditions.[15] To our delight, 5a was the major product when using DMSO as the promoter, regardless of the reaction conditions (equivalents of DMSO, solvent, temperature) (Table 1). The conditions shown in entry 3 were selected as optimal and used to subsequently determine the

scope of the reaction (see below).

Table 1. Optimization of Reaction Conditions

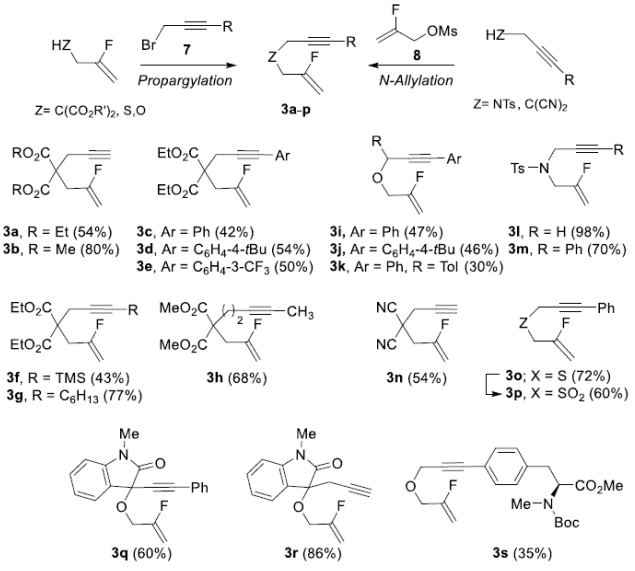


3a 4a 5a

entry	promoter	*n*	solvent	*t* (°C)	*t* (h)	4a (%)	5a (%)
1	NMO	10	CH_2Cl_2	rt	4	41	–
2	NMO	10	DCE	50	4	60	–
3	DMSO	1	CH_2Cl_2	40	4	–	70
4	DMSO	2	CH_2Cl_2	40	4	–	67
5	DMSO	3	CH_2Cl_2	40	4	–	71
6	DMSO	3	toluene	60	18	–	68

Before disclosing our findings regarding the scope of the reaction,a brief description of the synthesis of the starting materials will be outlined (Scheme 4). Most malonate derivatives 3 were synthesized by an analogous route to that depicted in Scheme 2, namely hydrofluorination of the corresponding propargyl malonate 1, followed by propargyla- tion of intermediates 2 with suitable propargyl bromides 7 (Scheme 4). In addition, the availability of fluoroallyl alcohol allowed us to envision an alternative *metal-free* approach that, in addition, was also amenable for the preparation of heteroatom tethered enyne derivatives 3i–s (Scheme 4). Direct propargyl ether formation by Williamson's synthesis afforded 3i,j in moderate yields. For the synthesis of chiral ether 3k, an alternative $FeCl_3$-catalyzed methodology was required.[16] Mesylate 8, first described by Mykhailiuk,[17] allowed the preparation of *N*- and *S*-tethered substrates 3l,m,o,p. Moreover, this approach proved to be the only alternative for the preparation of malononitrile-derived analog 3n, since propargyl malononitrile was reluctant to Hammond's hydro- fluorination conditions. In order to showcase the applicability of our methodology for the synthesis of complex scaffolds of pharmaceutical interest,[18] isatin derivatives 3q,r were prepared by an analogous strategy (Scheme 4). Furthermore, a phenylalanine residue was attached to the triple bond of the enyne scaffold 3s (Scheme 4).

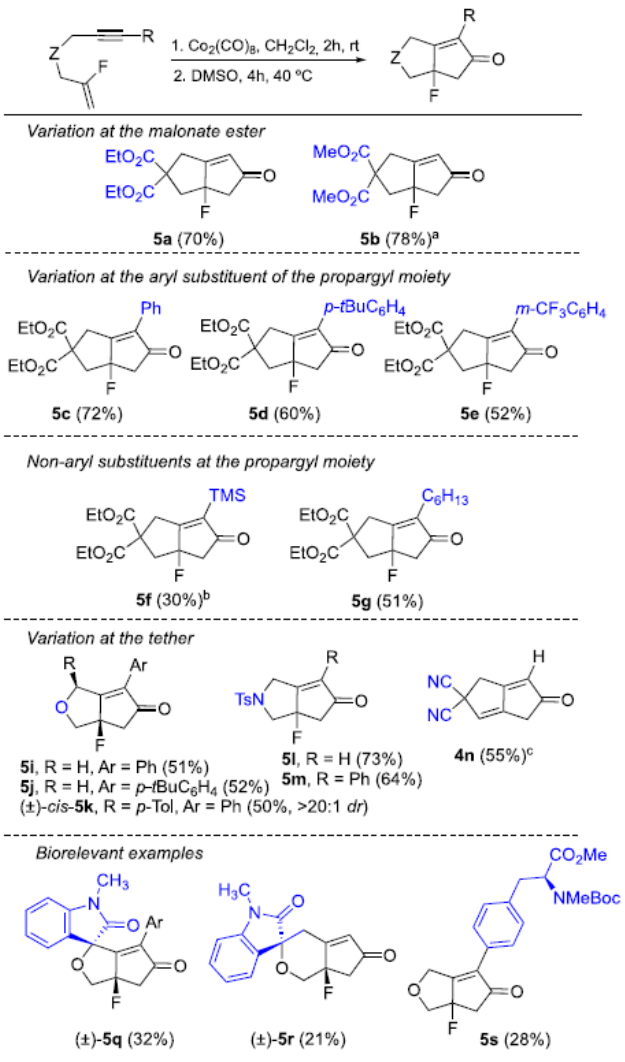
Scheme 4. Synthesis of Starting Materials 3a–s



With this small library of substrates 3a–s in hand, we set outto explore the scope and limitations of the PKR reaction

conditions optimized for 3a (Scheme 5). First, as expected, a change in the ester substituent at the malonate moiety had no noticeable impact on the reaction efficiency (Scheme 5, 5a,b). Similarly, moderate to good yields were obtained for derivatives bearing aryl substitutents at the propargyl moiety regardless of their electronic nature (Scheme 5, 5c–e). On the other hand, while alkyl-substituted derivative 5g was afforded in the same chemical yield range as the aryl substituted ones, a significant drop in reactivity was obtained for the correspond- ing TMS-substituted derivative 5f. This diminished reactivity translated in both a poor chemical yield and an extended reaction time.[19] Unfortunately, the use of homopropargyl derivative 3h did not allow the preparation of the corresponding 6,5-bicyclic system. Regarding the use of tethering functionalities other than malonates, while heter- oatomic moieties such as ethers or tosylamine were well- tolerated (Scheme 5, 5i–m), the use of a sulfur-based tether in 3o and 3p was unsuccessful.[20] Noteworthy, the use of chiral ether 3k afforded the corresponding product 5k in moderate yield and complete diastereoselectivity (Scheme 5).[21] On the other hand, elimination product 4n was exclusively obtained when using malononitrile as the spacer, under a variety of reaction conditions. To our delight, isatin derivatives 3q,r afforded the corresponding spirocyclic derivatives 5q,r as single diastereoisomers, albeit in low yields (Scheme 5).[21] It is worth noting that the presence of a quaternary stereocenter in the tether enabled the formation of the hitherto reluctant 6,5 bicyclic system, presumably due to the Thorpe–Ingold effect. We were also delighted to achieve the formation of amino acid derivative 5s, in moderate yield (Scheme 5).

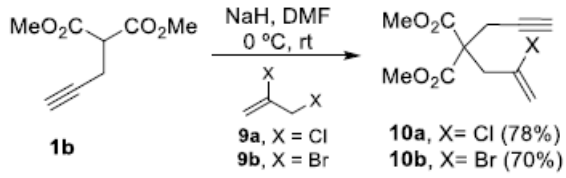
Scheme 5. Scope and Limitations



[a]5b was prepared in a gram scale procedure (×10, 70%). [b]18 h at 40 °C. [c]Direct PKR product not observed.

As commented in the introduction, neither fluoro olefins nor other vinyl halides have been used as olefinic counterparts in enynes for the intramolecular PKR. Intrigued by this fact, and with the aim of extending the scope of this transformation, we set out to explore the use of the corresponding chloro- and bromo-derivatives 10a,b. The commercial availability of the corresponding 2,3-dihalopropene derivatives 9a,b resulted in a straightforward one-step synthesis from dimethyl propargyl malonate 1b (Scheme 6).

Scheme 6. Synthesis of Chloro and Bromo Analogs



Disappointingly, under various reaction conditions the corresponding PKR products were not observed in the crude reaction mixtures. By using the conditions optimized for the fluorinated analogs 3, the major isolated product was the dimeric species 11 (Scheme 7). It is noteworthy that 11 was isolated as a single regio- and diastereoisomer. Although the desired product could not be isolated, the presence of the cyclopentenone subunit in the final product allowed the assumption that PKR products 12a,b had indeed been formed and then transformed into the observed final product. The formation of this unexpected product may be explained by the inherent diminished strength of the C−X bond along the halide elements C−F > C−Cl > C−Br > C−I. These weakened C−X bonds along with the position of the halide at a tertiary carbon and the presence of stoichiometric amounts of cobalt, known to be prone to promote radical pathways,[22] indicate that 11 was formed by dimerization of radical I arising from 12 (Scheme 7).

In conclusion, the synthesis of a new family of fluorinated enynes has been achieved for the first time, including malonates and heteroatoms as tethering units. These fluorinated building blocks have shown to be competent substrates for the intramolecular Pauson−Khand reaction, by using appropriate reaction conditions that preclude the inherent tendency of the obtained adducts to eliminate HF. Moreover, the unprecedented bicyclic cyclopentenones featur- ing a fluorine atom at a fully substituted bridgehead carbon would be difficult to access by current synthetic method- ologies.[23] Finally, the strength of the C−F bond hampers the radical pathway observed for other halogen derivatives, showcasing the unique reactivity of organofluorine com- pounds. Further studies aimed at the development of a catalytic, ideally enantioselective, variant of this transformation are currently underway.[24] In addition, the versatility of 1,6- enynes as substrates for transition-metal-catalyzed trans- formations is also under study with our new fluorinated analogs.[25]

The authors are grateful to the Spanish MINECO (CTQ2017-84249-P) and the Generalitat Valenciana (PROMETEOII/2014/073) for their financial support.

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