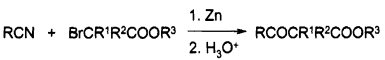
APPENDIX

APPLICATION OF BLAISE REACTION FOR THE SYNTHESIS OF β-KETO ESTERS: A FACILE SYNTHESIS OF THE PRECURSOR FOR NAZAROV REAGENT

1 Introduction

Development in the methodologies for the construction of the C-C bonds in the synthesis of complex non-natural and natural products have taken place in an incremental manner through pioneering studies made by eminent organic chemists for more than the past 150 years. Such reactions discovered, described and explored –in are generally named after their discoverers, e.g., Grignard reaction, Wittig reaction, Diels-Alder reaction, Friedel-Crafts acylation, etc.[1] On such named reaction is the Blaise reaction discovered by Blaise in 1902.[2] In this reaction, a nitrile **1** is reacted with the zinc enolate of ethyl bromoacetate (or 2-alkyl-2-bromoacetates) **2** to yield the corresponding β-keto ester **3** (Scheme 1).



Scheme 1

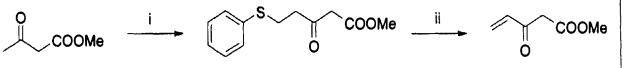
The Blaise reaction closely resembles the Reformatsky reaction in which the zinc enolate of an α-halo ester is reacted with a carbonyl compound to give the corresponding β-keto esters.[3] Unlike the relatively more well-known Reformatsky reaction, the Blaise reaction has found little application in organic synthesis, due to problems of low yield and competing side reactions. Recent developments in organometallic chemistry, however, have rekindled interest in developing this reaction as a formidable tool for synthetic organic chemists, particularly because the starting materials like 2-bromoacetates and nitriles are easy to prepare are commercially available and the β-keto ester functional group in the product is highly versatile for

further transformation.[4] Moreover, the Blaise reaction can be truncated to produce β-amino-α,β-unsaturated esters, which are useful for the synthesis of heterocycles and β-amino acids. Overall, the Blaise conversion of nitriles into the corresponding β-keto esters or β-amino acrylates constitutes a two-carbon homologation. The Blaise reaction is a classical reaction, introduced over a century ago, for the synthesis of β-keto esters from nitriles by employing ethyl bromoacetate **2** and zinc.[2] To improve efficacy of the reaction, activation of zinc was necessary and it could be achieved by 3*N* HCl,[5] ultrasound[6] or methanesulfonic acid[7] The Blaise reaction found use in the total synthesis of natural products,[8] industrial chemicals,[9] and some monosaccharide β-amino acid hybrids.[10]. Recently we have published review of literature on the Blaise reaction and its application for the construction of complex molecules of biological interest.[11]

In the present work we have developed a facile, efficient and high yielding two-step synthesis of 3-oxo-5-arylthiopentanoates - the precursors for the Nazarov reagent - from low-cost bench top chemicals like thiophenols **7**, acrylonitrile, zinc and ethyl bromoacetate **2** *via* the Blaise reaction.[12]

The β-keto esters of the type, methyl 3-oxo-4-pentenoate **4** (Nazarov reagents) are widely used in the Robinson annelation reactions, particularly in the total synthesis of natural products.[13] The initial preparations of **4** had elimination of ethanol or HCl incorporated into the last step.[14] However, under the reaction conditions employed for elimination reaction, **4** was polymerizing rapidly and therefore it was very difficult to get reproducible results.[15] To overcome the capricious nature of **4**, a repository of alternative methods based on, i. retro-Diels-Alder reaction to generate unsaturation in the last step,[16] ii. base induced condensation of acrolein and ethyl acetate followed by Jones oxidation,[17] iii. the treatment of acrolein with ethyl lithiodiazoacetate followed by rhodium(II) acetate mediated rearrangement of carbene intermediates,[18] iv. Wittig-Horner-Emmons-olefination of γ-phosporylated ethyl acetoacetate with aldehydes or ketones,[19] have been introduced for its preparation. However, each one of these methods require stringent conditions or not amenable for large-scale synthesis at low-cost.

Scheme 2



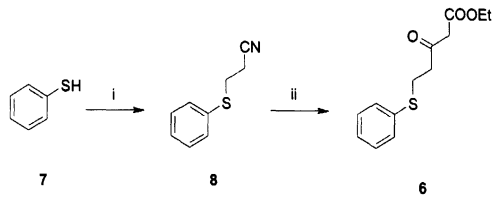
5 6 4

Reagents and conditions: i) a) BuLi, THF; b) $PhSCH_2I$, 63%; ii) a) $NaIO_4$, MeOH, H_2O; b) $CHCl_3$, reflux, 97%.

In 1974 Trost and Kunz reported a four-step preparation of **4** wherein last step involved dehydrosulfenylation (Scheme 2).[20]. The stable precursor to **4**, namely, methyl 3-oxo-5-arylthiopentanoate **6** was prepared by alkylation of the dianion of methyl acetoacetate with (iodomethyl)phenylsulfide in 63% yield. Nevertheless, (iodomethyl)phenylsulfide had to be prepared from thioanisole in two steps in 89% yield. Trost and Kunz also reported an alternative synthesis of **6** from β-propiodiacetone and thiophenol in four steps in 62–76% overall yield by following a related procedure developed by Heathcock and coworkers.[8] The sodium metaperiodate mediated oxidation of **6** to sulfoxide followed by phenylsulfenic acid elimination in refluxing chloroform provided Nazarov reagent in nearly quantitative yield. It is possible to employ the β-keto ester **6**, a stable equivalent of **4**, to realize the olefin functionally in later steps. As an example, Trost and Jiang used **3** in their synthesis of densely substituted cyclopentyl core of anti-tumor antibiotic viridenomycin.[21] . Moreover, the arylthio group in **6** can be reductively removed at a later stage with Raney Ni to reveal ethyl substitution.[22] Now, we wish to report a facile and high yielding synthesis of **6**, namely, ethyl 3-oxo-5-arylthiopentanoates using low-cost bench-top chemicals *via* the Blaise reaction.

2. Results and Discussion

Scheme 3



7 **8** **6**

Reagents and conditions: i) CH_2=CHCN, Et_3N, $CHCl_3$, rt, 2 h, 97-98%; ii) Zn, TMSCl (3 mol%), $BrCH_2COOEt$, THF, reflux, 4 h, 96-98%.

When the Blaise transformation of 3-phenylthiopropionitrile **8**[23] - prepared from thiophenol **7** and acrylonitrile - into ethyl 3-oxo-5-phenylthiopentanoate **6** was tried with ethyl bromoacetate (2 equiv) and pre-activated zinc (2 equiv) - prepared by washing with 3 *N* HCl according to Kishi's procedure,[17] the reaction proceeded to give the β-keto ester **6** in only 20% yield (Scheme 3; Table 1, entry 1). There was improvement in the yield of the β-keto ester **6** (48-53%, entry 2 and 4) when pre-activation of zinc was carried out with 1 mol% of strong organic acids like trifluoroacetic acid or methanesulfonic acid.[19] The yield of the desired product **6** improved to 68–72% when 3 mol% of strong Brønsted acids like trifluoroacetic acid or methanesulfonic acid were employed for zinc activation (entry 3 and 5). However, these acids, however, were also responsible for concomitant elimination of thiophenol along with the formation of β-keto ester **6,** thus, lowering its yield. The yield of **6** was 67% when 1 mol% of trimethylsilyl chloride (TMSCl) was employed for zinc activation.[24] We were delighted to find that the yield of **6** was nearly quantitative when 3 mol% of TMSCl was employed. Next, we tried the transformation with 1 equiv zinc and 2 equiv of ethyl bromoacetate, the reaction proceed to provide the β-keto ester **6** in 91% yield, but at half of run with 2 equiv of zinc and 2 equiv of ethyl bromoacetate. With 1 equiv of zinc and 1 equiv of zinc and I equiv of ethyl bromoacetate, only 60% conversion to β-keto ester was take place even after 12 h of the reaction. Based on these experiments,

we concluded that the transformation works well, with 2 equiv of zinc, 2 equiv of ethyl bromoacetate and 3 mol% of TMSCl in THF reflux.

Table 1. Effect of Zn activator in the yield of **6**

Entry	Acid	Amount (mol%)	Time (h)	Yield[a] (%)
1	3 *N* HCl	--	24	20
2	CF_3COOH	1	8	48
3	CF_3COOH	3	4	72
4	CH_3SO_3H	1	9	53
5	CH_3SO_3H	3	4	68
6	TMSCl	1	7	67
7	TMSCl	3	4	98

[a] Isolated yield after column chromatography

In conclusion, we have described a convenient, efficient and facile procedure for the synthesis of ethyl 3-oxo-5-arylthiopentanoates **6**, the precursors for Nazarov reagent, using bench-top low-cost chemicals.

3. Experimental Section

Synthesis of ethyl 3-oxo-5-phenylthiopentanoate 6:

To the stirred suspension of zinc 4.0 g (zinc dust, <10 micron, 61.3 mmol) in THF (25 mL) TMSCl (100 mg, 3 mol%) was added at r.t. The mixture was refluxed for 15 min and the nitrile **8** (5 g, 30.6 mmol), ethyl bromoacetate **2**10.25 g (61.3 mmol) was added drop wise simultaneously over 30 min. with pressure equalizer at this temperature. The reaction was continued the refluxing for 4 h while monitoring it by GC-MS. After completion of the reaction, the mixture was cooled to 0-5 °C and aq 3 *N* HCl (20 mL) was added drop wise. After all the organic volatiles were removed in vacuo, the remaining mixture was extracted with diethyl ether (2 × 15 mL). The separated organic layer was washed with cold water (50 mL), brine (15 mL), dried (anhyd. Na_2SO_4) and concentrated. The residue on silica gel (100-200 mesh) column chromatographic purification with increasing amounts of EtOAc in hexanes afforded

ethyl 3-oxo-5-phenylthiopentanoate **6** (7.6g, 98%). The ^{1}H NMR spectrum of **6** indicated that it is present in keto and enol tautomers in the ratio of 89:11. The NMR spectral data given below is that of the keto-isomer, culled from the spectra of the mixture of keto-enol tautomers. R_f (90:10 hexane/ethyl acetate) = 0.52; IR v max (Neat) 3459, 3332, 2981, 2933, 1741, 1716, 1562, 1481, 1164, 1025, 740 cm $^{-1}$; 1H NMR (400MHz, $CDCl_3$) 12.09 (s), 7.13-7.34 (m, 5H), 4.15 (q, J = 6.9 Hz, 2H), 3.35 (s, 2H), 3.1 (t, J = 6.9 Hz, 2H), 2.83 (t, J = 6.9 Hz, 2H), 1.25 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 200.1, 166.5, 129.5, 128.9, 126.2, 96.1, 61.1, 49.1, 42.4, 27.1, 14.1 ppm.

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