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New odourless protocols for efficient Pauson–Khand annulations

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An inexpensive and commercially available odourless additive, dodecyl methyl sulfide, has been shown to be a highly effective promoter in the Pauson–Khand cyclisation of both intra- and intermolecular substrates, affording good to excellent yields of cyclopentenone products.

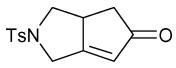
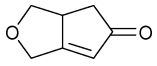
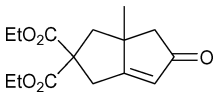
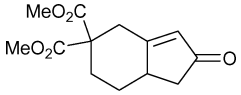
The transition metal-mediated [2+2+1] cycloaddition involving an alkyne, an alkene, and carbon monoxide represents one of the most effective and widely utilised methods of generating highly substituted cyclopentenones in a single step.[1] The stoichiometric cobalt-mediated process, the Pauson–Khand (P–K) reaction, was first reported in 1971 and was conducted under relatively harsh thermal conditions.[2] Given that the originally utilised procedures generally only produced low yields, it is perhaps unsurprising that considerable effort has been exerted on the development of milder and higher yielding protocols for the P–K annulation.

In this regard, although the use of dry state absorption,[3] ultrasound,[4] and phosphine oxides[4a] have, in certain cases, led to yield and rate enhancements, their applicability is somewhat limited. Unquestionably the most significant advance in promotion techniques has arisen from the use of tertiary amine *N*-oxides as promoters,[5] allowing reactions to be carried out with elevated levels of efficiency at room temperature or below. The use of amines as additives has also been reported by Sugihara and co-workers,[6] however, more recently the same workers have shown that alkyl methyl sulfides can be employed as effective promoters of the P–K cyclisation.[7] In particular, *n*-butyl methyl sulfide (*n*-BuSMe) in 1,2-dichloroethane was found to be the optimum additive over the examples presented. This sulfide additive technique is particularly noteworthy for its ability to promote several P–K reactions which fail completely or perform poorly under alternative conditions. Having stated this, although highly effective, the main drawback of this technique is the volatility, extremely unpleasant odour, and lachrymatory effect of the low molecular weight sulfide employed. Moreover, *n*-butyl methyl sulfide is both expensive and unrecoverable from the reaction mixture, and thus cannot be potentially recycled. To circumvent these issues somewhat, in 2000 we reported on the use of a high loading polymer-supported sulfide analogue, which was both odourless and recyclable over a minimum of 5 cycles.[8] Although this proved to be a highly efficient additive and paralleled the promotion efficacy of *n*-BuSMe, we were keen to develop a more economical and practically acceptable solution-phase sulfide promoter strategy, where the additive would possess little detectable obnoxious odour. In this respect, we noted that Node and co-workers had recently reported the use of *n*-dodecyl methyl sulfide (DodSMe) and dodecyl methyl sulfoxide as completely odourless alternatives for Corey–Kim and Swern oxidations, respectively.[9] Given the low volatility and negligible odour of DodSMe, coupled with its commercial availability and low cost,† we felt that this agent could be exploited as a more readily applicable promoter of P–K reactions. We now report the results from our preliminary studies in this area.

To initiate these studies, DodSMe (97%, Avocado†) was firstly dried and purified *via* Kugelrohr distillation prior to employment within any P–K processes. Initially, we decided to investigate the optimum number of equivalents of DodSMe required, using the *N*-tosyl 1,6-enyne substrate (Entry 1, Table 1). Pleasingly, from the outset of this study it appeared that DodSMe had the desired beneficial promotion effect in the intramolecular P–K reaction. Furthermore, from these preliminary reactions we identified that 3.5 equivalents of the sulfide was optimum, with a good 66% yield of the product being obtained in this initial example.‡

Following the establishment of this procedure, we examined several alternative intramolecular P–K annulations and the results from this study are shown in Table 1. Entries 2 and 3 clearly exemplify that DodSMe is a highly effective promoter of the intramolecular cyclisation of 1,6-enyne substrates to produce [5,5]-fused bicyclic cyclopentenones. Furthermore, the 1,7-enyne example (Entry 4) also demonstrates the efficacy of this technique with the preparation of the less accessible [6,5]-fused bicyclic system in good yield.

Table 1 Dodecyl methyl sulfide (DodSMe) promoted intramolecular Pauson–Khand (P–K) annulations

Entry[a]	Product	Yield (%)[b]
1		66
2		81
3		71
4		75

[a] All reactions carried out in 1,2-DCE (0.1 M) at 83 °C for 30 minutes. [b] Isolated yields following purification.

It should be noted that for each of the examples shown we also employed the more volatile *n*-BuSMe. In every case, the yields obtained utilising our odourless and less costly DodSMe protocol were at least comparable with those from use of the considerably less practically convenient sulfide.

To further test this protocol, the stench-free conditions were applied to a more elaborate system. In this regard, the key P–K cyclisation of a total synthesis programme currently on-going within our laboratory, aimed towards the preparation of 2-*epi*-α-cedren-3-one, employs the enyne substrate shown in Scheme 1. Pleasingly, the reaction proceeded to stereospecifically construct the tricyclic system shown in an excellent 92% yield. Moreover, when *n*-BuSMe was employed with the same substrate, a lower yield of 83% was obtained.

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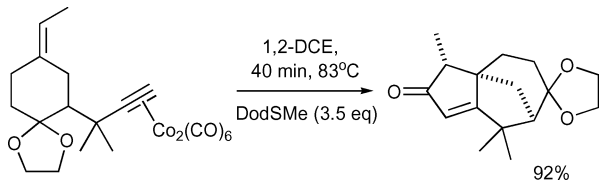
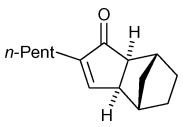
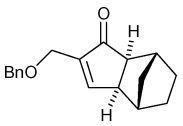
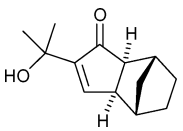
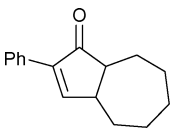
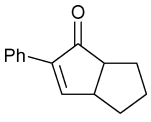
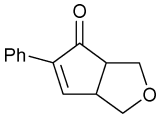


Scheme 1 DodSMe promoted construction of the core [5.3.1.0] undecane skeleton of 2-*epi*-α-cedren-3-one.

Following successful application with a panel of intramolecular substrates, we next examined a range of, normally more demanding, intermolecular reactions. Gratifyingly, as the results in Table 2 display, the newly developed DodSMe stench-free promotion conditions operated equally well for the intermolecular processes tested. Utilising the reactive olefin, norbornene, with various alkyne cobalt complexes led to the requisite cyclopentenone products in high yield (Entries 1, 2, and 3).

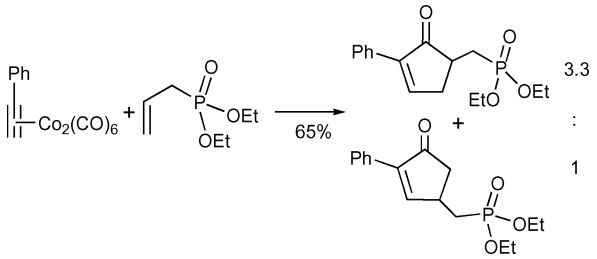
More notably, this technique also produces good yields of cyclopentenone products when unstrained and, thus, generally less reactive alkenes are employed. In this regard, when cycloheptene was employed (Entry 4), the DodSMe promoter system gave a yield of 66% with this unreactive alkene.§ As Entries 5 and 6 illustrate, good yields were also obtained with cyclopentene and 2,5-dihydrofuran. These results are particularly pleasing as these olefinic substrates have previously required dual ultrasound–amine *N*-oxide promotion techniques to deliver similar levels of cyclisation efficiency.[4b]

Table 2 DodSMe promoted intermolecular P–K annulations

Entry	Time	Product	Yield (%)[c]
1	120 min[a]		89
2	30 min[a]		86
3	40 min[a]		86
4	90 min[a]		66[d]
5	5 days[b]		62[e]
6	5 days[b]		55[e]

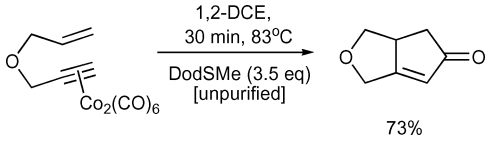
[a] Reactions carried out in 1,2-DCE (0.1 M) at 83 °C. [b] Reactions carried out in 1,2-DCE (0.1 M) at 35 °C. [c] Isolated yields following purification. [d] Four equivalents of DodSMe employed. [e] Five equivalents of DodSMe employed.

As an additional test of this methodology, we investigated the use of DodSMe in a regioselective P–K process, recently developed within our laboratories.[11] In the example shown in Scheme 2, the odour-free technique allowed the acyclic diethyl allyl phosphonate to react with the alkyne cobalt complex of phenylacetylene to give the cyclopentenone products in 65% yield and with a regioselectivity of 3.3 : 1.¶ The use of *n*-BuSMe led to a lower 54% yield and a similar level of regioselection.



Scheme 2 Odour-free sulfide promotion in a regioselective P–K reaction. *Reagents and conditions*: DodSMe (3.5 eq.), 1,2-DCE, 83 °C, 18 h.

To further enhance the overall practical utility of this methodology, we attempted to employ the DodSMe additive in unpurified form and as supplied. Taking the allyl propargyl ether as a suitable P–K example substrate (Scheme 3), undistilled sulfide was used in, otherwise, identical fashion to that described above. Subsequently, the anticipated cyclopentenone product was obtained in only a slightly reduced yield of 73% (*cf.* 81% when using the purified DodSMe). Therefore, this feature further adds to the practical accessibility of this protocol, especially when compared to the alternative sulfide promotion techniques.



Scheme 3 Use of unpurified DodSMe promoter.

In conclusion, conditions have now been developed that allow inexpensive, commercially available, and directly utilisable dodecyl methyl sulfide to be employed as an efficient promoter of both intra- and intermolecular Pauson–Khand cyclisations. Moreover, this technique is particularly notable as it avoids the obnoxious smell associated with the previously reported sulfide promoters, whilst mirroring and, in many cases, enhancing the excellent promotion efficiencies associated with this class of reagent.

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Notes and references

† DodSMe: £21.90 per 50 g, Avocado Research Chemicals, Heysham, Lancashire, LA3 2XY, UK; *n*-BuSMe: £72.00 per 5 mL, TCI Organic Chemicals, TCI Europe, B-2070 Zwijndrecht, Belgium.

‡ Representative experimental procedure: To a solution of hexacarbonyl-[μ-[4-methyl-*N*-[2-propen-1-yl]-*N*-[(2,3-η:2,3-η)-2-propyn-1-yl]benzenesulfonamide]]dicobalt-(Co–Co) (0.16 g, 0.3 mmol) in 1,2-DCE (3 ml, 0.1 M) under an atmosphere of N_2 was added DodSMe (0.227 g, 1.05 mmol). The reaction mixture was then heated to reflux (83 °C) for 30 minutes. After this time, the 1,2-DCE was removed under reduced pressure and the residue purified directly by silica chromatography using Et_2O as the eluant. The product, 2,3,3a,4-tetrahydro-(*p*-toluenesulfonyl)cyclopenta[*c*]pyrrol-5(1*H*)-one, was obtained as a colourless solid (55 mg, 66%), mp 143–145 °C. Analysis was consistent with that

described in the literature;[10] IR (CH_2Cl_2) 1716, 1663, 1653 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.74 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 5.99 (s, 1H), 4.34 (d, ^2J = 16.5 Hz, 1H), 4.01–4.06 (m, 2H), 3.15 (m, 1H), 2.57–2.66 (m, 2H), 2.45 (s, 3H), 2.06 (dd, ^2J = 17.9 Hz, J = 3.7 Hz, 1H) ppm. All other compounds exhibited satisfactory spectral and analytical data.

§ It should be noted that Sugihara has reported that cycloheptene cyclises with the dicobalthexacarbonyl complex of phenylacetylene under *n*-BuSMe promoted conditions to give the expected cyclopentenone product in an 85% yield.[7] However, in our hands, we found this to be a capricious process and, over 5 attempts, the maximum yield obtained for this cyclisation, with *n*-BuSMe as the additive, was only a moderate 49%. In every other instance where *n*-BuSMe had been previously employed, the yields obtained with this additive within our laboratory were in line with those obtained by Sugihara *et al.*

¶ The specific cyclopentenone regioisomers from the allyl phosphonate process were identified by ^{1}H NMR spectroscopy and, in particular, from the splitting patterns of the olefinic and adjacent protons.

1 (*a*) P. L. Pauson, *Tetrahedron*, 1985, **41**, 5855; (*b*) N. E. Schore, *Comprehensive Organic Synthesis*, B. M. Trost and I. Fleming, Eds., Pergamon Press, Oxford, 1991, vol. 5, p. 1037; (*c*) N. E. Schore, *Org. React.*, 1991, **40**, 1; (*d*) N. E. Schore, *Comprehensive Organometallic Chemistry II*, E. W. Abel, F. G. A. Stone and G. Wilkinson, Eds., Elsevier, New York, 1995, vol. 12, p. 703; (*e*) O. Geis and H.-G. Schmalz, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 911; (*f*) Y. K. Chung, *Coord. Chem. Rev.*, 1999, **188**, 297; (*g*) K. M. Brummond and J. L. Kent, *Tetrahedron*, 2000, **56**, 3263; (*h*) C. S. Chin, G. Won, D. Chong, M. Kim and H. Lee, *Acc. Chem. Res.*, 2002, **35**, 218.

2 (*a*) I. U. Khand, G. R. Knox, P. L. Pauson and W. E. Watts, *J. Chem. Soc., Chem. Commun.*, 1971, 36; (*b*) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts and M. I. Foreman, *J. Chem. Soc., Perkin Trans. 1*, 1973, 977.

3 (*a*) W. A. Smit, S. L. Kireev, O. M. Nefedov and V. A. Tarasov, *Tetrahedron Lett.*, 1989, **30**, 4021; (*b*) W. A. Smit, S. O. Simonyan, V. A. Tarasov, G. S. Mikaelin, I. I. Ibragimov, R. Caple, D. E. Froen and A. Kreager, *Synthesis*, 1989, 472; (*c*) W. A. Smit, A. S. Gybin, S. O. Simonyan, A. S. Shashkov, V. A. Tarasov and I. I. Ibragimov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1985, 2650; (*d*) S. O. Simonyan, W. A. Smit, A. S. Gybin, A. S. Shashkov, G. S. Mikaelin, I. I. Ibragimov, R. Caple and D. E. Froen, *Tetrahedron Lett.*, 1986, **27**, 1245; (*e*) W. A. Smit, A. S. Gybin, A. S. Shashkov, Y. T. Strychov, L. G. Kyz'mina, G. S. Mikaelin, R. Caple and E. D. Swanson, *Tetrahedron Lett.*, 1986, **27**, 1241.

4 (*a*) D. C. Billington, I. M. Helps, P. L. Pauson, W. Thomson and D. Willison, *J. Organomet. Chem.*, 1988, **354**, 233; for the use of a combination of high intensity ultrasound and amine *N*-oxides to deliver significantly more effective cyclisations, see:; (*b*) J. G. Ford, W. J. Kerr, G. G. Kirk, D. M. Lindsay and D. M. Middlemiss, *Synlett*, 2000, 1415.

5 (*a*) S. Shambayati, W. E. Crowe and S. L. Schreiber, *Tetrahedron Lett.*, 1990, **31**, 5289; (*b*) N. Jeong, Y. K. Chung, B. Y. Lee, S. H. Lee and S.-E. Yoo, *Synlett*, 1991, 204; (*c*) Y. K. Chung, B. Y. Lee, N. Jeong, M. Hudecek and P. L. Pauson, *Organometallics*, 1993, **12**, 220; (*d*) A. R. Gordon, C. Johnstone and W. J. Kerr, *Synlett*, 1995, 1083; (*e*) J. G. Donkervoort, A. R. Gordon, C. Johnstone, W. J. Kerr and U. Lange, *Tetrahedron*, 1996, **52**, 7391.

6 T. Sugihara, M. Yamada, H. Ban, M. Yamaguchi and C. Kaneko, *Angew. Chem. Int. Ed.*, 1997, **36**, 2801.

7 T. Sugihara, M. Yamada, M. Yamaguchi and M. Nishizawa, *Synlett*, 1999, 771.

8 W. J. Kerr, D. M. Lindsay, M. McLaughlin and P. L. Pauson, *Chem. Commun.*, 2000, 1467.

9 (*a*) K. Nishide, S.-I. Ohsugi, M. Fudesaka, S. Kodama and M. Node, *Tetrahedron Lett.*, 2002, **43**, 5177; (*b*) S.-I. Oshugi, K. Nishide, K. Oono, K. Okuyama, M. Fudesaka, S. Kodama and M. Node, *Tetrahedron*, 2003, **59**, 8393.

10 M. E. Krafft, L. V. R. Boñaga and C. Hirosawa, *J. Org. Chem.*, 2001, **66**, 3004.

11 J. A. Brown, T. Janecki and W. J. Kerr, unpublished results.