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## Nazarov reagents and their use in organic synthesis



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## 1. Introduction

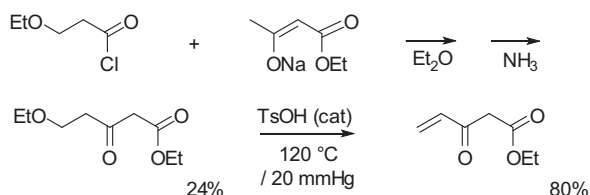
Continuously growing interest in the chemistry of biologically active and naturally occurring compounds possessing cyclic structures has resulted in the development of numerous simple and effective annulation methods.

The Robinson annulation reaction converts a cyclic ketone to an unsaturated bicyclic ketone with one additional six-membered ring.<sup>1</sup> This reaction has been used in the synthesis of a wide range of compounds including terpenes and steroids. However, the use of methylvinyl ketone suffers from low yields as it easily polymerized. Various compounds have been tested to replace methylvinyl ketone, such as the precursor trimethylsilylvinylmethylketone.<sup>2</sup>

**Abbreviations:** acac, acetylacetonate; AcCl, acetyl chloride; AIBN, 2,2'-azobis(2-methylpropionitrile); All, allyl; Bz, benzoyl; CBZ, carboxybenzyloxy; Cp, cyclopentadienyl; dba, dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, *N,N*-dicyclohexylcarbodiimide; DCM, dichloromethane; DIBALH, diisobutylaluminum hydride; DMAP, 4-dimethylaminopyridine; DMF, *N,N*-dimethylformamide; ee, enantiomeric excess; EWG, electron withdrawing group; KHMDs, potassium bis(trimethylsilyl)amide; LDA, lithium diisopropylamide; MOM, methoxymethyl; MS, molecular sieves; Ms, methanesulfonyl; PCC, pyridinium chlorochromate; PDC, pyridinium dichromate; Ph, phenyl; Piv, pivaloyl; PPA, polyphosphoric acid; TBDMS, or TBS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; Tf, trifluoromethanesulfonyl; TMS, trimethylsilyl; Triton<sup>®</sup> B, benzyltrimethylammonium hydroxide; Ts, *para*-toluenesulfonyl.

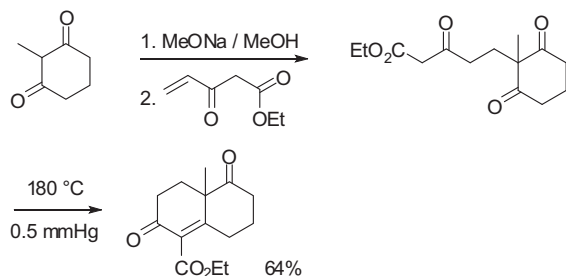
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In 1953 Nazarov<sup>3</sup> proposed a new reagent, a vinyl ketone that has been activated as a  $\beta$ -keto ester, and since known as the Nazarov reagent.<sup>4,5</sup> Ethyl and methyl 3-oxo-4-pentenoate (CAS number, 22418-80-0 and 37734-05-7, respectively) have been used in synthesis since the work of Nazarov and Zavyalov, who were the first to show their usefulness in the annulation of cyclic  $\beta$ -diketones. However, the original synthetic method only gave 20% overall yield of the desired vinyl ketone (Scheme 1).



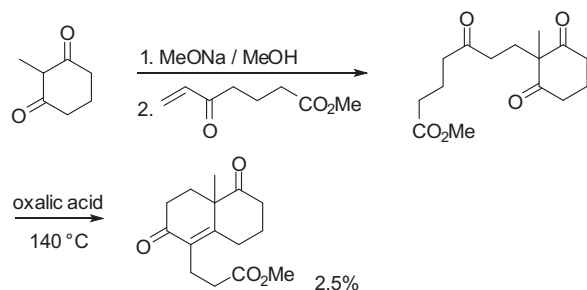
Scheme 1.

Nazarov first showed the importance of his reagent by performing the Michael addition of the enolate of methylcyclohexanedione and the subsequent heat- and vacuum-promoted cyclization (Scheme 2).



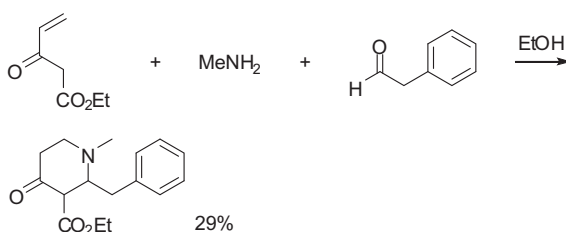
Scheme 2.

The activation of the reagent requires the presence of the  $\beta$ -keto ester moiety. Indeed, in the same paper, Nazarov showed that under identical conditions, the bis-homo reagent cyclized in a very low yield (Scheme 3).



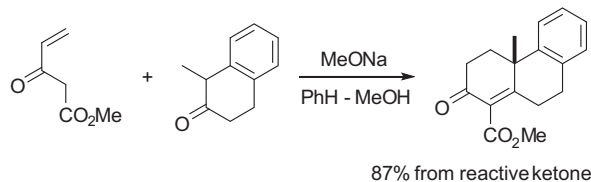
Scheme 3.

In 1962 this synthetic pathway was exploited by Hohenlohe–Oehringen for the preparation of a piperidone scaffold (Scheme 4).<sup>6</sup>



Scheme 4.

In 1963, Wenkert described 'the extraordinary usefulness and versatility of the yet rarely employed Nazarov reagent'. Starting from 3-ethoxypropionoyl chloride, Wenkert obtained methyl 3-oxo-4-pentenoate (methyl acrylate) in 24% yield. It was used to prepare abietic acid derivatives by annulation from an abnormally acidic monoketone (Scheme 5).<sup>7</sup> The same building principle was used by Mori for the synthesis of some oxygenated kauranes.<sup>8</sup>



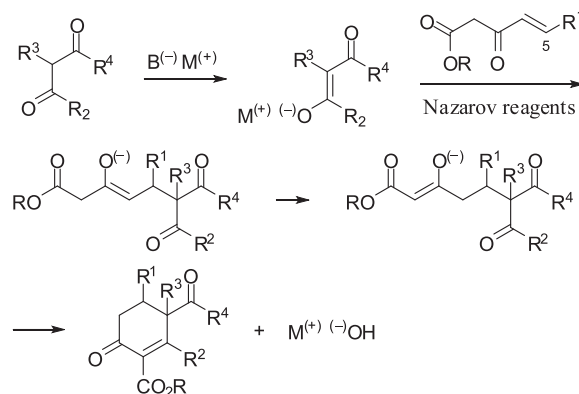
Scheme 5.

Micro-reviews on Nazarov reagents have been published.<sup>9</sup>

Usually, compounds where the carboalkoxy group in the original Nazarov reagents is replaced by a phosphonate, sulfone or sulfoxide function are also named Nazarov reagents.

## 2. Reactivity of Nazarov reagents

The Nazarov reagents lead to a cycle according to two processes. In the first process described by Nazarov himself, a stabilized carbanion induces a Michael addition on the vinyl ketone moiety of the reagent. Then an intramolecular aldolisation ends the cyclization. In this way, the Nazarov reagent appears, in the first step, as an *electrophilic reagent* and the overall reaction resembles to the Robinson annulation (Scheme 6). Of course, its reactivity as electrophilic reagent depends on the substitution on the C(5) carbon atom, and when a disubstitution occurs the Michael addition step is disfavoured.



Scheme 6.

Various other nucleophilic reagents, in particular enamines, can be used in the Michael addition step (Scheme 7).

In the second process, the enolization of the  $\beta$ -keto ester moiety of the reagent leads to a stabilized carbanion, which can react with an electrophilic Michael acceptor. In this case, it first reacts as a *nucleophilic reagent* (Scheme 8).

Two successive Michael additions occur, and some papers invoke a tandem Michael addition or Michael–Michael addition. But for selected cases, the stereochemistry of the products resulting from this hypothetical tandem Michael addition suggests a concerted Diels–Alder reaction. More recent syntheses of functionalized *cis*-decalines based on the so-called Deslongchamps annulation involve this mechanism (Scheme 9).

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