An Efficient and Practical Synthesis of Aryl and Hetaryl α-Keto Esters

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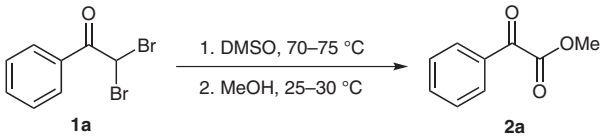
In fond memory of Professor C. V Asokan, Mahatma Gandhi University, Kottayam, India

Abstract: A general and highly efficient method was developed for the synthesis of α-keto esters by oxidative esterification of 2,2-dibromo-1-(het)arylethanones by sequential treatment with dimethyl sulfoxide and an alkanol. The versatility of the reaction was established by synthesizing a range of α-keto esters by treatment of 2,2-dibromoethanones, derived from aryl or hetaryl ketones, with dimethyl sulfoxide and a cyclic or acyclic primary or secondary alcohol. The mechanism of the reaction was established by means of a detailed study.

Key words: ketones, esters, oxidations, esterifications, alcohols

α-Keto acid esters are important structural units in many biologically active compounds and they serve as backbones in compounds such as 3-deoxy-D-manno-2-octulosonic acid (KDO) and sialic acid (*N*-acetylneuraminic acid).[1] Aryl α-keto esters are widely used as key intermediates for the synthesis of many bioactive compounds and in asymmetric syntheses of α-hydroxy carboxylic acids.[2] Some α-keto esters also exhibit anti-sunburn effects.[3]

Several methods for synthesizing α-keto esters have been reported in the literature. These highly electrophilic synthons can be prepared by chemoselective cross coupling of monoesters of dicarboxylic acid chlorides with organometallic reagents,[4] by photochemical alcoholysis of a trichloroacetyl group,[5] by double carbopalladative esterification reactions,[6] by Friedel–Craft acylation,[7] by hydrolysis and esterification of alkyl cyanides,[8] or by acylation or alkylation of monosubstituted 1,3-dithianes,[9] among other methods. Noteworthy oxidative approaches for the synthesis of α-keto esters include oxidation of terminal haloalkynes,[10] oxidation of α-hydroxy esters with pyridinium chlorochromate[11] or Dess–Martin periodinane,[12] and oxidation of aryl ketones with selenium dioxide.[13] Oxidation of α-alkoxy esters with molybdenum trioxide–hydrogen peroxide–3,5-dimethylpyrazole adduct ($MoO_3 \cdot H_2O_2$–DMPZ) in the presence of a strong base is also a noteworthy method for the synthesis of α-keto esters.[14] Despite the availability of numerous methods for the synthesis of α-keto esters, the importance of this class of compounds has stimulated much activity in the development of new synthetic processes. Here, we report a practical route to the synthesis of α-keto esters from 2,2-dibromo-1-(het)arylethanones by using dimethyl sulfoxide as the oxidizing agent. The synthesis of ethyl oxo(phenyl)acetate (**2a**) from 2,2-dibromo-1-phenylethanone (**1a**) under oxidative esterification reaction conditions is outlined in Scheme 1. The starting material **1a** was prepared by bromination of acetophenone with bromine in dioxane at room temperature.[15]



Scheme 1

To optimize the oxidative esterification process, we examined the oxidative esterification reaction under several types of reaction conditions. Initially, we tried stirring 2,2-dibromo-1-phenylethanone (**1a**) in six volumes of dimethyl sulfoxide at 50–55 °C until the starting material disappeared (about 34 hours); this was followed by esterification with methanol at room temperature to give ethyl oxo(phenyl)acetate (**2a**) in 74% isolated yield. The mixture could not be stirred when the reaction was performed in less than five volumes of dimethyl sulfoxide. The oxidative esterification reaction was completed within 14 hours when the reaction was performed in six volumes of dimethyl sulfoxide at 70–75 °C, followed by esterification with methanol at room temperature (Table 1), and the product was isolated in 75% yield. The oxidative esterification reaction was also attempted at 80–85 °C and the expected product was isolated in 71% isolated yield after quenching of the reaction mass with methanol. A high exothermicity was observed when the reaction was performed at above 100 °C.

The optimal conditions for oxidative esterification of **1a** are therefore a temperature of 70–75 °C with the reaction performed in six volumes of dimethyl sulfoxide. The reaction took almost 14–16 hours to complete, and the product was esterified with methanol (0.6 mL, 1 volume) at room temperature. The product **2a** was purified by column chromatography and isolated as a colorless liquid in 75% yield, although thin-layer chromatography and NMR

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Table 1 Yields from Oxidative Esterification of 2,2-Dibromo-1-phenylethanone under Various Conditions

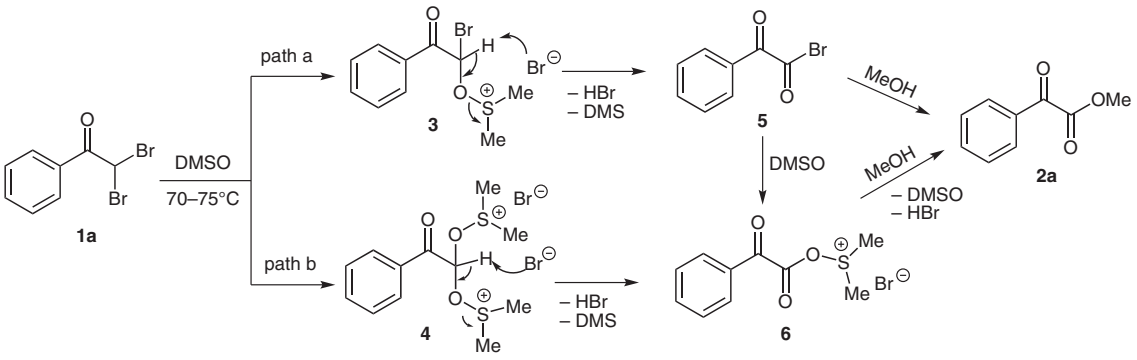
Temp (°C)	Time (h)	Yield (%)
50–55	34	74
70–75	14	75
80–85	8	71
70–75	8	58

spectroscopy of the crude reaction mixture indicated more than 90–95% product formation. The methyl oxo(phenyl)acetate (**2a**) product was characterized by means of IR, NMR, and mass spectroscopy.[16]

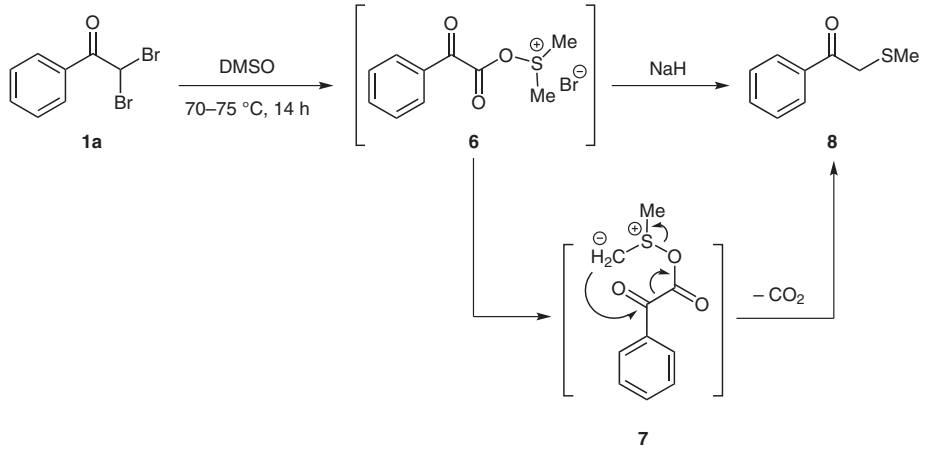
To elucidate the mechanism of the transformation, we performed the reaction in deuterated dimethyl sulfoxide under the optimized reaction conditions. Initially, 2,2-dibromo-1-phenylethanone (**1a**) was stirred in dimethyl sulfoxide-d_6 at room temperature and the ^{1}H NMR spectra of the reaction mass was recorded. Four signals were observed at δ = 7.59 (t, 2 H, ArH), 7.73 (t, 1 H, ArH), 7.89 (s, 1 H, CH), and 8.10 (d, 2 H, ArH); these correspond to the spectrum of **1a**, showing that no reaction occurred at room temperature. When the solution of the dibromo ketone **1a** in six volumes of dimethyl sulfoxide-d_6 was heated to 70–75 °C and then cooled to room temperature, the ^{1}H NMR spectrum showed three multiplets at δ = 7.59 (t, 2 H, ArH), 7.73 (t, 1 H, ArH), and 8.10 (d, 2 H, ArH) ppm, along with a broad peak at δ = 9.85 ppm. Notably, the singlet at δ = 7.89 ppm had disappeared from the NMR spectrum. The reaction mass was then quenched with methanol-d_4 and the NMR spectrum was recorded again. The product was identified as deuterated methyl oxo(phenyl)acetate (**2a**) by spectral and analytical methods. The absence of a methine proton in the ^{1}H NMR spectrum recorded after heating **1a** in dimethyl sulfoxide-d_6 clearly indicated that oxidation had occurred well before the addition of methanol to the reaction mixture. In a separate deuterium–hydrogen exchange study, the broad proton peak observed at δ = 9.85 ppm after heating **1a** with dimethyl sulfoxide-d_6 was found to be exchangeable with deuterium oxide, and this peak was assumed to correspond to hydrogen bromide in the form of the hydrobromide salt of dimethyl sulfoxide-d_6.

On the basis of these studies, the formation of the alkoxy sulfoxonium bromide **3** by the displacement of bromide ion from **1a** by dimethyl sulfoxide is probably the first step of the oxidative esterification reaction (Scheme 2).[17] On heating, the alkoxy sulfoxonium species **3** undergoes a 1,2-elimination reaction to give the aldehyde **4.** Addition of dimethyl sulfoxide to the aldehyde followed by reaction with bromo(dimethyl)sulfonium bromide, generated in situ, gives the acetal intermediate **5**. Oxidation of intermediate **5** gives dimethyl{[oxo(phenyl)acetyl]oxy}sulfonium bromide (**6**), which reacts with methanol to give the keto ester **2a**, with concomitant elimination of dimethyl sulfoxide. The alkoxy sulfoxonium bromide **3** could also react with dimethyl sulfoxide to give intermediate **5** directly. The acid bromide **5** could then react with methanol to form the oxo(phenyl)acetate **2a**. In NMR studies, however, the sulfoxonium species **3**, the alkoxy disulfoxonium species **4**, and the acid bromide **5** were not detected, clearly suggesting that the rate of displacement of bromine atoms by dimethyl sulfoxide is rather slow and that 1,2-elimination and further oxidation occur immediately after displacement of bromine.

To prove that dimethyl{[oxo(phenyl)acetyl]oxy}sulfonium bromide (**6**) is an intermediate in this unique oxidation reaction, we stirred a solution of 2,2-dibromo-1-phenylethanone (**1a**) in dimethyl sulfoxide for 14–15 hours at 70–75 °C until **1a** disappeared. The mixture was then cooled to 30–35°C and added to a suspension of sodium hydride in dimethyl sulfoxide. The mixture was then stirred for another 1.5–2 hours until the intermediate **6** disappeared. After aqueous extractive workup and column chromatography, the major product isolated was identified as 2-(methylsulfanyl)-1-phenylethanone (**8**) by means of NMR and mass spectroscopy and other analytical methods. The formation of 2-(methylsulfanyl)-1-phenylethanone (**8**) is assumed to occur through the deprotonation of sulfonium bromide **6** by sodium hydride, further nucleophilic attack of the methylene anion on the α-carbonyl carbon, and concomitant elimination of carbon dioxide. The formation of 2-(methylsulfanyl)-1-phenylethanone (**8**) conclusively proves that dimethyl{[oxo(phenyl)acetyl]oxy}sulfonium bromide (**6**) is an intermediate in the oxidative esterification reaction (Scheme 3).

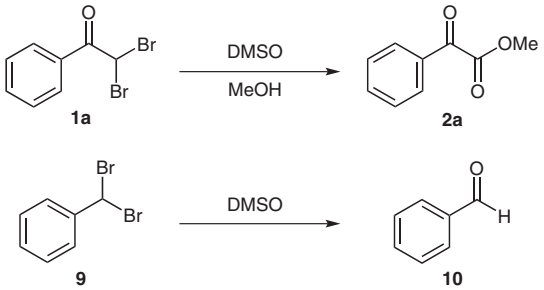


Scheme 2 Mechanism of the oxidative esterification reaction



Scheme 3

It is worthwhile comparing the conversion of α-bromoalkanes (for example, **9**) into the corresponding aldehydes (for example, **10**)[18] with the present ester-formation reaction of dibromo ketones (Scheme 4). Although dimethyl sulfoxide is used in both reactions, the conversions of the geminal dibromides into aldehydes and into esters are fundamentally different processes. Because it is highly acidic, the methine proton in **1a** is eliminated to form hydrogen bromide, whereas dibromine is eliminated from the geminal dibromo compound **9**. Our new transformation is a unique oxidation process in which the oxidation state of the methine group bearing the dibromo group in the starting material is different from that in the product as a result of the oxidative esterification reaction. Therefore, oxygen transfer from sulfoxide can occur in both oxidative and nonoxidative ways, depending on the nature of the substrate.



Scheme 4

To establish the versatility of our oxidative esterification reaction, we subjected a series of aryl and hetaryl dibromoethanones **1a–i** to oxidative esterification to give the corresponding keto esters **2a–s** in good yields. All the starting dihalides required for the oxidative esterification reaction were prepared according to the reported procedures and used without further purification. All the products were characterized by means of ^{1}H and ^{13}C NMR, mass, and IR spectroscopy and, in a few cases, by elemental analysis. All the oxidation reactions were performed at elevated temperatures and the subsequent esterification was carried out at room temperature with the appropriate alcohol (Table 2).

Our attempts to carry out the oxidative esterification reaction on alkoxy-substituted aryldibromoethanones **1f** (entry 16) or **1g** (entry 17) under the optimized reaction conditions (70–75 °C, 14 h) were unsuccessful and they generally resulted in decomposition of the starting materials and formation of complex product mixtures. However when the reaction was carried out at 40–45 °C, for 55–60 hours, the expected products **2p** and **2q** were isolated in 35 and 49% yield, respectively. The low yields of the alkoxy-substituted aryl keto ester from the oxidative esterification reactions were probably due to the demethylation of the alkoxy groups by the hydrobromic acid liberated during the reaction. Attempts to use organic or inorganic bases to improve the yield of the oxidative esterification reaction of alkoxy-substituted dibromoarylethanones were unsuccessful. Oxidative esterification of 1,1-dibromo-3,3-dimethylbutan-2-one or other aliphatic geminal dibromides did not yield the expected products.

Interestingly, the reactions of dibromoethanones with propane-1,3-diol could be fine-tuned by changing the proportion of propane-1,3-diol used in the reactions to provide either monoesters or diesters. Thus, oxidation of dibromoethanones **1a** and **1b** with dimethyl sulfoxide at 70–75 °C and subsequent quenching with two equivalents of propane-1,3-diol gave the corresponding diesters **9a** and **9b** as the sole products in 70 and 68% yields, respectively (Scheme 5). When the reaction was quenched with a large excess of propane-1,3-diol, the corresponding monoesters were obtained as the major products (Table 1, entries 8 and 10). The reaction of the dibromoethanone derived from *N*-tosyl-3-acetylindole (**1g**) with propane-1,3-diol was also attempted, and the diester **12** was obtained in 50% yield.

Table 2 Scope of Oxidative Esterification of 2,2-Dibromo-1-(het)arylethanones by Dimethyl Sulfoxide and Alkanols

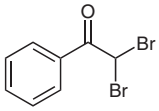
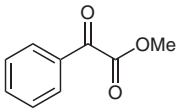
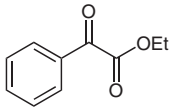
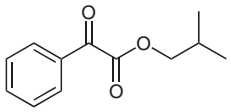
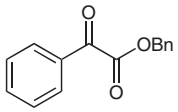
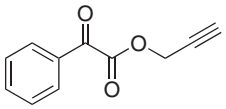
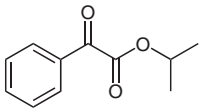
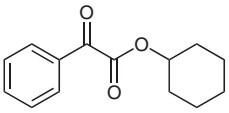
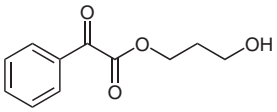
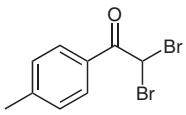
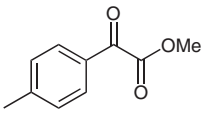
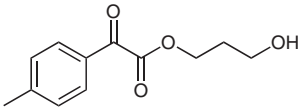
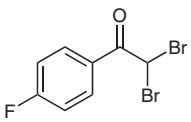
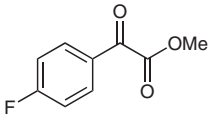
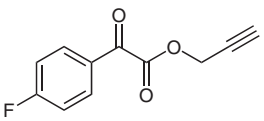
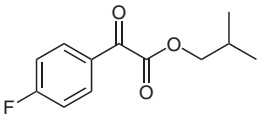
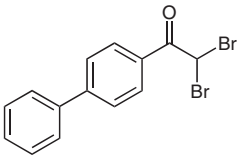
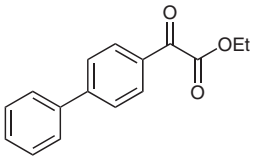
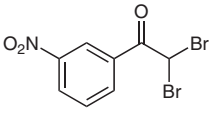
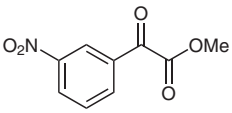
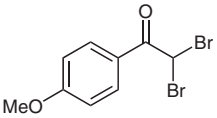
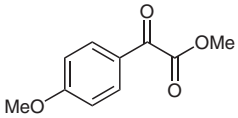
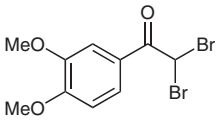
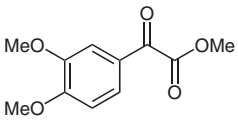
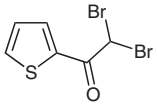
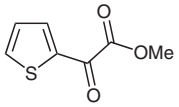
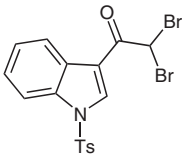
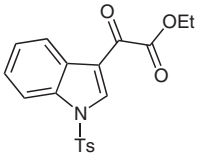
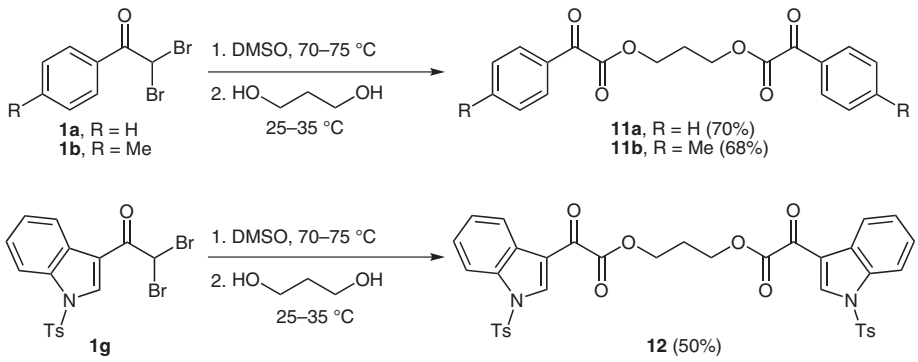
Entry	Dibromoethanone		Alcohol	α-Keto ester		Yield (%)	Physical state/mp
1	**1a**		MeOH	**2a**		75	viscous liquid[16]
2	**1a**		EtOH	**2b**		74	viscous liquid[19]
3	**1a**		*i*-BuOH	**1c**		68	viscous liquid[20]
4	**1a**		BnOH	**2d**		70	viscous liquid[9]
5	**1a**		$HC{\equiv}CCH_2OH$	**2e**		68	viscous liquid[21]
6	**1a**		*i*-PrOH	**2f**		61	viscous liquid[22]
7	**1a**		CyOH	**2g**		54	viscous liquid[6]
8	**1a**		$HO(CH_2)_3OH$	**2h**		65	viscous liquid
9	**1b**		MeOH	**2i**		76	viscous liquid[23]
10	**1b**		$HO(CH_2)_3OH$	**2j**		65	viscous liquid
11	**1c**		MeOH	**2k**		70	46–48 °C[24]
12	**1c**		$HC{\equiv}CCH_2OH$	**2l**		67	viscous liquid
13	**1c**		*i*-BuOH	**2m**		65	viscous liquid[25]

Table 2 Scope of Oxidative Esterification of 2,2-Dibromo-1-(het)arylethanones by Dimethyl Sulfoxide and Alkanols (continued)

Entry	Dibromoethanone	Alcohol	α-Keto ester	Yield (%)	Physical state/mp
14	**1d** 	MeOH	**2n** 	70	viscous liquid[26]
15	**1e** 	MeOH	**2o** 	72	viscous liquid[27]
16	**1f** 	MeOH	**2p** 	35	48–50 °C[28]
17	**1g** 	MeOH	**2q** 	49	60–62 °C[28]
18	**1h** 	MeOH	**2r** 	70	viscous liquid[29]
19	**1i** 	EtOH	**2s** 	67	89–90 °C

In conclusion, we have developed a simple and efficient method for the transformation of acyl dibromo compounds into the corresponding esters. The reaction can be carried out conveniently and proceeds with excellent yield to give pure products. The conversion of dihalo compounds into the corresponding esters provides an alternative route for the transformation of an aromatic acyl group into an ester in two steps under relatively mild conditions and in high yield. To best of our knowledge, this is the first report of the use of the dimethyl sulfoxide/alkanol combination to convert a geminal dibromo compound into the corresponding ester. We are currently examining the scope and limitations of this reaction for the preparation of other important functional groups and building blocks.

All reactants and reagents were used as received from commercial sources without further purification or were prepared as described in the literature. Reaction mixtures were stirred by using Teflon-coated magnetic stirring bars. TLC plates were visualized by UV radiation or by spraying with Pancaldi reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O]. Products were purified by flash column chromatography on silica gel (60–120 mesh). Melting points were determined by using an electrothermal melting-point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1650 Fourier-transform spectrometer. NMR spectra were measured in $CDCl_3$, acetone, or DMSO-d_6 (all with TMS as the internal standard) on a Varian Gemini 400-MHz Fourier-transform NMR spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in Hz. Mass spectra were recorded on an HP-5989A quadrupole mass spectrometer.



Scheme 5

2,2-Dibromo-1-phenylethanone (1a)
Br_2 (29.3 g, 0.18 mol) was added dropwise over 20 min to anhyd 1,4-dioxane (60 mL) at 25–30 °C under a minimum flow of N_2 and the mixture was kept under these conditions for 30 min. A soln of PhCOMe (10 g, 0.8 mol) in dioxane (40 mL) was added and the mixture was stirred for another 2–3 h. The reaction was then quenched in ice-cold H_2O (1 L, 10 volumes with respect to 1,4-dioxane) and the solid was filtered off and washed with chilled hexane; yield: 21 g (90%).

(Het)aryl α-Keto Esters 2a–2o, 2r, and 2s; General Procedure
The dibromo ketone (1.0 g) was dissolved in anhyd DMSO (6 mL) under argon. (The moisture content of the DMSO should be less than 0.5%, otherwise some keto acid will be formed in the reaction.) The mixture was then slowly heated to 70–75 °C for 1–2 h. (**Note:** *If the temperature of the reaction mixture rises to above 100 °C, the reaction will become very violent.*) The mixture was kept at 70–75 °C for another 14–16 h, then cooled to r.t. The alcohol (0.6 mL) was added and the mixture was stirred for 1–2 h. The mixture was then diluted with H_2O (60 mL) and extracted with EtOAc (4 × 30 mL). The combined organic layer was washed successively with H_2O (3 × 30 mL) and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude products were 95–96% pure, and analytically pure samples were obtained by column chromatography (hexane–EtOAc).

Alkoxy(het)aryl α-Keto Esters (2p and 2q); General Procedure
The reaction was carried out as described in the general procedure above, except that the reaction mixture was maintained at 40–45 °C for 55–60 h after adding the DMSO at r.t.

Methyl Oxo(phenyl)acetate (2a)
Pale-yellow liquid; yield: 445 mg (75%).

IR (KBr): 669, 928, 1008, 1174, 1215, 1436, 1598, 1691, 1740, 2853, 2925 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.98 (s, 3 H), 7.52 (t, *J* = 7.8 Hz, 2 H, ArH), 7.66 (t, *J* = 7.4 Hz, 1 H, ArH), 8.03 (d, *J* = 7.6 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.7, 128.8, 130.0, 132.4, 134.9, 164.0, 186.0.

MS: *m/z* = 165 [M + 1], 187 [M + 23].

Prop-2-yn-1-yl Oxo(phenyl)acetate (2e)
Pale-yellow liquid; yield: 470 mg (68%).

IR (neat): 761, 785, 1020, 1173, 1192, 1288, 1370, 1450, 1597, 1691, 1745, 2132, 3067, 3309 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.60 (s, 1 H), 4.96 (s, 2 H), 7.53 (t, *J* = 7 Hz, 2 H, ArH), 7.68 (t, *J* = 7 Hz, 1 H, ArH), 8.03 (d, *J* = 6.8 Hz, 2 H, ArH).

MS: *m/z* = 189 [M + 1], 212 [M + Na].

3-Hydroxypropyl Oxo(phenyl)acetate (2h)
Pink liquid; yield: 485 mg (65%).

IR (neat): 786, 908, 1176, 1597, 1691, 1735, 2253, 2855, 2927, 2961, 3436 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (s, 1 H, OH), 2.02 (quint, *J* = 6.0 Hz, 2 H), 3.78 (t, *J* = 7.4 Hz, 2 H), 4.54 (t, *J* = 6.2 Hz, 2 H), 7.51 (t, *J* = 7.6 Hz, 2 H, ArH), 7.66 (t, *J* = 7.4 Hz, 1 H, ArH), 8.00 (d, *J* = 7.2 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.3, 58.9, 63.2, 128.8, 129.9, 132.3, 134.9, 163.8, 186.1.

MS: *m/z* = 209 [M + 1], 231 [M + Na].

3-Hydroxypropyl (4-methylphenyl)(oxo)acetate (2j)
Pink liquid; yield: 494 mg (65%).

IR (neat): 669, 758, 845, 928, 1001, 1029, 1174, 1216, 1261, 1606, 1682, 1735, 2400, 2927, 2961, 3020 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 1 H, OH), 2.02 (quint, *J* = 6.4 Hz, 2 H), 2.44 (s, 3 H), 3.79 (t, *J* = 6 Hz, 2 H), 4.54 (t, *J* = 6.2 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H, ArH), 7.91 (d, *J* = 8.0 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 31.3, 58.9, 63.1, 129.6, 129.8, 130.1, 146.3, 164.0, 185.8.

MS: *m/z* = 223 [M + 1], 245 [M + Na].

Ethyl (1-Tosyl-1*H*-indol-3-yl)(oxo)acetate (2q)
Yellow solid; yield: 527 mg (67%); mp 89–90 °C.

IR (KBr): 813, 984, 1019, 1104, 1134, 1177, 1382, 1146, 1530, 1668, 1731, 1919, 2926 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (t, *J* = 7.0 Hz, 3 H), 2.37 (s, 3 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 7.28 (dd, *J* = 8.0, 4.4 Hz, 2 H, ArH), 7.39 (m, 2 H), 7.88 (d, *J* = 8.4 Hz, 2 H), 7.96 (dd, *J* = 1.6, 2.0 Hz, 1 H, ArH), 8.36 (dd, *J* = 2.0, 2.0 Hz, 1 H, ArH), 8.84 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 21.5, 62.5, 113.0, 116.9, 122.8, 125.1, 126.0, 127.2, 127.5, 130.2, 134.1, 134.3, 136.7, 146.1, 161.5, 178.6.

MS: *m/z* = 372 [M + 1], 394 [M + 23].

Anal. Calcd for $C_{19}H_{17}NO_5S$: C, 61.44; H, 4.61; N, 3.77. Found: C, 61.43; H, 4.60; N, 3.75.

Propane-1,3-diyl Bis[2-oxo-2-(het)aryl]acetates 11a, 11b, and 12; General Procedure
The dibromo ketone (1 g, 0.0035 mol) was dissolved in anhyd DMSO (6 mL) under argon. (The moisture content should be less than 0.5%, otherwise some keto acid will be formed in the reaction.) The soln was then slowly heated to 70–75 °C and maintained at this temperature for about 14–15 h. The mixture was then cooled to r.t., propane-1,3-diol (0.138 g, 0.0018 mol) was added, and the mixture was stirred for 1–2 h. The mixture was then diluted with H_2O (100 mL) and extracted with EtOAc (4 × 30 mL). The combined organic layer was washed successively with (3 × 30 mL) and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The pure product was isolated by column chromatography (hexane–EtOAc).

Propane-1,3-diyl Bis[oxo(phenyl)acetate] (11a)
Pink liquid; yield: 850 mg (70%).

IR (neat): 651, 908, 1195, 1451, 1598, 1692, 1740, 2254 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.28 (q, 2 H), 4.53 (t, *J* = 6.2 Hz, 4 H), 7.53 (t, *J* = 7.9 Hz, 4 H, ArH), 7.66 (t, *J* = 7.6 Hz, 2 H, ArH), 8.01 (d, *J* = 7.6 Hz, 4 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.7, 62.3, 128.9, 129.9, 132.2, 134.9, 163.5, 185.8.

MS: *m/z* = 341 [M + 1], 363 [M + Na].

Propane-1,3-diyl Bis[(4-methylphenyl)(oxo)acetate] (11b)
Pink liquid; yield: 860 mg (68%).

IR (neat): 756, 1022, 1172, 1216, 1305, 1606, 1682, 1737, 2927, 3021 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.27 (t, *J* = 6.2 Hz, 2 H), 2.44 (s, 6 H), 4.51 (t, *J* = 6.2 Hz, 4 H), 7.31 (d, *J* = 8 Hz, 4 H, ArH), 7.90 (d, *J* = 8 Hz, 4 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 27.7, 62.2, 129.6, 129.8, 130.1, 146.3, 163.7, 185.5.

MS: *m/z* = 369 [M + 1], 391 [M + Na].

Propane-1,3-diyl Bis[(1-tosyl-1*H*-indol-3-yl)(oxo)acetate] (12)
Yellow low-melting solid; yield: 770 mg (50%).

IR (neat): 1040, 1170, 1216, 1311, 1608, 1692, 1757, 2927, 3025 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.68 (m, 2 H,), 2.36 (s, 6 H), 4.58 (t, *J* = 6.0 Hz, 4 H), 7.27 (d, *J* = 4 Hz, 4 H, ArH), 7.35 (t, *J* = 7.6 Hz, 2 H, ArH), 7.40 (t, *J* = 7.4 Hz, 2 H ArH), 7.90 (d, *J* = 8.4 Hz, 4 H, ArH), 7.97 (d, *J* = 8.0 Hz, 2 H ArH), 8.29 (d, *J* = 7.6 Hz, 2 H, ArH), 8.88 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 27.6, 62.7, 113.1, 116.9, 122.9, 125.2, 126.1, 127.3, 127.6, 130.3, 134.2, 134.5, 136.9, 146.2, 161.4, 178.1.

MS: *m/z* = 727 [M + 1], 749 [M + Na].

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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References

(1) Li, L.-S.; Wu, Y.-L. *Tetrahedron Lett.* **2002**, *43*, 2427.
(2) (a) Patel, D. V.; Reilly, G. K.; Ryono, D. E.; Free, C. A.; Smith, S. A.; Petrillo, E. W. Jr. *J. Med. Chem.* **1993**, *36*, 2431. (b) O'Cain, T. D.; Rich, D. H. *J. Med. Chem.* **1992**, *35*, 451. (c) Iwanowicz, E. J.; Lin, J.; Roberts, D. G. M.; Michel, I. M.; Seiler, S. M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1607. (d) Angelastro, M. R.; Mehdi, S.; Burkhart, J. P.; Peet, N. P.; Bey, P. *J. Med. Chem.* **1990**, *33*, 11. (e) Yuan, W.; Wong, C. H.; Haeggstroem, J. Z.; Wetterholm, A.; Samuelsson, B. *J. Am. Chem. Soc.* **1992**, *114*, 6552. (f) Yuan, W.; Munoz, B.; Wong, C. H.; Haeggstroem, J. Z.; Wetterholm, A.; Samuelsson, B. *J. Med. Chem.* **1993**, *36*, 211. (g) Photis, J. M. *Tetrahedron Lett.* **1980**, *21*, 3539. (h) Valentine, D. Jr.; Scott, J. W. *Synthesis* **1978**, 329.
(3) Schulte, K.; Meinzinger, E. DE 949,521, **1956**; *Chem. Abstr.* **1958**, *52*, 19024.
(4) (a) Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron Lett.* **1996**, *42*, 13513. (b) Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron Lett.* **1995**, *36*, 7305.
(5) Izawa, Y.; Tomioka, H.; Natsume, M.; Beppu, S.; Tsuji, H. *J. Org. Chem.* **1980**, *45*, 4835.
(6) (a) Ozawa, V.; Kawasaki, N.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1985**, 567. (b) Hiroshi, D.; Sadao, D.; Kazuo, Z. JP 60-19750, **1985**; *Chem. Abstr.* **1985**, *103*, 5904c. (c) Sakakura, T.; Yamashita, H.; Kobayashi, T.; Hayashi, T.; Tanaka, M. *J. Org. Chem.* **1987**, *52*, 5733.
(7) Micetich, R. G. *Org. Prep. Proced. Int.* **1970**, *2*, 249.
(8) Photis, J. M. *Tetrahedron Lett.* **1980**, *21*, 3539.
(9) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.
(10) (a) Che, C.-M.; Yu, W.-Y.; Chan, P.-M.; Cheng, W.-C.; Peng, S.-M.; Lau, K.-C.; Li, W.-K. *J. Am. Chem. Soc.* **2000**, *122*, 11380. (b) Dayan, S.; Ben-David, I.; Rozen, S. *J. Org. Chem.* **2000**, *65*, 8816. (c) Walsh, C. J.; Mandal, B. K. *J. Org. Chem.* **1999**, *64*, 6102. (d) Präler, O. C.; Sauer, J. *Tetrahedron Lett.* **1998**, *39*, 8821. (e) Zibuck, R.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 237. (f) Torii, S.; Inokuchi, T.; Hirata, Y. *Synthesis* **1987**, 377. (g) Lee, D. G.; Lee, E. J.; Brown, K. C. *ACS Symp. Ser.* **1987**, *326*, 82. (h) Wolfe, S.; Ingold, C. F. *J. Am. Chem. Soc.* **1983**, *105*, 7755.
(11) Yamada, K.; Kato, M.; Iyoda, M.; Hirata, Y. *J. Chem. Soc., Chem. Commun.* **1973**, 499.
(12) Burkhart, J. P.; Peet, N. P.; Bey, P. *Tetrahedron Lett.* **1988**, *29*, 3433.
(13) Zhuang, J.; Wang, C.; Xie, F.; Zhang, W. *Tetrahedron* **2009**, *65*, 9797.
(14) Das, S.; Bhowmick, T.; Punniyamurthy, T.; Dey, D.; Nath, J.; Chaudhuri, M. K. *Tetrahedron Lett.* **2003**, *44*, 4915.
(15) (a) Shanmugapriya, D.; Shankar, R.; Satyanarayana, G.; Dahanukar, V. H.; Syam Kumar, U. K.; Vembu, N. *Synlett* **2008**, 2945. (b) Klingenberg, J. *Org. Synth. Coll. Vol. IV*; John Wiley & Sons: London, **1963**, 110. (c) Bigelow, L. A.; Hanslick, R. S. *Org. Synth. Coll. Vol. II*; John Wiley & Sons: London, **1943**, 244.
(16) Baer, E.; Kates, M. *J. Am. Chem. Soc.* **1945**, *47*, 1482.
(17) (a) Johnson, C. R.; Jones, M. P. *J. Org. Chem.* **1967**, *32*, 2014. (b) Johnson, C. R.; Rigau, J. J. *J. Am. Chem. Soc.* **1969**, *91*, 5398. (c) Khuddus, M. A.; Swern, D. *J. Am. Chem. Soc.* **1973**, *95*, 8393. (d) Zhang, J.; Saito, S.; Koizumi, T. *J. Org. Chem.* **1998**, *63*, 5265. (e) Smith, G.; Winstein, S. *Tetrahedron* **1958**, *3*, 317.
(18) Li, W.; Li, J.; Vincentis, D. D.; Mansour, T. S. *Tetrahedron Lett.* **2004**, *45*, 1071.
(19) Schaefer, J. P.; Corey, E. J. *J. Org. Chem.* **1959**, *24*, 1825.
(20) Sakakura, T.; Yamashita, H.; Kobayashi, T.; Hayashi, T.; Tanaka, M. *J. Org. Chem.* **1987**, *52*, 5733.
(21) Heaney, F.; Fenlon, J.; O'Mahony, C.; McArdle, P.; Cunningham, D. *Org. Biomol. Chem.* **2003**, *1*, 4302.
(22) Hu, S.; Neckers, D. C. *J. Org. Chem.* **1996**, *61*, 6407.
(23) Muller, A. J.; Nishiyama, K.; Griffin, G. W.; Ishikawa, K.; Gibson, D. M. *J. Org. Chem.* **1982**, *47*, 2342.
(24) Hjelmencrantz, A.; Berg, U. *J. Org. Chem.* **2002**, *67*, 3585.
(25) Domagala, J. M. *Tetrahedron Lett.* **1980**, *21*, 4997.
(26) Gross, H.; Freiberg, J. *Chem. Ber.* **1967**, *100*, 3777.
(27) Banerjee, S. K.; Shankar, R.; Sachdeva, O. M. P. *Z. Phys. Chem. (Leipzig)* **1986**, *267*, 931.
(28) Mallinger, A.; Le Gall, T.; Misokowski, C. *J. Org. Chem.* **2009**, *74*, 1124.
(29) (a) Fabbri, C.; Bietti, M.; Lanzalunga, O. *J. Org. Chem.* **2005**, *70*, 2720. (b) Raap, M. *Org. Prep. Proced. Int.* **1971**, *3*, 167. (c) Chrétien, A.; Chataigner, I.; L'Hélias, N.; Piettre, S. R. *J. Org. Chem.* **2003**, *68*, 7990.