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McMurry intermolecular cross-coupling between an ester and a ketone: scope and limitations

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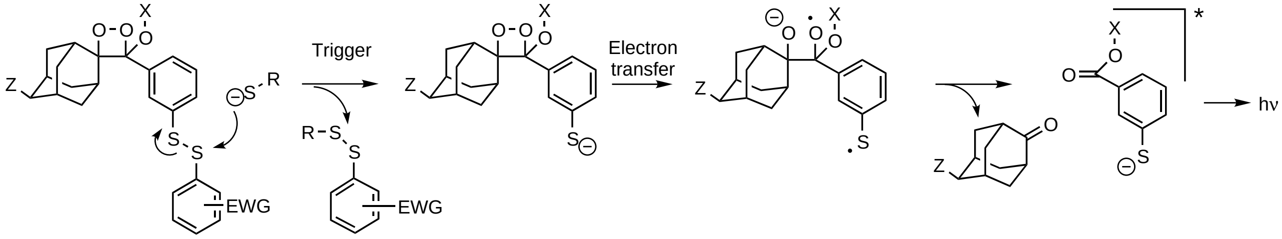
Abstract—In the course of our studies towards the synthesis of a dioxetane bearing chemiluminescent probe for the detection of thiols, we were faced with the synthesis of sterically hindered benzylic enol ethers. This issue was solved via the use of an intermolecular McMurry cross-coupling between an ester and a ketone. In this article, together with the synthesis of the chemiluminescent probe, the scope and limitations of this low valent titanium based carbon–carbon double bond formation are discussed. © 2002 Elsevier Science Ltd. All rights reserved.

In the course of our studies towards the synthesis of chemiluminescent probes for the detection of thiols, our efforts were led on 1,2-dioxetane disulfides (Scheme 1).[1,2] These probes were conceived by analogy with the chemiluminescent 1,2-dioxetane substrates used for the detection of phosphatase activities.[3–5] The strategy we chose is depicted on Scheme 1. Nucleophilic addition of a thiolate on an unsymmetrical disulfide compound should cleave the sulfur–sulfur bond, yielding in the formation of an unstable thiophenolate. Cleavage of the 1,2-dioxetane ring, through chemically induced electron exchange luminescence (CIEEL), should then lead to an excited *m*-mercapto benzoate anion, whose decay to the ground state should provide light, as for the corresponding *m*-oxobenzoate anion. In order to synthesize first generation chemiluminescent probes **1** and **2**, we were faced with the need to build a sterically hindered benzylic enol ether, as depicted on Scheme 2.

It is no longer necessary to demonstrate the remarkable efficiency of low-valent titanium compounds for carbon–carbon bond forming.[6] McMurry coupling reaction is for instance a very powerful tool to achieve reductive coupling of aldehydes or ketone to alkenes.[7] Yet, due to the particularly high reactivity of the titanium intermediate, its scope is drastically limited to the homo-dimerisation of ketones and aldehyde, or to intramolecular cross-coupling reactions. It must also be acknowledged that this reaction suffers from a serious lack of reproducibility, having a bad reputation as being tricky and highly 'co-workers and suppliers dependent'. Mixed coupling reactions usually lead to a statistical mixture of all possible alkene, thus reasonable yield of a single cross-coupling product requires the use of an excess of one of the two substrates. Few examples of preparatively useful results have been obtained if the substrates in question exhibit sufficiently different redox potentials.[8,9]



Scheme 1. Proposed mechanism for light emission wijth the designed chemiluminescent reagents for the chemiluminescent probes.

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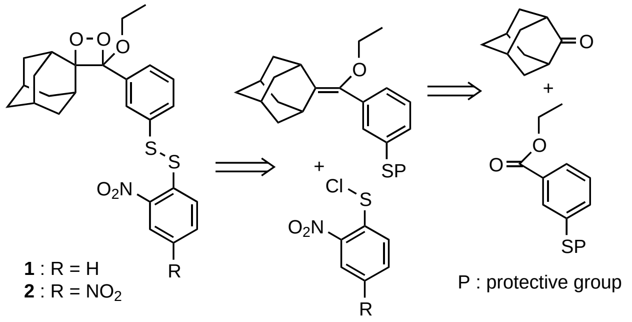
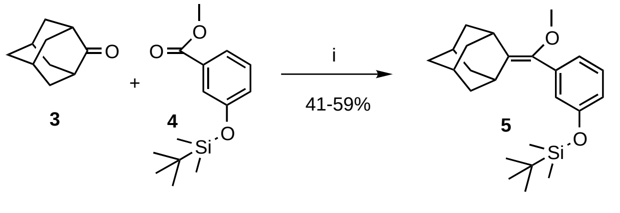


Scheme 2. Structure and retrosynthetic scheme for chemiluminescent probes **1** and **2**.

Keto-esters cross-coupling cyclisations via intramolecular alkylidenation reactions on treatment with low-valent titanium have been scarcely described.[10,11] Highest yields have been obtained with titanium species formed from $TiCl_3/LiAlH_4$ in the presence of triethylamine. Yet, aqueous work-up of the reaction mixtures hydrolyzes the enol ethers initially formed, and leads to the respective cyclic ketones as the final products.[12] Apart from descriptions in patents,[2,13,14] intermolecular McMurry cross-coupling are described as inefficient, yielding mainly the homodimerized product bis(adamantylene). Hindered ketones such as adamantanone or ditert-butyl ketone are required. Low functional groups compatibility, and both availability and efficiency of the low valent titanium reagents are considered as a major issue.[15] In a few cases, this issue has been circumvented by replacing the McMurry condensation by a Wadsworth–Emmons reaction between α-alkoxyphosphonates and hindered ketones.[15] Yet, formation of the phosphonates required use of a strong Lewis acid ($TiCl_4$), followed by basic reaction conditions (LDA), dramatically lowering the functional groups compatibility of this alternative route. We thus decided to study the scope and the limitations of the intermolecular McMurry condensation between a benzylic ester and a hindered ketone.

In order to clear the low reproducibility and efficiency issues up, a first screening of the reaction conditions with 2-adamantanone **3** and benzoate **4** was undertaken (Scheme 3). For this purpose, the already described[6,10] low valent titanium source $TiCl_3/LiAlH_4$ in the presence of triethylamine was used.



Scheme 3. McMurry condensation of adamantanone **3** on 3-*tert*-butyldimethylsilyloxy methylbenzoate **4**. (i) $TiCl_3$ (10 equiv.), $LiAlH_4$ (5 equiv.), Et_3N (6 equiv.), THF, 70°C, 20 h.

The following experimental conclusions were drawn:

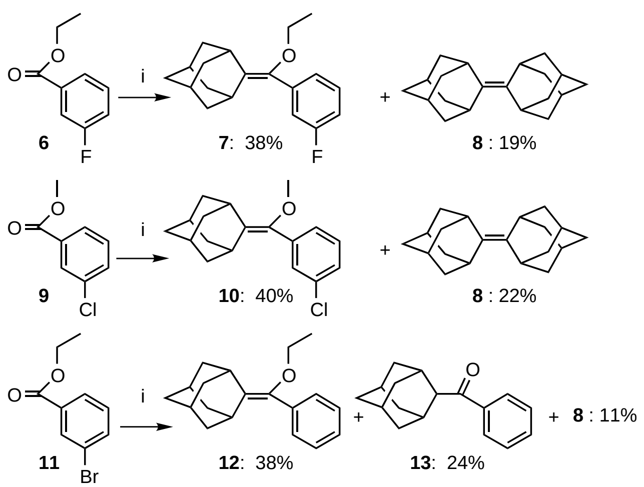
- Oxygen and moisture traces have to be cautiously precluded, thence the reaction was best performed in a glove box, under nitrogen.
- Reagents had to be freshly purchased and kept under nitrogen atmosphere. Noteworthy, lower yields were obtained with $TiCl_3$ in solution or from other commercial sources than Fluka. Use of 1 M solution of $LiAlH_4$ in diethyl ether also gave superior yields.
- The reaction had to be led in THF via a three steps procedure. First activation of $TiCl_3$ with a careful addition of hydride (0°C), followed by refluxing with the amine, and finally very slow addition (over a 3 h period of time) of a mixture of ketone and benzoate, still in refluxing THF.
- If both carbonyl compounds were added together and very slowly, use of a large excess of ketone was NOT necessary. Best yields were obtained with a simple 1.2 excess of 2-adamantanone **3** over benzoate **4**. On the other hand, a 10 times excess of $TiCl_3$; a 5 times excess of $LiAlH_4$ and a 6 times excess of triethylamine were required.
- Best treatment was obtained by partitioning the crude reaction mixture with same amount of diethyl ether and water, and extracting thrice the aqueous phase with diethyl ether. Crude reaction mixtures yielded enol ether **5** together with low amounts of bis(adamantylene), which were easily separated through silicagel chromatography. Enol ether proved moderately stable to such conditions. Addition of ca. 0.1% triethylamine in the mobile phase was required.

With those optimized reaction conditions in hand, the McMurry condensation was assayed by a wide range of co-workers, from undergraduate student to post-doctoral fellow. According to the experimental skill of the 'co-worker', purified yields in enol ether **5** varied between 41 and 59%, thus showing an acceptable reproducibility.

If deprotection of the silyl ether could be performed in high yields (nBu$_4$NF/THF), activation of the phenol group into trifluoromethyl sulfonate, mesylate or tosylate ended up in hydrolysis of the fragile enol ether moiety. With the goal in mind to introduce the required sulfur atom via substitution of aryl halides, and in order to widen the scope and study the limitations of the McMurry intermolecular cross coupling reaction, the condensation was then undertaken on 2-adamantanone and 3-halogenated benzoates (Scheme 4).

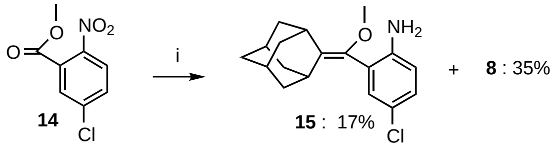
The reaction gave satisfactory yields on aryl fluoride **6** and aryl chloride **9**. Byproduct Bis(adamantylene) **8** was isolated in, respectively, 22 and 19% yield. On the contrary, aryl bromide **11** was totally reduced under the McMurry reaction conditions, yielding 38% enol ether **12** together with low amounts (24%) of hydrolyzed ketone **13**.

Our attempts to perform arylic substitution of the chlorine or fluorine atoms of enol ether **7** and **10** by a sulfur bearing nucleophile or by a more reactive halo-



Scheme 4. McMurry coupling of adamantanone on 3-halobenzoates. (i) $TiCl_3$ (10 equiv.), $LiAlH_4$ (5 equiv.), Et_3N (6 equiv.), **3** (1.2 equiv.), THF, 70°C, 20 h.

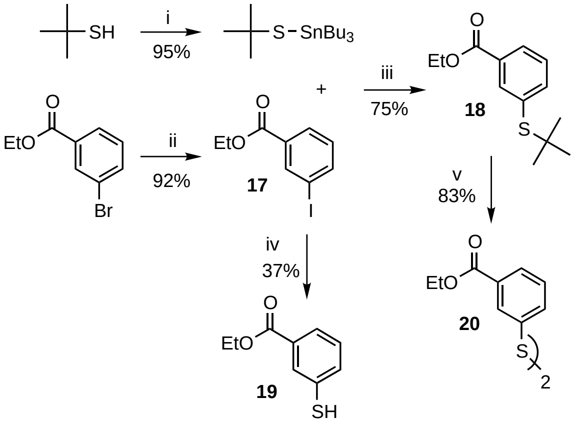
gen group were unsuccessful, or ended up in hydrolysis of the fragile enol ether function. Use of an activated aryl halide using a *p*-substituted nitro function could not be achieved, since during the McMurry condensation of 2-adamantanone on 2-nitro-5-chlorobenzoate **14**, the nitroaryl function was reduced in aniline, and enol ether **15** proved too unstable to be purified in reasonable yields (Scheme 5).



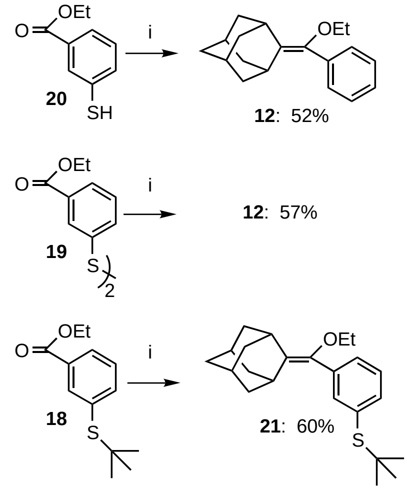
Scheme 5. McMurry condensation with 2-nitrobenzoate. (i) $TiCl_3$ (10 equiv.), $LiAlH_4$ (5 equiv.), Et_3N (6 equiv.), **3** (1.2 equiv.), THF, 70°C, 20 h.

Although a thiophenol would appear poorly stable under the harsh reaction conditions of the McMurry condensation, we decided to test the intermolecular McMurry cross coupling on arylic mercapto compounds **18**–**20** (Scheme 6).

These benzoates were synthesized using 3-iodo ethylbenzoate **17** as starting material. Compound **17** was obtained in high yields through an halogen exchange which could be performed using a combination of KI and CuI (3/1) at 155°C in HPMA.[16] Thiophenol **19** was synthesized in one step, although in moderate yield from **17**, using thiourea as the sulfur source, via a nickel based catalytic process described by Takagi.[17] S-*t*Bu protected thiophenol **18** was synthesized in high yields via a Stille-like coupling[18] of *tert* butylsulfanyl tributyltin **16** on iodide **17**. Disulfide **20** was synthesized from **18** using the Dickman procedure,[19] using DMSO as the oxidative specie.



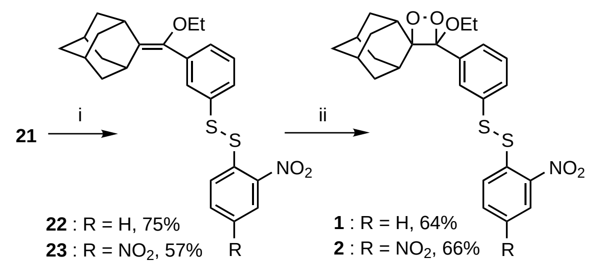
Scheme 6. Synthesis of 3-mercapto substituted ethyl benzoates. (i) Bu_3SnCl, Et_3N, CCl_4, 18 h; (ii) KI (15 equiv.), CuI (5 equiv.), HPMA, 155°C, 3 days; (iii) $Pd(PPh_3)_4$, toluene, 110°C, 48 h; (iv) thiourea, $NiBr_2$, $NaBH_3CN$, DMF; (v) HBr, AcOH, DMSO, 3 h.



Scheme 7. McMurry coupling of *m*-mercapto benzoates. (i) $TiCl_3$ (10 equiv.), $LiAlH_4$ (5 equiv.), Et_3N (6 equiv.), **3** (1.2 equiv.), THF, 70°C, 20 h.

McMurry coupling performed on **19** and **20** expectedly yielded reduced enol ether **12** (Scheme 7). On the other hand, the *tert*-butyl protective group on **18** allowed isolation of enol ether **21** in 60% yield.

Chemiluminescent probes **1** and **2** were then obtained in acceptable yields from **21** in a two-step procedure (Scheme 8). The first step was a mild and controlled addition of activated sulfenyl chlorides on the protected sulfur atom. Contrary to the described reaction procedure,[19] use of an external source of acid (HBr/AcOH) proved not necessary. Enol ether function remains particularly fragile, and once partially hydrolyzed, purification from corresponding ketone could not be achieved using conventional chromatographic techniques. In order to obtain acceptable yields in unsymmetrically substituted disulfides **22** and **23**, we found that the reaction had to be carefully monitored, and stopped once ca. one third of the starting material was consumed. Recovered starting material could be recycled



Scheme 8. Final steps for the synthesis of chemiluminescent probes **1**and **2**. (i) R = H, 2-nitrophenyl sulfuryl chloride, THF, 2 h; R = NO_2: 2,4-dinitrophenyl sulfuryl chloride, THF, 2 h; (ii) $(PhO)_3P$, O_3, −78 to 20°C, CH_2Cl_2. Yields are given once starting material was recycled (see text).

ending up in a global 75% yield in **22** and 57% yield in **23** after three reaction batches.

The final step of the synthesis of 1,2-dioxetanes **1** and **2** was the careful [2+2] cycloaddition of singlet oxygen $^1O_2$ on enol ether. In view of the great sensitivity of the disulfide bond to highly oxidative oxygenated species, oxygen bubbling under UV light irradiation seemed unacceptable. In order to monitor precisely the amount of $^1O_2$ delivered, we decided to use triphenylphosphite ozonide, which slowly delivers $^1O_2$ upon heating from −78°C to room temperature.[20,21] Using this singlet oxygen source, fragile 1,2-dioxetane chemiluminescent probes **1** and **2** were synthesized in 25 and 22% yield, respectively, after careful silica gel chromatography. No trace of by-products displaying oxidation at any of the two sulfur atoms was detected. Recovered starting material could be recycled. Practical yields in **1** and **2** could then be estimated at 64 and 66%, respectively.

In conclusion, for the synthesis of chemiluminescent probes **1** and **2**, we experimented the scope and limitations of an unprecedented intermolecular cross-coupling McMurry condensation of hindered ketones on 3-substituted benzoates. The reaction conditions were assayed in order to ensure a good reproducibility. Acceptable yields were obtained with arylfluorides, chlorides, protected phenols and thiophenols. Other attempts ended up in the reduction of the aromatic substituting function. Luminescence properties of **1** and **2** will be reported in due time.[1]

Acknowledgements

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References

1. Sabelle, S.; Renard, P. Y.; Pecorella, K.; de Suzoni-Dézard, S.; Créminon, C.; Grassi, J.; Mioskowski, C. *J. Am. Chem. Soc.*, in press.
2. Grassi, J.; Sabelle, S.; Renard, P. Y. Fr. Patent, WO 0044719, 2000; *Chem. Abstr.* **2000**, *133*, 150547
3. Bronstein, I.; Edwards, B.; Voyta, J. C. *J. Biolumin. Chemilumin.* **1988**, *2*, 186.
4. Bronstein, I.; Voyta, J. C.; Thorpe, G. H. G.; Kricka, L. J.; Amstrong, G. *Clin. Chem.* **1989**, *35*, 1146–1441.
5. Edwards, B.; Sparks, A.; Voyta, J. C.; Strong, R.; Murphy, O.; Bronstein, I. *J. Org. Chem.* **1990**, *55*, 6225–6229.
6. Fürstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2442–2469.
7. McMurry, J. E. *Chem. Rev.* **1989**, 1513–1524.
8. McMurry, J. E.; Krepski, L. R. *J. Org. Chem.* **1976**, *41*, 3929.
9. Paquette, L. A.; Yan, T.-H.; Wells, G. J. *J. Org. Chem.* **1984**, *49*, 3610.
10. Schaap, P.; Handley, R. S.; Giri, B. P. *Tetrahedron Lett.* **1987**, *28*, 935–938.
11. Fürstner, A.; Huppert, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468.
12. McMurry, J. E.; Miller, D. D. *J. Am. Chem. Soc.* **1983**, *105*, 1660.
13. Arghavani, Z.; Akhaven-Tafti, H.; Desilva, R.; Thakur, K. US Patent US 6036892, 2000; *Chem. Abstr.* **2000**, *132*, 207841.
14. Schaap, A. P.; Akhavan-Tafti, H. US Patent WO9007511, 1990; *Chem. Abstr.* **1991**, *114*, 181726.
15. Roeschlaub, C. A.; Sammes, P. G. *Perkin Trans. 1* **2000**, 2243–2248.
16. Suzuki, H.; Kondo, A.; Ogawa, T. *Chem. Lett.* **1985**, 411–412.
17. Takagi, K. *Chem. Lett.* **1985**, 1307–1308.
18. Terada, M.; Migita, T.; Sano, H.; Ogata, T.; Kosagi, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3657.
19. Dickman, D. A.; Chemburkar, S.; Konopacki, D. B.; Elisseou, E. M. *Synthesis* **1993**, 573–574.
20. Murray, R. W.; Kaplan, M. L. *J. Am. Chem. Soc.* **1969**, *91*, 5358–5364.
21. Stephenson, L. M.; Zielinski, M. B. *J. Am. Chem. Soc.* **1982**, *104*, 5819–5820.