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Synthesis of ethyl arylacetates by means of Friedel–Crafts reactions of aromatic compounds with ethyl α-chloro-α-(ethylthio)acetate catalysed by ytterbium triflate

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Abstract

An efficient Friedel–Crafts alkylation of aromatic compounds with ethyl α-chloro-α-(ethylthio)acetate catalysed by ytterbium triflate, followed by desulfurisation of the product provides a convenient methodology for the synthesis of ethyl arylacetates of aromatic and heteroaromatic compounds.

Keywords: catalysis; Friedel–Crafts reaction; lanthanides; substitution.

The Friedel–Crafts reaction is generally achieved using a Lewis acid as the catalyst. A common problem, particularly in industrial processes, is that the Friedel–Crafts reaction requires stoichiometric amounts of the Lewis acid which cannot be reused because of its instability in the usual aqueous work up.

Lanthanide trifluoromethanesulfonates[1] [lanthanide triflates; $Ln(OTf)_3$] work efficiently as versatile Lewis acids and have been employed in a number of reactions both in organic and aqueous media in catalytic quantities. Since the first utilisation of $Yb(OTf)_3$ by Forsberg et al.,[2] it has found wide utility in organic synthesis and recently Kobayashi et al.[1a] have used $Yb(OTf)_3$ as the catalyst in Friedel–Crafts acylation reactions. It was demonstrated in these reactions that the catalysts were easily recovered after the reactions were completed and could be reused.

As one of many synthetic applications of α-chlorosulfides, Tamura[3] has accomplished the preparation of arylacetates by the Friedel–Crafts reaction of ethyl α-chloro-α-(methylthio)acetate in the presence of stoichiometric quantities of a Lewis acid such as $SnCl_4$ or $TiCl_4$. Subsequently, this methodology has been extended by Arai[4] for the synthesis of naproxen.

Herein, we describe an excellent preparative method for the synthesis of ethyl aryl-acetates by Friedel–Crafts reactions of aromatic compounds with ethyl α-chloro-α-(ethylthio)acetate **1** using

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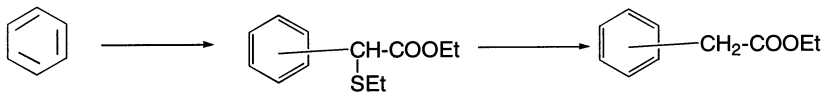
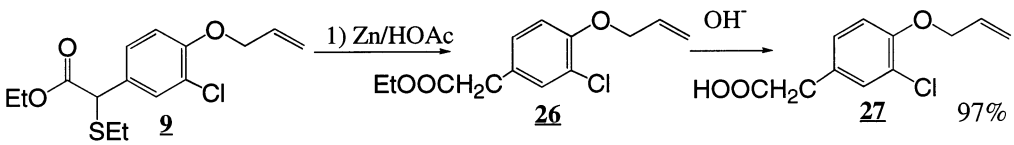
$Yb(OTf)_3$ as the right catalyst, followed by desulfurisation of the resulting ethyl-α-(ethylthio)arylacetates (Eq. (1)). The results in this regard are presented in Table 1.



(1)

Initially, the reaction of anisole **2** with ethyl α-chloro-α-(ethylthio)acetate **1** (1.1 equiv.) in the presence of $Yb(OTf)_3$ (5 mol%) was carried out in CH_3NO_2 at room temperature to give the product **3** in 92% yield (*para*:*ortho* 2.5:1). In the case of phenol **4**, the reaction also proceeded smoothly at room temperature and afforded the product **5** in excellent yield. This method has also been applied to aryl alkyl ethers such as **6** and **8** and the products **7** and **9**, respectively, were isolated in excellent yields. It is worth mentioning that the allyl group in **9** survived the reaction conditions. Compound **9** after desulfurisation and saponification afforded the anti-inflammatory agent, alclofenac **27**[3] in 97% yield.



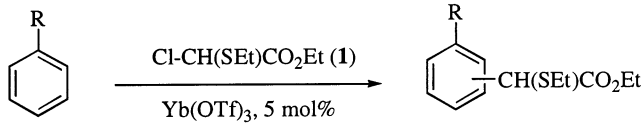
This reaction has been extended to substituted benzenes such as toluene **10** and xylene **12** (50°, 12–14 h) and the corresponding products **11** and **13** were obtained in almost quantitative yields. Next, we examined the reaction of naphthalene, **14** with **1** and isolated the α-substituted product **15** in 85% yield. In the case of substituted naphthalenes such as **16** and **18**, the corresponding products **17** and **19**, respectively, were obtained in moderate yields as a mixture of 1 and 6-substituted products. The reactivity of substrate **22** containing the acetamido group was much slower under the reaction conditions and gave the product **23** with poor conversion. The reaction of methyl 3,5-dimethoxybenzoate **20** with **1** was very sluggish at room temperature but at 50°C the *ortho* product **21** was obtained in good yield, the methyl ester surviving the reaction conditions.

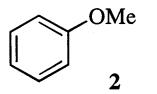
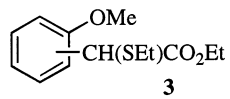
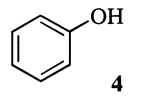
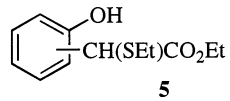
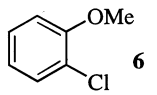
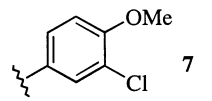
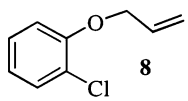
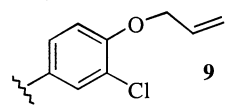
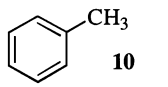
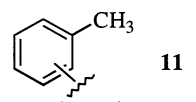
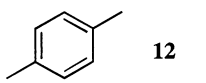
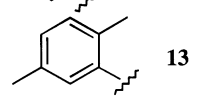
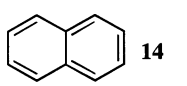
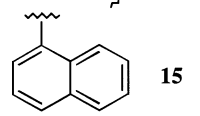
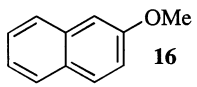
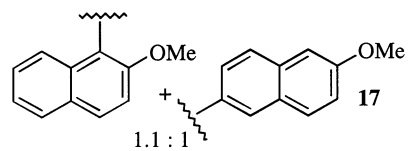
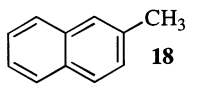
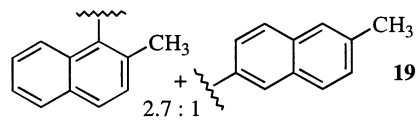
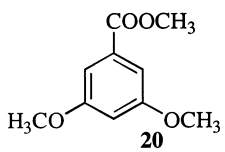
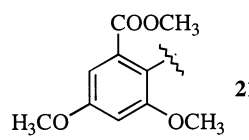
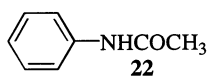
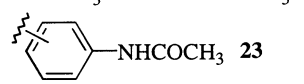
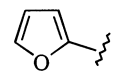
Heteroaromatic compounds such as furan, **14**, which is sensitive to acidic conditions, were also found to react with **1** affording the *ortho* substituted furan **25** in excellent yield, whereas both mono and disubstituted products were obtained when this reaction was carried out in the presence of $ZnCl_2$.[3] The direct insertion of ethyl acetate was not possible using α-bromo ethyl acetate in the presence of $Yb(OTf)_3$.

In conclusion, $Yb(OTf)_3$ is an excellent catalyst for the insertion of ethyl acetate to aromatic and heteroaromatic nuclei under mild conditions. Generally, a variety of functional groups are tolerated and this method has distinct advantages over the classical Friedel–Crafts alkylation reaction. Thus, we believe this method will find useful application in organic synthesis.

Typical experimental procedure: A mixture of $Yb(OTf)_3$ (28 mg, 0.046 mmol), *ortho* allyloxychlorobenzene **8** (155 mg, 0.92 mmol) and ethyl α-chloro-α-(ethylthio)acetate (184 mg, 1 mmol) in distilled nitromethane (1 mL) was stirred at room temperature for 5 h and the reaction mixture was filtered through a pad of Celite and directly loaded for chromatographic separation onto silica gel. The product was eluted with 2% EtOAc in petroleum ether (60–80°C) to give **9**[3] as a colourless oil (246 mg, 85%). ^1H NMR ($CDCl_3$) δ: 1.22 (two triplets, $J=7.2$ Hz, 6H); 2.50 (q, $J=7.4$ Hz, 2H); 4.20 (q, $J=7.0$ Hz, 2H); 4.48 (s, 1H); 4.60 (dt, $J_1=5.1$, $J_2=1.5$ Hz, 2H); 5.30

Table 1



Entry	Substrate	time (h)	Product	Ratio[a] para : ortho	Yield[c] (%)
1.	 **2**	1	 **3**	2.5 : 1	92
2.	 **4**	6	 **5**	2.5 : 1	82
3.	 **6**	5	 **7**	---	80
4.	 **8**	5	 **9**	---	85
5.	 **10**	12[b]	 **11**	6 : 1	90
6.	 **12**	14[b]	 **13**	----	quantitative
7.	 **14**	15[b]	 **15**	---	85
8.	 **16**	7	 1.1 : 1	---	42
9.	 **18**	10	 2.7 : 1	---	50
10.	 **20**	4	 **21**	----	58 (82)[d]
11.	 **22**	16[b]	 **23**	1 : 1	29 (100)[d]
12.	 **24**	6	 **25**	----	81

a) Ratio was calculated on the basis of ^{1}H NMR; b) Reaction was done at 50^{0}C; c) Isolated yields;
d) Yield based on recovered starting material

(dd, $J_1 = 11$, $J_2 = 1.5$ Hz, 1H); 5.44 (dd, $J_1 = 17$, $J_2 = 1.5$ Hz, 1H); 6.05 (m, 1H); 6.85 (d, $J = 8.0$ Hz, 1H); 7.30 (dd, $J_1 = 8.7$, $J_2 = 2.1$ Hz, 1H); 7.49 (d, $J = 2.4$ Hz, 1H).

Acknowledgements

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