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One-pot preparation of methyl 2-diazo-3-oxopropionates comprising an aqueous 'sulfonyl-azide-free' (SAFE) diazo transfer step

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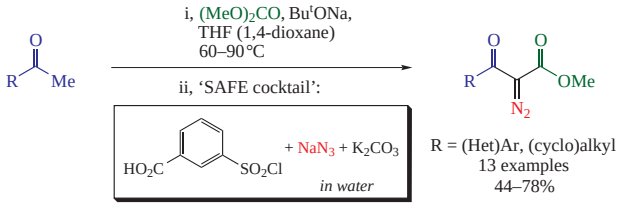
Methyl 2-diazo-3-oxopropionates were obtained by *in situ* methoxycarbonylation of methyl ketones followed by diazo transfer onto active methylene group of the intermediate β-oxo esters. At the second stage, 'sulfonyl-azide-free' (SAFE) diazo transfer protocol in aqueous medium was employed.



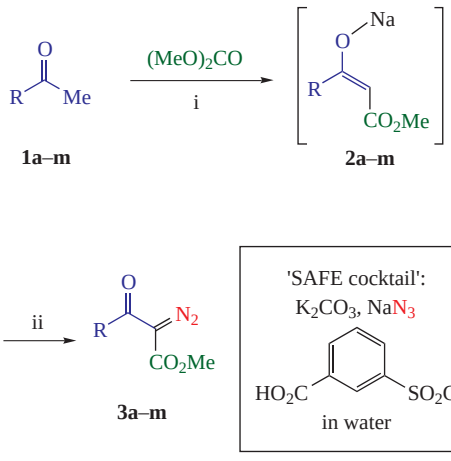
Keywords: methoxycarbonylation, β-oxopropionates, diazo transfer, SAFE cocktail, insertion reactions.

Diazo compounds represent a distinctly versatile class of substances whose reactivity toward a range of chemical transformations can be triggered by decomposition into the carbene species with loss of a nitrogen molecule.[1,2] Transfer of the diazo function onto suitably CH-acidic substrates (the so-called Regitz diazo transfer) remains the most popular method to prepare diazo compounds.[3,4] Along with its practical simplicity, the method carries the hazard of having to prepare and handle potentially explosive[5] sulfonyl azide reagents such as tosyl azide, the most commonly employed reagent in diazo transfer reactions.[6]

Recently, we developed a new effective procedure for the Regitz diazo transfer in basic aqueous medium that entailed *in situ* generation of the diazo transfer reagent from *m*-carboxybenzenesulfonyl chloride and sodium azide without the need to isolate and handle the potentially explosive sulfonyl azide. The method was therefore dubbed as 'sulfonyl-azide-free' (SAFE) diazo transfer.[7–9] It is also the first method applicable to the preparation of arrays of diazo compounds, suitable for combinatorial chemistry applications (previously reliant on the limited supply of commercially available diazo compounds).[7]

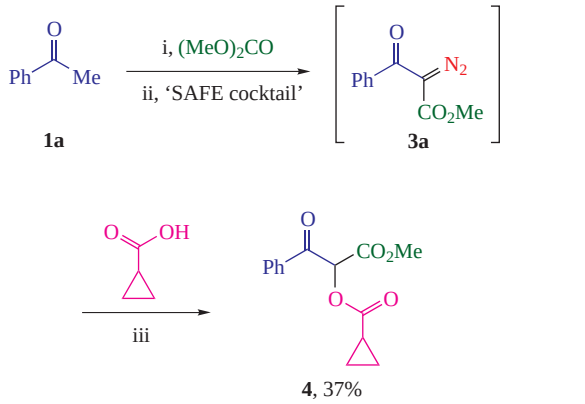
Sufficient α-CH-acidity of the substrates is the pre-requisite for efficient diazo transfer in general, and for the SAFE diazo transfer in particular. Insufficiently CH-acidic substrates such as monocarbonyl ones can be activated towards the SAFE diazo transfer by *in situ* formylation. Upon diazo transfer, the formyl group is lost, the overall result being the conversion of the starting monocarbonyl compound into the corresponding α-diazo derivative.[10] We reasoned that various methyl ketones can be alternatively activated towards the SAFE diazo transfer if they are first converted to β-keto esters. Should these substrates for subsequent diazo transfer become suitable, the β-keto acetate moiety would remain thus expanding the substrate scope and the range of densely functionalized products attainable by the SAFE diazo transfer protocol. Herein, we report the practical implementation of this strategy.

After brief experimentation with the reagent ratios and the base, methyl ketones **1** were converted into the corresponding methyl 3-oxopropionates **2** upon reaction (conducted at 60–90 °C over 2–16 hours) with dimethyl carbonate (1.5 equiv.) and sodium *tert*-butoxide (1.75 equiv.) in THF or 1,4-dioxane (Scheme 1). Notably, reducing the amount of base to 1.5 equiv. or the amount of dimethyl carbonate to 1.2 equiv. caused incomplete conversion. On the other hand, raising the amount of these reagents did not lead to significant improvement of the reaction outcome. Once the methoxycarbonylation was complete, a 1.5 equiv. aliquot of the basic aqueous 'SAFE cocktail' was added at room temperature. Within 2 h, intermediate keto esters **2** (in the form of sodium enolates) were converted to diazo compounds **3**, most of which were new except for the reported previously **3a**,[11] **3c**[12] and **3l**[11] (see Scheme 1).



a R = Ph, 75%
b R = 3-FC_6H_4, 71%
c R = 2-thienyl, 75%
d R = 2-ClC_6H_4, 65%
e R = 4-$Bu^tC_6H_4$, 67%
f R = 4-BrC_6H_4, 73%
g R = 1-naphthyl, 75%
h R = 2,4-$(MeO)_2C_6H_3$, 78%
i R = *c*-C_3H_5, 45%
j R = 1,3-benzodioxol-5-yl, 50%
k R = $Ph(CH_2)_2$, 44%
l R = 4-FC_6H_4, 52%
m R = 1-methylpyrrol-2-yl, 61%

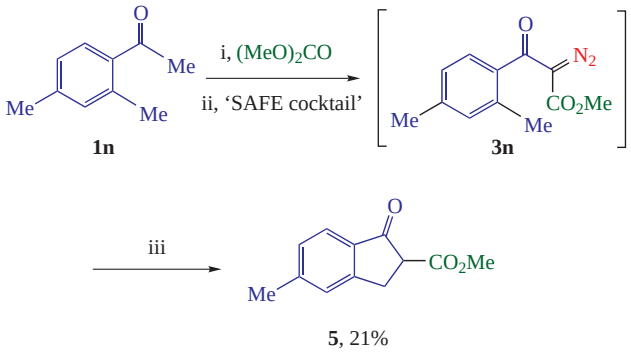
Scheme 1 *Reagents and conditions*: i, $(MeO)_2CO$ (1.5 equiv.), Bu^tONa (1.75 equiv.), THF or dioxane, 60–90 °C, 2–16 h; ii, 'SAFE cocktail', water. Yields after column chromatography are given for **3j**,**k**,**l**.



Scheme 2 *Reagents and conditions*: i, $(MeO)_2CO$ (1.5 equiv.), Bu^{t}ONa (1.75 equiv.), THF, 60 °C, 16 h; ii, 'SAFE cocktail', water, 2 h; iii, $Rh_2(esp)_2$ (2 mol%), CH_2Cl_2, 18 h.

Crude methyl α-diazo-β-oxopropionates thus obtained were deemed sufficiently pure to be introduced into the subsequent Rh^{II}-catalyzed transformations typical of diazo compounds. Indeed, crude diazo compound **3a** derived from acetophenone **1a**, without purification, was subjected to $Rh_2(esp)_2$-catalyzed intermolecular O–H insertion reaction with cyclopropanecarboxylic acid to give product **4** in moderate yield (Scheme 2).

In a similar fashion, 2,4-dimethylacetophenone **1n** was converted *via* intramolecular C–H insertion into the corresponding 2-methoxycarbonylindanone **5**[13] in 21% overall yield over three steps (Scheme 3).



Scheme 3 *Reagents and conditions*: i, $(MeO)_2CO$ (1.5 equiv.), Bu^{t}ONa (1.75 equiv.), THF, 60 °C, 16 h; ii, 'SAFE cocktail', water, 2 h; iii, $Rh_2(esp)_2$ (2 mol%), CH_2Cl_2, 18 h.

In summary, we have extended the application of the 'sulfonyl-azide-free' (SAFE) diazo transfer protocol to insufficiently acidic methyl ketones. The latter have been conveniently activated by methoxycarbonylation and treated with the 'SAFE cocktail'. The resulting diazo compounds were isolated in good to excellent yield over two steps, mostly without the need for chromatography. The 1-diazo-2-oxopropionates thus obtained can be used directly in Rh^{II}-catalyzed transformations typical of diazo compounds such as intermolecular O–H insertion and intramolecular C–H insertion.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.05.016.

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