Russian Chemical Bulletin, International Edition, Vol. 61, No. 9, pp. 1733—1735, September, 2012

Adamantylation of β-dicarbonyl compounds

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Reactions of adamantan-1-ol with β-dicarbonyl compounds in 1,2-dichloroethane in the presence of $In(OTf)_3$, $Ga(OTf)_3$, $Sc(OTf)_3$, or $Cu(OTf)_2$ give the corresponding adamantylated derivatives in 45—93% yields.

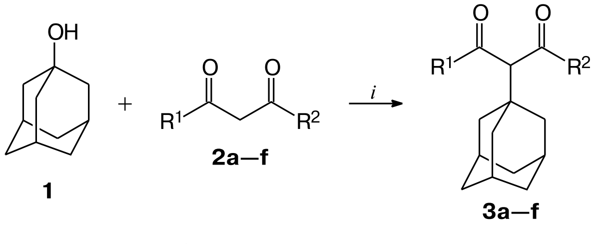
Key words: β-dicarbonyl compounds, adamantan-1-ol, adamantylation, Lewis acids, indium(III) triflate.

β-Dicarbonyl compounds take an important role in organic synthesis.[1] In the last few years, methods for benzylation,[2] allylation,[3] and especially propargylation[4] of β-dicarbonyl compounds with appropriate alcohols in the presence of Lewis acids have been under active development. This method is suitable for alcohols easily generating the corresponding carbocations.

We found it interesting to study the possibility of obtaining adamantylated β-dicarbonyl compounds because they can further be used as starting materials for the synthesis of biologically active heterocycles.[5] Known routes to such compounds involve reactions of cobalt(II), copper(II), and zinc β-diketonates with 1-bromoadamantane,[6] reactions of 1,3-dehydroadamantane with β-dicarbonyl compounds,[7] or acid-catalyzed alkylation of the latter with adamantan-1-ol in nitromethane[8,9] or trifluoroacetic acid.[10]

In the present work, we propose a simple and efficient procedure for adamantylation of various β-dicarbonyl compounds with adamantan-1-ol in the presence of such Lewis acids as $Sc(OTf)_3$, $Ga(OTf)_3$, $In(OTf)_3$, or $Cu(OTf)_2$ (Scheme 1).

Scheme 1



i. $M(OTf)_n$ (5 mol.%), $Cl(CH_2)_2Cl$.

2, **3:** $R^1 = R^2 = Me$ (**a**); $R^1 = R^2 = Ph$ (**b**); $R^1 = Me$, $R^2 = OEt$ (**c**);
$R^1 = Ph$, $R^2 = OEt$ (**d**); $R^1 = OEt$, $R^2 = OEt$ (**e**);
$R^1 + R^2 = —CH_2C(Me_2)CH_2—$ (**f**)

The reaction conditions were optimized for adamantylation of acetylacetone (**2a**) with an equimolar amount of adamantan-1-ol; the concentration of the catalyst was 5 mol.% (Table 1). The use of $FeCl_3$ on silica gel or ZnI_2 as catalysts failed: product **3a** was not detected even in trace amounts. Adamantylation in toluene did not afford the target product; instead, we obtained 1-(4-tolyl)adamantane in a nearly quantitative yield. The highest yield of compound **3a** was achieved in boiling 1,2-dichloroethane with indium(III) triflate as a catalyst. The use of scandium, gallium, and copper(II) triflates provided close yields.

Dibenzoylmethane (**2b**), ethyl acetoacetate (**2c**), and ethyl benzoylacetate (**2d**) were also efficiently adamantyl-

Table 1. Adamantylation of β-dicarbonyl compounds

β-Dicarbonyl compound	Catalyst	Solvent	Product	Yield (%)
2a	$In(OTf)_3$	CH_2Cl_2	**3a**	14
		1,2-DCE	**3a**	93
		1,2-DCE[a]	**3a**	0
		$MeNO_2$	**3a**	54
		$PhCH_3$	**3a**	0[b]
	$Ga(OTf)_3$	1,2-DCE	**3a**	89
	$Sc(OTf)_3$	1,2-DCE	**3a**	91
	$Cu(OTf)_2$	1,2-DCE	**3a**	90
	$FeCl_3/SiO_2$	1,2-DCE	**3a**	0
	ZnI_2	1,2-DCE	**3a**	0
2b	$In(OTf)_3$	1,2-DCE	**3b**	92
2c	$In(OTf)_3$	1,2-DCE	**3c**	83
2d	$In(OTf)_3$	1,2-DCE	**3d**	80
2e	$In(OTf)_3$	1,2-DCE	**3e**	45
2f	$In(OTf)_3$	1,2-DCE	**2f**	7
		$MeNO_2$	**2f**	85

[a] At ~20 °C.

[b] The reaction product is 1-(4-tolyl)adamantane.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 1717—1719, September, 2012.

ated in 1,2-dichloroethane with indium(III) triflate as a catalyst (see Table 1). The moderate yield of the target product in the adamantylation of diethyl malonate (**2e**) is explained by the low content of its enol form.[11] In contrast, adamantylation of dimedone (**2f**) was efficient only in nitromethane: the yield of compound **3f** was 85% against its 7% yield in 1,2-dichloroethane. This fact confirms that the reaction mechanism involves addition of the carbocation to an enolized β-dicarbonyl compound.[12]

The target products can easily be isolated by flash chromatography; the reaction mixtures should first be treated with dilute HCl and concentrated.

To sum up, we proposed a convenient atom economical preparation of adamantylated β-dicarbonyl compounds. The procedure meets "green chemistry" philosophy: the catalyst used in the reaction can be recovered without considerable loss in its activity[13] and water is the only secondary product.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECA400 instrument in $CDCl_3$ (Aldrich) with reference to the signals for the residual protons of the solvent. IR spectra were recorded on a Shimadzu IR Prestige instrument. The course of the reactions was monitored by GC-MS on a Shimadzu GC-2010 instrument equipped with a Shimadzu QP-2010 Plus mass-selective detector (Supelko SLB-5ms column (30 m), programmed heating from 60 to 265 °C at a rate of 30 deg min^{-1}).

β-Dicarbonyl compounds **2a**,**c**—**e** (Aldrich) were distilled *in vacuo* before use; adamantan-1-ol (**1**) (Aldrich) was used as purchased. Solvents were prepared using standard laboratory procedures.[14] Metal triflates were prepared as described earlier.[15]

3-(1-Adamantyl)pentane-2,4-dione (3a). A flask equipped with a reflux condenser was charged with 1,2-dichloroethane (10 mL) and $In(OTf)_3$ (0.185 g, 0.33 mmol). Then a solution of adamantan-1-ol (1 g, 6.57 mmol) and acetylacetone (**2a**) (0.65 g, 6.57 mmol) in 1,2-dichloroethane (25 mL) was added. The reaction mixture was refluxed with stirring for 2 h and transferred to a separatory funnel containing 2 *M* HCl (20 mL). The organic layer was separated and the product from the aqueous phase was extracted with $CHCl_3$ (3×10 mL). The combined organic extracts were concentrated on a rotary evaporator and the residue was sublimed *in vacuo*. Yield 1.32 g (86%), m.p. 53 °C. IR (KBr), ν/cm^{-1}: 2974, 2910, 2893, 2846 (C_{sp^3}—H), 1697, 1687 (C=O). ^{1}H NMR (399.78 MHz, $CDCl_3$), δ: 1.59—1.70 (m, 12 H, CH_2); 1.96 (m, 3 H, CH); 2.18 (s, 6 H, Me); 3.51 (s, 1 H, CH). ^{13}C NMR (100.52 MHz, $CDCl_3$), δ: 28.64 (CH), 33.21 (Me), 36.60 (CH_2), 40.45 (CH_2), 45.35 (C), 78.25 (CH), 204.61 (C=O). MS (EI, 70 eV), m/z (I_{rel} (%)): 234 $[M]^+$ (4), 192 (16), 135 (100).

2-(1-Adamantyl)-1,3-diphenylpropane-1,3-dione (3b) was obtained as described for compound **3a** from adamantan-1-ol (1 g, 6.57 mmol) and dibenzoylmethane (**2b**) (1.47 g, 6.57 mol) in the presence of $In(OTf)_3$ (0.185 g, 0.33 mmol). Compound **3b** was recrystallized from methanol. Yield 2.17 g (92%), m.p. 211 °C. IR (KBr), ν/cm^{-1}: 3064 (C_{sp^2}—H), 2906, 2891, 2843 (C_{sp^3}—H), 1697, 1653 (C=O), 1593, 1446 (C_{sp^2}—C_{sp^2}). ^{1}H NMR (399.78 MHz, $CDCl_3$), δ: 1.53—1.94 (m, 12 H, CH_2); 2.04 (m, 3 H, CH); 5.41 (s, 1 H, CH); 7.35—7.39 (m, 4 H); 7.47—7.51 (m, 2 H); 7.88—7.90 (m, 4 H). ^{13}C NMR (100.52 MHz, $CDCl_3$), δ: 29.13 (CH), 39.86 (CH_2), 40.30 (CH_2), 45.53 (C), 63.61 (CH), 128.47, 128.84, 133.19, 138.38 (Ph), 194.20 (C=O). MS (EI, 70 eV), m/z (I_{rel} (%)): 340 $[M]^+$ (21), 253 (21), 135 (6), 105 (100).

Ethyl 2-(1-adamantyl)-3-oxobutanoate (3c) was obtained as described for compound **3a** from adamantan-1-ol (1 g, 6.57 mmol) and ethyl acetoacetate (**2c**) (0.86 g, 6.57 mmol) in the presence of $In(OTf)_3$ (0.185 g, 0.33 mmol). Compound **3c** was isolated by flash chromatography with hexane—ethyl acetate (10 : 3) as an eluent. Yield 1.44 g (83%), yellowish oil. IR (thin film), ν/cm^{-1}: 2978, 2904, 2848 (C_{sp^3}—H), 1745, 1737, 1732, 1714, 1703 (C=O). ^{1}H NMR (399.78 MHz, $CDCl_3$), δ: 1.25 (t, 3 H, J = 7 Hz); 1.60—1.79 (m, 12 H, CH_2); 1.96 (m, 3 H, CH); 2.21 (s, 3 H); 3.17 (s, 1 H, CH); 4.12—4.17 (m, 2 H, CH_2). ^{13}C NMR (100.52 MHz, $CDCl_3$), δ: 14.28 (Me), 28.64 (CH), 32.21 (Me), 36.70 (CH_2), 37.05 (CH_2), 40.13 (C), 60.82 (CH), 69.95 (CH_2), 168.75 (C=O), 203.45 (C=O). MS (EI, 70 eV), m/z (I_{rel} (%)): 264 $[M]^+$ (2), 222 (10), 135 (100), 119 (8), 105 (5).

Ethyl 2-(1-adamantyl)-3-oxo-3-phenylpropanoate (3d) was obtained as described for compound **3a** from adamantan-1-ol (1 g, 6.57 mmol) and ethyl benzoylacetate (**2d**) (1.26 g, 6.57 mmol) in the presence of $In(OTf)_3$ (0.185 g, 0.33 mmol). Compound **3d** was isolated by flash chromatography with hexane—ethyl acetate (10 : 3) as an eluent. Yield 1.71 g (80%), yellowish oil. IR (thin film), ν/cm^{-1}: 3061 (C_{sp^2}—H), 2978, 2904, 2848 (C_{sp^3}—H), 1745, 1732, 1693, 1681 (C=O), 1595, 1446 (C_{sp^2}—C_{sp^2}). ^{1}H NMR (399.78 MHz, $CDCl_3$), δ: 1.18 (t, 3 H, J = 7 Hz); 1.62—1.87 (m, 12 H, CH_2); 1.96 (m, 3 H, CH); 4.09—4.14 (m, 2 H, CH_2); 4.20 (s, 1 H, CH); 7.43—7.47 (m, 2 H); 7.53—7.57 (m, 1 H); 7.94—7.96 (m, 2 H). ^{13}C NMR (100.52 MHz, $CDCl_3$), δ: 14.23 (Me), 28.72 (CH), 36.81 (CH_2), 37.55 (C), 40.38 (CH_2), 60.93 (CH), 62.85 (CH_2), 167.97 (C=O), 195.02 (C=O). MS (EI, 70 eV), m/z (I_{rel} (%)): 326 $[M]^+$ (8), 308 (7), 252 (17), 235 (23), 135 (14), 105 (100).

Diethyl (1-adamantyl)malonate (3e) was obtained as described for compound **3a** from adamantan-1-ol (1 g, 6.57 mmol) and diethyl malonate (**2e**) (1.26 g, 6.57 mmol) in the presence of $In(OTf)_3$ (0.185 g, 0.33 mmol). Compound **3e** was isolated by flash chromatography with hexane—ethyl acetate (10 : 3) as an eluent. Yield 0.86 g (45%), colorless oil. IR (thin film), ν/cm^{-1}: 2980, 2906, 2848 (C_{sp3}—H), 1755, 1728 (C=O). ^{1}H NMR (399.78 MHz, $CDCl_3$), δ: 1.20 (t, 6 H, J = 7 Hz); 1.57—1.72 (m, 12 H, CH_2); 1.92 (m, 3 H, CH); 3.01 (s, 1 H, CH); 4.08—4.15 (m, 4 H, CH_2). ^{13}C NMR (100.52 MHz, $CDCl_3$), δ: 14.21 (Me), 28.59 (CH), 35.95 (C), 36.72 (CH_2), 39.87 (CH_2), 60.74 (CH), 62.53 (CH_2), 167.82 (C=O). MS (EI, 70 eV), m/z (I_{rel} (%)): 294 $[M]^+$ (4), 220 (7), 135 (100), 105 (5).

2-(1-Adamantyl)-5,5-dimethylcyclohexane-1,3-dione (3f) was obtained as described for compound **3a** from adamantan-1-ol (1 g, 6.57 mmol) and dimedone (**2f**) (0.92 g, 6.57 mmol) in nitromethane (20 mL) in the presence of $In(OTf)_3$ (0.185 g, 0.33 mmol). Compound **3f** was isolated by flash chromatography with hexane—ethyl acetate (10 : 4) as an eluent. Yield 1.53 g (85%), colorless crystals, m.p. 160 °C (*cf.* Ref. 7c: m.p. 113 °C). IR (KBr), ν/cm^{-1}: 2956, 2945, 2906, 2881, 2848 (C_{sp3}—H), 1710, 1691 (C=O). ^{1}H NMR (399.78 MHz, $CDCl_3$), δ: 0.81 (s, 3 H, Me); 1.13 (s, 3 H, Me); 1.57—1.68 (m, 12 H, CH_2); 1.99 (m, 3 H, CH); 2.42—2.52 (m, 4 H, CH_2); 2.70 (s, 1 H, CH). ^{13}C NMR (100.52 MHz, $CDCl_3$), δ: 26.96 (Me), 29.03 (CH), 30.40 (C), 30.72 (Me), 36.39 (CH_2), 38.27 (C), 41.90 (CH_2), 56.00 (CH_2), 76.89 (CH), 207.98 (C=O). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 274 $[M]^+$ (6), 190 (4), 135 (100), 105 (3).

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Received July 9, 2012;
in revised form September 10, 2012