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A practical variation on the Leuckart reaction

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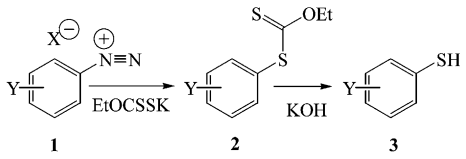
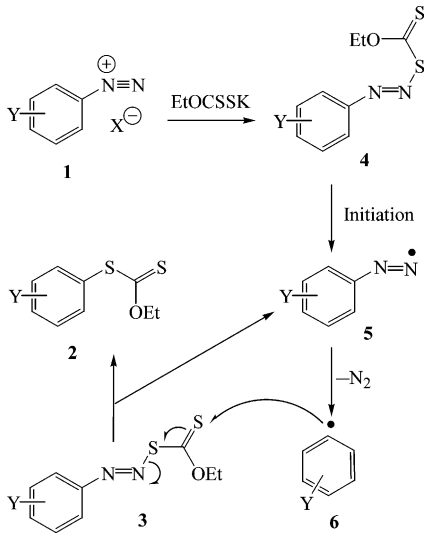
Abstract—*S*-Aryldiazo xanthates, derived from the corresponding diazonium salts by reaction with potassium *O*-ethyl xanthate, undergo a radical chain reaction with loss of nitrogen; the intermediate aromatic radical can be captured by an internal olefin to give bicyclic xanthates in good overall yield.

One of the oldest methods for the synthesis of thiophenols is the Leuckart reaction.[1] In this reaction, an aryl diazonium salt **1** is treated with potassium *O*-ethyl xanthate to give an aryl xanthate **2**, which is then cleaved with alkali into the thiophenol **3** (Scheme 1). This synthesis, however, comes with a serious warning of an explosion hazard[2] and this has presumably hindered mechanistic studies to understand the workings of the process and, perhaps even more, its application for the large scale preparation of thiophenols.

As part of a wider study on the reduction of aryldiazonium salts, Beckwith and co-workers[3] examined the case of thiolates and concluded that the thiodediazoniation proceeded via an $S_{RN}1$ type mechanism: electron transfer, followed by loss of nitrogen and formation of aromatic radicals. The latter could indeed be intercepted by an internal olefin. One example involved a xanthate salt as the thiolate component.[3a] In contrast to other thiolates, however, it is possible to propose an alternative mechanism, outlined in Scheme 2, which could be operating in the case of xanthates. The *S*-aryldiazo xanthate **4**, formed when the diazonium salt is combined with potassium *O*-ethyl xanthate, can in fact undergo a chain reaction similar to the one we have proposed for aliphatic xanthates and upon which much of our recent research has been based.[4] The chain process would be expected to be highly effective in view of the weakness of the N–S bond.



Scheme 1.



Scheme 2.

In the original Leuckart process, the ice-cold solution of the requisite aniline in aqueous mineral acid is diazotised by addition of sodium nitrite followed by addition of potassium *O*-ethyl xanthate.[1,2] The

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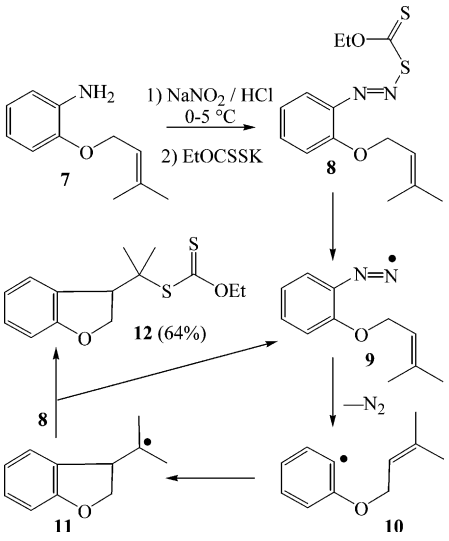


Scheme 3.

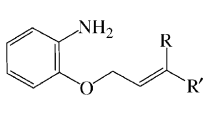
formation of the *S*-aryldiazo xanthate intermediate **4** must be rapid and, since it is usually not water soluble, it would in most cases separate from the solution. If a spontaneous initiation takes place, by adventitious radicals generated, for example, by the ambient lighting or by a slight decomposition of the diazonium salt, then an exceedingly efficient chain process sets in the essentially neat material causing an exothermic evolution of nitrogen, leading in some cases to an explosion. The danger of an explosion obviously increases with the scale at which the Leuckart reaction is performed.

In order to remedy this problem, and at the same time to exploit the synthetic potential of the intermediate aryl radical, we decided to modify the experimental procedure and perform the reaction in a two phase system. Thus, an inert organic solvent would be added *before* incorporating the xanthate salt. In this way, the *S*-aryldiazo xanthate never accumulates and the radical chain reaction takes place on the diluted substance, in the organic phase. It would, moreover, be easy to regulate its concentration by controlling the rate of addition of the xanthate salt.

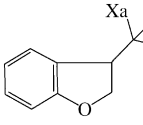
We tested the feasibility of this modification using *O*-prenylated 2-aminophenol **7** as the aniline partner. Once the diazotisation was complete, cyclohexane was added and the medium deoxygenated by bubbling nitrogen to avoid interference by triplet oxygen. The potassium *O*-ethyl xanthate was then incorporated in portions and with vigorous stirring. Thin layer chromatography examination of the organic phase indicated the presence of an intermediate, presumably the putative diazo xanthate **8**, which smoothly evolved into the expected dihydrobenzofuran **12**. The latter was isolated in overall 64% yield based on the starting aniline **7**.[6] The intermediate aryl radical **10** is captured by the internal olefin, but the chain is otherwise propagated in the expected manner, as depicted in Scheme 3.

This modification of the Leuckart reaction was applied to various substituted anilines. The results are compiled in the Table 1.[5] The yields, calculated from the free aniline, are generally synthetically quite acceptable. Five- or six-membered rings, containing an oxygen, nitrogen or a sulfur, can be constructed, and various substituents are tolerated on the aromatic ring. The internal olefinic trap can also be substituted. In this respect, the case of **24** is especially interesting since the terminal carbon has now the oxidation level of an aldehyde. For compounds **14**, **22**, **24**, **28** and **30**, we observed, not surprisingly, little stereoselectivity and an essentially 1:1 mixture of diastereoisomers was obtained. It is also wor-

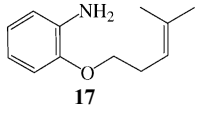
Table 1. Internal capture of aryl radicals (Xa = EtOCSS–)



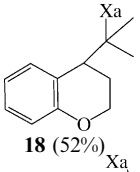
13, R = H, R′ = Me;
15, R = R′ = Me



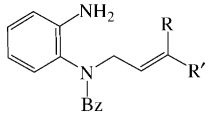
14, R = H, R′ = Me (49%);
16, R = R′ = Me (64%)



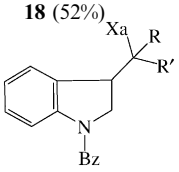
17



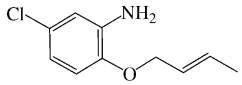
18 (52%)



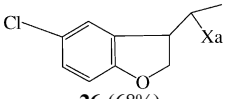
19, R =R′ = Me;
21, R = H, R′ = Me;
23, R = H, R′ = Cl



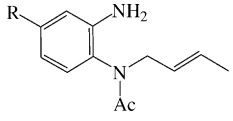
20, R =R′ = Me (55%);
22, R = H, R′ = Me (66%);
24, R = H, R′ = Cl (58%)



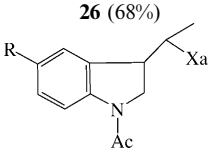
25



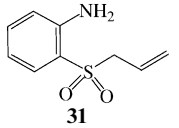
26 (68%)



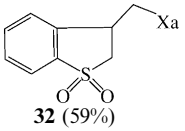
27, R =MeO;
29, R = CF_3



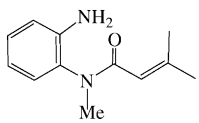
28, R =MeO (61%);
30, R = CF_3 (73%)



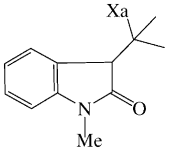
31



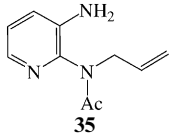
32 (59%)



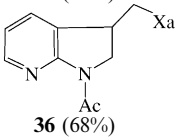
33



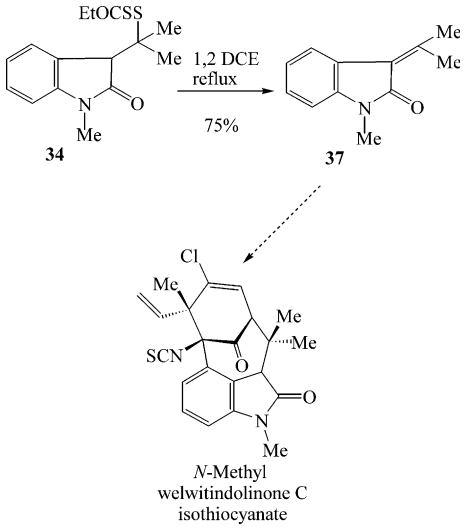
34 (68%)



35



36 (68%)



Scheme 4.

thy of note that the process is compatible with a pyridine ring and azaindolines such as **36** are readily accessible. Such derivatives are currently in great demand by medicinal chemists in view of their potential as kinase inhibitors.[7]

Experimentally, the process is extremely easy to perform. The reagents are cheap and readily available, and no heavy metals are involved. Little waste is generated and scale up should be straightforward since the issue of a chain reaction taking place in neat *S*-aryldiazo xanthate has been completely circumvented. Although cyclohexane was suitable for the examples described herein, other solvents (toluene, chlorobenzene, etc.) could also be used in principle.

Last but not least, the adducts are highly functionalised. The xanthate group can be converted into a number of other functionalities or serve as a convenient entry into the rich chemistry of sulfur. It can, of course, also act as a starting point for another radical sequence. Compound **34** embodies a portion of the structure of welwitindolinones,[8] which loses the xanthate group upon heating in 1,2-dichloroethane to give unsaturated oxindole **37** in 75% yield (Scheme 4). In this case, β-elimination is especially favoured due to the acidity of the hydrogen on C-3 of the oxindole structure.

Acknowledgements

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2. See, for example: Vogel, A. I. *Practical Organic Chemistry*, 3rd ed.; Longman: London, 1970; p 597; For a review on the radical chemistry of arenediazonium salts, see: Galli, C. *Chem. Rev.* **1988**, *88*, 765–792.
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5. Typical procedure: to a mixture of the corresponding aniline (*n* mmol) and ice (0.5*n* g) was added concentrated HCl (1.9*n* mmol) dropwise at 0 °C. The medium was deoxygenated by bubbling nitrogen. A deoxygenated solution of sodium nitrite (1.05*n* mmol) was added dropwise while strictly maintaining the reaction temperature at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. Once the diazotisation was complete, cold, deoxygenated cyclohexane (2*n* mL) was added to the aqueous solution. Xanthate salt (1.2*n* mL) was carefully added, in portions and with vigorous stirring. The reaction was stirred another 5 min and quenched with ice. The reaction was diluted with ether (20 mL), and washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography.
6. When this compound was prepared using the usual Leuckart reactions, the yield was only 40% instead of 64% under our modified conditions. We thank Dr. Gilles Ouvry for performing this reaction.
7. (a) Cheung, M.; Hunter, R. N., III; Peel, M. R.; Lackey, K. E. *Heterocyles* **2001**, *55*, 1583–1590, and references cited therein; (b) Ting, P. C.; Kaminski, J. J.; Sherlock, M. H.; Tom, W. C.; Lee, J. F.; Bryant, R. W.; Watnick, A. S.; McPhail, A. T. *J. Med. Chem.* **1990**, *33*, 2697–2706; (c) Kumar, V.; Dority, J. A.; Bacon, E. R.; Singh, B.; Lesher, G. Y. *J. Org. Chem.* **1992**, *25*, 6995–6998; For a recent approach to such structures involving radical addition to the pyridine ring, see: (d) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671–3674.
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