RSC Advances



View Article Online

View Journal | View Issue

PAPER

Check for updates

Cite this: RSC Adv., 2017, 7, 49215

Received 2nd October 2017 Accepted 14th October 2017

DOI: 10.1039/c7ra10888e

rsc.li/rsc-advances

Introduction

Sulfur-containing compounds are key structural cores of bioactive products, medicinally important compounds, and organic materials and thus, of great chemical relevance.1 In particular, α -acyloxy sulfides and their analogues are frequently used in various synthetic applications: as valuable precursors in the preparation of complex synthetic intermediates² and bioactive natural products.³ Well-established strategies to prepare these compounds include: (i) Pummerer-type rearrangement of alkyl sulfoxides;⁴ (ii) nucleophilic reaction of α substituted alkyl sulfides;5 (iii) anti-Markovnikov addition of vinyl esters with arylthiols;6 (iv) addition of aryl disulfides with (acyloxymethyl)magnesium chlorides;⁷ (v) anodic oxidation of sulfides.8 Recent advances, by Shi et al. report that alkyl sulfides can be converted to α -acyloxy sulfides in the presence of hypervalent iodine reagents and tetra-n-butylammonium bromide.9 Alternatively, Yuan developed an elegant goldcatalyzed iodine(m)-mediated direct oxidative acyloxylation of C(sp³)-H bonds of methyl sulfides.¹⁰ It is interesting to point out that it is known that benzoyl peroxide could undergo decomposition in the presence of organic sulfides¹¹ to form several products including: sulfoxides, sulfenic acid, olefins, disulfides and *α*-benzoyloxy substitution adducts. Surprisingly, despite some scattered procedures,12 typically requiring high reaction temperatures, the relevance of this latter transformation in organic synthesis has been highly overlooked so far. It is likely that this transformation is scarcely described from the point of view of preparation, due to the fact that α -benzoyloxy substituted products are generally obtained in poor chemical

α -Benzoyloxylation of β -keto sulfides at ambient temperature⁺

Enrico Piras,^a Francesco Secci,^a Pierluigi Caboni,^b Maria Francesca Casula^b and Angelo Frongia^{*}

A facile and efficient protocol for the α -benzoyloxylation of β -keto sulfides is presented. This methodology provides a step-economical, mild and practical access to highly functionalized α -O-benzoyloxy substituted β -keto sulfides, including those with quaternary carbons, which are not easily obtained through currently available methods.

yield and/or with low selectivity in combination with significant amounts of the corresponding sulfoxides.

In this work we address a general protocol for the synthesis of α -O-benzoyl substituted β -keto sulfides by the reaction strategy shown in Scheme 1. Based on literature, we speculated that the nucleophilic attack of the sulfur atom of a β -keto sulfide 1 on the O–O bond of benzoyl peroxide 2 would form an intermediate sulfonium salt **A** bearing fairly acidic hydrogens, due to the inductive effect of the positive sulfur and the presence of the carbonyl function. We hypothesize that intermediate **A** would be deprotonated at ambient temperature by the benzoate anion (Scheme 1, path a), previously formed during the course of the reaction, leading to a sulfur-stabilized carbonium ion **B** poised



Scheme 1 Uncatalyzed synthesis of α -O-benzoyl substituted β -keto sulfides 3.

[&]quot;Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Complesso Universitario di Monserrato, S.S. 554, Bivio per Sestu, I-09042, Monserrato, Cagliari, Italy. E-mail: afrongia@unica.it

^bDipartimento di Scienze della Vita e dell'Ambiente, Università degli Studi di Cagliari, Via Ospedale 72, 09124, Cagliari, Italy

[†] Electronic supplementary information (ESI) available: Detailed synthetic procedures and characterization of new compounds. See DOI: 10.1039/c7ra10888e



Scheme 2 α -O-Acyl-and benzoyl substituted β -keto sulfides in organic synthesis.

to undergo a Pummerer-like rearrangement *via* intermediate C. Considering that the alternative path b and c (in the case of disubstituted β -keto sulfides), leading to sulfoxide 4 and α -sulfanyl enone 6 respectively, should be less-favored as a result of both the enhanced α -proton acidity of A, as well as the increased electrophilicity of intermediate C, provided by the carbonyl group, the preferential formation of 3 with high level of selectivity can be reasonably expected. If successful, the proposed method would provide a general, straightforward, and mild synthetic route to *O*-benzoyloxy β -keto sulfides, avoiding the use of catalysts and saving energy as well as allowing transformation to be carried out at ambient temperature in response to the principle of sustainable chemistry.¹³

α-Acyloxy β-keto sulfides are important molecules due to their applications in different synthetic fields. Investigations into the reactivity of monosubstituted α-acyloxy β-keto sulfides have established them as valuable intermediates for the synthesis of α-acyloxy-and α-amino-thioester derivatives (Scheme 2; figure a) which can be easily transformed into the corresponding sulfur-free biologically active products.¹⁴ Moreover, disubstituted α-acyloxy β-keto sulfides (Scheme 2; figure b) play a key role as starting materials for the generation of monoenolized diketones,¹⁵ 1,2-diketones,¹⁶ dicarboxylic acids¹⁷ as well as carbocyclic α-hydroxy carboxylic acids.¹⁸ Surprisingly, synthetic strategies for the construction of these latter compounds are scarce and exclusively rely on the use of the Pummerer rearrangement¹⁹ and the acetoxylation reaction of phenyl thio ketones with lead tetraacetate.²⁰

Results and discussion

As a proof of concept for our study, the reaction of phenythio acetone **1a** and benzoyl peroxide **2** was carried out in CH_2Cl_2 at room temperature and monitored by GC-MS (Table 1, entry 1).

The investigated reaction took place extraordinarily smoothly without any kind of catalysts to afford **3a** in good conversion (78%) along with only a small amount of the expected by-product sulfoxide **4a** (12%, *via* path b, see: Scheme 1), benzoic acid **6** and benzoic anhydride **5**. These preliminary data indicated that the reaction is spontaneous, efficient and relatively rapid at room temperature. To confirm the reaction

Table 1 Optimization of the reaction conditions ^a			
Ph ^{-S}	Ph O-O Ph 2 O 1.1 equiv. Solvent, RT, 4 days	Ph^{S} Ph^{Ph} Ph^{Ph} Ph^{Ph} Ph^{Ph}	Ph ^{-S}
Entry	Solvent	$3\mathbf{a}^{b}$ (%)	$4\mathbf{a}^{b}$ (%)
1	CH_2Cl_2	78	12
2	1,4-Dioxane	79	12
3	Toluene	82	8
4	CH ₃ COOEt	76	13
5	CH_3CN	71	21
6 ^{<i>c</i>}	EtOH	46	13
7	n-Hexane	67	23
8	DMF	74	14
9	THF	75	12
10	DMSO	45	13
11	Acetone	79	11
12^d	Toluene	87 $(78)^e$	9

^{*a*} Reaction conditions: **1a** (333 μmol), benzoyl peroxide **2** (366 μmol), solvent (0.5 mL). ^{*b*} GC-MS yield. ^{*c*} 23% of 1-ethoxy-1-(phenylthio) propan-2-one was also observed (the formation of this product during the reaction is consistent with our mechanistic proposal). ^{*d*} 0.1 mL of solvent was used. ^{*e*} Isolated yield.

mechanism, selected control experiments were carried out (Scheme 3). In particular, the reaction was unaffected by the presence of radical scavenger such as butylated hydroxy-toluene (BHT). This result indicate that, as expected, the reaction likely proceeds through a nonradical pathway as illustrated in previously reported studies.¹¹ Furthermore, sulfoxide 7 failed to afford the corresponding *O*-benzoyloxylation products suggesting the requirement of a nucleophilic sulfur atom other than sufficiently acidic protons in alpha position for the success of this transformation at room temperature.

To further improve the control over the reaction and the conversion, the effect of solvent was investigated. All solvents tested in this study can provide good conversions except EtOH (46%) and DMSO (45%). The best result was obtained with toluene. The expected adduct 3a can be obtained in 82%



Scheme 3 Control experiments.^a ^aGC-MS yield.

Paper

conversion (Table 1, entry 3). Finally, in more concentrated solution the conversion of **3a** could be further increased to 87% (78% isolated yield, entry 12). With the optimal conditions for the α -benzoylation of phenylthioacetone in hand, the scope of the transformation was evaluated with respect to the presence of ring substituents on the phenylthio group (Scheme 4). Various *O*-benzoyl substituted substrates bearing electron-withdrawing (**1f**, **1g**); electron-donating groups (**1b**-**c**) and alogens (**1d**, **1e**) on the phenyl ring were synthesized using this methodology with high efficiency (69–78% yields; **3** : **4** ratio 84 : 16–91 : 9). Moreover, only a slightly decreased chemical yield (62%; **3** : **4** ratio 91 : 9) was observed in the case of *para*-nitro-substituted β -keto sulfide **1f** despite the relatively lower nucleophilicity of the sulfur atom. Notably, the steric hindrance



Scheme 4 Substrate scope.^{a,b,c} ^aReaction conditions: 1 (333 µmol), benzoyl peroxide (366 µmol), toluene (0.1 mL). ^bIsolated yield. ^c3 : 4 ratio determined by GC-MS. ^d3 : 4 ratio determined by ¹H NMR. ^eThe reaction was carried out for 5 days.

was very well tolerated in the case of *ortho*-; and *meta*substituted substrates such as **1i** and **1h** that gave the corresponding *O*-benzoyl substituted compounds **3i** (81%; **3** : **4** ratio 86 : 14) and **3h** (85%; **3** : **4** ratio 87 : 13) in high chemical yield.

Furthermore, naphthylthio ketone 1j also reacted well, affording the corresponding product 3j in 84% yield (3:4 ratio 96 : 4). Under the optimized conditions, phenyl selenide ketone 1k was well tolerated and the product 3k was obtained in 88% yield and excellent selectivity (3: 4 ratio > 99: 1). Linear (11) and branched (1m) 3-alkyl-substituted β -keto sulfides, despite the relatively greater steric hindrance, were both effective in the reaction leading to the desired products in good to high yields (79-82%; 3: 4 ratio 93: 7-97: 3). To our delight, a representative aromatic α -acyloxy β -keto sulfide **1n**, subjected to the same reaction conditions, was smoothly converted into the corresponding product with a good chemical yield (76%; 3:4 ratio 82:18). On the other hand, 2-(phenylthio)acetonitrile 1p and methyl 2-(phenylthio)acetate 10 also reacted with benzoyl peroxide to yield O-benzoyl substituted derivatives 3p (78%; 3:4 ratio 93:7) and 30 (68%; 3:4 ratio 85:15) respectively, albeit much more slowly than the corresponding ketone derivatives, requiring longer reaction times in order to obtain good yields. This seemed to be due to the higher pK_a value of the hydrogens adjacent to the ester and cyano group with respect to the corresponding ketone derivatives which disfavor the formation of the required intermediate B (see: Scheme 1). Next, encouraged by the above-mentioned positive results, the applicability of the reaction protocol to other substituted benzoyl peroxides was then preliminary investigated.

As a result, a decreased yield of 3t (68%), and the formation of a significant amount of sulfoxide 4(3: 4 ratio 74: 26)was observed in the case of benzoyl peroxides with a strong electron-withdrawing substituent such as -NO₂ on the aromatic ring compared to those with electron-donating group such as 3q (77% yield; 3:4 ratio 90:10), 3r (77%; 3: 4 ratio 88: 12) and alogens for example 3s (81%; 3: 4 ratio 84:16). This behavior may be related to the significantly more electrophilic character of the carbonyl of the benzoyl group (provided by the strong electron-withdrawing group) in intermediate sulfonium A which increases the reaction rate of path b (Scheme 1). β -Keto sulfides 1u and 1v, bearing an aliphatic group on sulfur performed very well, and delivered regioselectively the corresponding α -benzoyloxy β -keto sulfide 3u (80%; 3:4 ratio 94:6) and 3v (66%; 3:4 ratio 91:9) in good to high yields. Similarly, 1w also underwent efficient reaction (75% yield; 3: 4 ratio 97: 3) to afford only the mono benzoyloxylation product 3w.

Finally, the substrate scope was extended to include the synthesis of some challenging α -branched *O*-benzoyloxy β -keto sulfides. As summarized in Scheme 5, gratifyingly acyclic disubstituted β -keto sulfides **1aa–1ad** performed well and delivered the corresponding products **3aa–3ad** in moderate to good yields (63–77%; **3** : **4** ratio 80 : 20–94 : 6).

The reaction proved to be rather general; in addition to acyclic β -keto sulfides, cyclic β -keto sulfides **1ae–1ai** also could be used giving the corresponding quaternary adducts²¹ in moderate to high yields (63–80%; **3** : **4** ratio 73 : 27–96 : 4).



Scheme 5 Substrate scope for the formation of quaternary α -branched *O*-benzoyloxy β -keto sulfides.^{a,b,c} ^aFollowing the general procedure. ^bIsolated yield. ^c3 : 4 ratio determined by GC-MS. ^d3 : 4 ratio determined by ¹H NMR.

Interestingly, under these very mild reaction conditions, in all the cases examined only trace amount of the corresponding α , β -unsaturated sulfide by-product (Scheme 1, path c), which is the major drawback of the Pummerer reaction,^{19d,22} was detected.

Conclusions

In this work a practical and versatile α -benzoyloxylation of β keto sulfides under mild conditions is demonstrated. Through this procedure, a series of α -benzoyloxy- β -keto sulfides were obtained in moderate to high yields. Besides, α branched cyclic and acyclic β -keto sulfides were also compatible with the current protocol and provide the corresponding *O*-benzoyloxy β -keto sulfides in moderate to high yields. The wide functional group tolerance highlights the potential of this transformation as an effective method for the operationally simple installation of a benzoyloxy group in the α -position of a sulfur atom in the presence of a carbonyl group. We prospect that the impact of our findings will be beyond the research on sustainable organic synthetic approaches, due to the role of sulfur-bearing compounds in bioactive and medicinally relevant compounds.

Conflicts of interest

There are no conflicts to declare.

Financial support from the MIUR, by the University of Cagliari (FIR 2016-FIR 2017) and from RAS and Fondazione Banco di Sardegna is acknowledged. Sardinia Scientific Park Polaris is thanked for free access to IR spectrophotometer. We thank Dr Danilo Loche for aid in analyses and for useful discussions.

Notes and references

- 1 (a) P. Metzner and A. Thuillier, Sulfur Reagents in Organic Synthesis, Academic Press, San Diego, 1994; (b) R. J. Cremlyn, An Introduction to Organosulfur Chemistry, John Wiley & Sons, Chichester, 1996; (c) V. K. Aggarwal and C. L. Winn, Acc. Chem. Res., 2004, 37, 611-620; (d) T. Toru and C. Bolm, Organosulfur Chemistry in Asymmetric synthesis, Wiley-VCH, Weinheim, 2008; (e) X. Huang, S. Klimczyk and N. Maulide, Synthesis, 2012, 175–183; (f) L. Wang, W. He and Z. Yu, Chem. Soc. Rev., 2013, 42, 599-621; (g) F. Dénès, C. H. Schiesser and R. Renaud, Chem. Soc. Rev., 2013, 42, 7900-7942; (h) F. Dénès, M. Pichowicz, G. Povie and P. Renaud, Chem. Rev., 2014, 114, 2587-2693; (i) C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. Andy Hor and X. Liu, Chem. Soc. Rev., 2015, 44, 291-314; (j) B. M. Trost and M. Rao, Angew. Chem., Int. Ed., 2015, 54, 5026-5043; (k) L. A. Damani, Sulphur-Containing Drugs and Related Organic Compounds, Wiley, New York, 1989; (l) H. Liu and X. Jiang, Chem.-Asian J., 2013, 8, 2546-2563.
- 2 R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Wiley-VCH, New York, 2nd edn, 1999.
- 3 (a) S. Brand, M. F. Jones and C. M. Rayner, *Tetrahedron Lett.*, 1995, 36, 8493–8496; (b) P. Magnus, M. Giles, R. Bonnert, G. Johnson, L. McQuire, M. Deluca, A. Merritt, C. S. Kim and N. Vickert, *J. Am. Chem. Soc.*, 1993, 115, 8116–8129; (c) S. L. Schreiber and K. Satake, *J. Am. Chem. Soc.*, 1984, 106, 4186–4188.
- 4 (a) R. Pummerer, Chem. Ber., 1909, 42, 2282-2291; (b)
 A. Padwa, D. E. Gunn Jr and M. H. Osterhout, Synthesis, 1997, 1353-1377; (c) S. K. Bur and A. Padwa, Chem. Rev., 2004, 104, 2401-2432; (d) K. S. Feldman, Tetrahedron, 2006, 62, 5003-5034; (e) S. Akai and Y. Kita, Top. Curr. Chem., 2007, 274, 35-76; (f) L. H. S. Smith, S. C. Coote, H. F. Sneddon and D. J. Procter, Angew. Chem., Int. Ed., 2010, 49, 5832-5844; (g) O. de Lucchi, U. Miotti and G. Modena, The Pummerer Reaction of Sulfinyl Compounds, Org. React., 2004, 40(3), 157-405.
- 5 (a) T. Benneche, P. Strande and U. Wiggen, Acta Chem. Scand., 1988, 43, 74–77; (b) S. Avolio, C. Malan and P. M. Knochel, Synlett, 1999, 1820–1822; (c) G. A. Kraus and H. Maeda, Tetrahedron Lett., 1995, 36, 2599–2602; (d) S. Brand, M. F. Jones and C. M. Rayner, Tetrahedron Lett., 1995, 36, 8493–8496; (e) T. Koizumi, T. Fuchigami and T. Nonaka, Chem. Lett., 1987, 1095–1096; (f) T. Koizumi, T. Fuchigami and T. Nonaka, Bull. Chem. Soc. Jpn., 1989, 62, 219–225; (g) D. Uguen, Tetrahedron Lett., 1984, 25, 541– 542.

This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

- 6 R.-S. Lee, J. Chin. Chem. Soc., 1997, 44, 77-80.
- 7 R. Blanc, K. Groll, S. Bernhardt, P. N. Stockmann and P. Knochel, *Synthesis*, 2014, 1052–1058.
- 8 (a) J. Nokami, M. Hatate, S. Wakabayashi and R. Okawara, *Tetrahedron Lett.*, 1980, 21, 2557–2558; (b) T. Fuchigami,
 Y. Nakagawa and T. Nonaka, *Tetrahedron Lett.*, 1986, 27, 3869–3872; (c) T. Fuchigami, K. Yamamoto and
 Y. Nakagawa, *J. Org. Chem.*, 1991, 56, 137–142; (d)
 T. Fuchigami, K. Yamamoto and H. Yano, *J. Org. Chem.*, 1992, 57, 2946–2950.
- 9 D. Zhu, D. Chang, S. Gan and L. Shi, RSC Adv., 2016, 6, 27983–27987.
- 10 S.-R. Guo, P. S. Kumar, Y.-Q. Yuan and M.-H. Yang, *Eur. J. Org. Chem.*, 2016, 4260–4264.
- 11 (a) W. A. Pryor and H. T. Bickley, J. Org. Chem., 1972, 37, 2885–2893; (b) D. I. Davies, D. H. Hey and B. Summers, J. Chem. Soc. C, 1970, 2653–2660; (c) H. B. Henbest, J. A. W. Reid and C. J. M. Stirling, J. Chem. Soc., 1964, 1220–1223; (d) L. Horner and E. Jürgen, Liebigs Ann. Chem., 1957, 602, 135–153; (e) W. A. Pryor and W. H. Hendrickson Jr, J. Am. Chem. Soc., 1983, 105, 7114–7122; (f) G. Sosnovsky, Tetrahedron, 1962, 18, 15–19.
- 12 (a) K. Gollmer and H. Ringsdorf, Makromol. Chem., 1969,
 121, 227-257; (b) Yu. I. Puzin, G. V. Leplyanin,
 E. A. Kozheparova and G. A. Tolstikov, Dokl. Akad. Nauk SSSR, 1991, 320, 349-352; (c) M. Hojo, R. Masuda, T. Ichi,
 K. Yoshinaga, S. Munehira and M. Yamada, Synthesis,
 1982, 424-426; (d) N. E. Allen, D. B. Boyd, J. B. Campbell,
 J. B. Deeter, T. K. Elzey, B. J. Foster, L. D. Hatfield,
 J. N. Hobbs Jr, W. J. Hornback, D. C. Hunden, N. D. Jones,
 M. D. Kinnick, J. M. Morin Jr, J. E. Munme,
 J. K. Swartzendruber and D. G. Vogt, Tetrahedron, 1989, 45,
 1905-1928; (e) J. E. Baldwin, C. Lowe and C. J. Schofield, Tetrahedron Lett., 1986, 27, 3461-3464; (f) J. E. Baldwin,
 M. A. Christie, S. B. Haber and L. I. Kruse, J. Am. Chem. Soc., 1976, 98, 3045-3047.
- 13 (a) M. B. Gawande, V. D. B. Bonifàcio, R. Luque, P. S. Branco and R. S. Varma, *ChemSusChem*, 2014, 7, 24-44; (b)

G. Brahmachari and B. Banerjee, *Curr. Green Chem.*, 2015, 2, 274–305.

- 14 (a) T. Suzuki, Y. Honda, K. Izawa and R. M. Williams, J. Org. Chem., 2005, 70, 7317–7323; (b) F. Capitta, A. Frongia, P. P. Piras, P. Pitzanti and F. Secci, Org. Biomol. Chem., 2012, 10, 490–494; (c) F. Capitta, A. Frongia, P. P. Piras, P. Pitzanti and F. Secci, Adv. Synth. Catal., 2010, 352, 2955– 2960; (d) F. Capitta, N. Melis, F. Secci, G. Romanazzi and A. Frongia, J. Sulfur Chem., 2014, 35, 649–660.
- 15 Y. Sugihara, A. Yamato and I. Murata, *Tetrahedron Lett.*, 1981, 22, 3257–3260.
- 16 B. M. Trost, C. Pissot-Soldermann and I. Chen, *Chem.–Eur. J.*, 2005, **11**, 951–959.
- 17 B. M. Trost, Chem. Rev., 1978, 78, 363-382.
- 18 B. M. Trost and H. Hiemstra, *Tetrahedron*, 1986, 42, 3323–3332.
- 19 (a) M. Naora, T. Murae, T. Tsuyuki and T. Takahashi, Bull. Chem. Soc. Jpn., 1986, 59, 1767–1776; (b) T. Patonay, E. Patonay-Péli and G. Litkei, Tetrahedron, 1987, 43, 1827– 1834; (c) F. Eiden and F. Meinel, Arch. Pharm., 1979, 312, 302–312; (d) S. Ito, Y. Kubota and M. Asami, Chem. Lett., 2016, 45, 16–18; (e) B. M. Trost and A. J. Bridges, J. Am. Chem. Soc., 1976, 98, 5017–5019; (f) G. H. Posner, E. Asirvatham and S. F. Ali, J. Chem. Soc., Chem. Commun., 1985, 542–543.
- 20 (a) M. D. Lawlor, T. W. Lee and R. L. Danheiser, J. Org. Chem., 2000, 65, 4375-4384; (b) B. M. Trost and A. J. Bridges, J. Am. Chem. Soc., 1976, 4, 5017-5019; (c) D. G. McCarthy, C. C. Collins, J. P. O'Driscoll and S. E. Lawrence, J. Chem. Soc., Perkin Trans. 1, 1999, 3667-3675; (d) P. A. Wender, H. Kogen, H. Y. Lee, J. D. Munger Jr, R. S. Wilhelm and P. D. Williams, J. Am. Chem. Soc., 1989, 111, 8957-8958; (e) D. M. X. Donnelly, B. M. Fitzpatrick, B. A. O'Reilly and J.-P. Finet, Tetrahedron, 1993, 49, 7967-7976.
- 21 J.-S. Yu, H. M. Huang, P.-G. Ding, X.-S. Hu, F. Zhou and J. Zhou, *ACS Catal.*, 2016, **6**, 5319–5344.
- 22 J. Durman, J. I. Grayson, P. J. Hunt and S. Warren, J. Chem. Soc., Perkin Trans. 1, 1986, 1939–1945.