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Electron–rich Triarylbismuthines as Selective Condensation Reagent under Neutral Conditions. Condensation of Aliphatic Carboxylic Acids with Amines and Alcohols
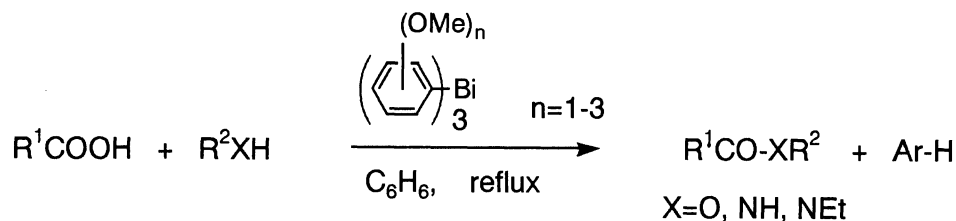
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On heating with amines or alcohols in the presence of tris(2–methoxy phenyl)– or tris(2,6–dimethoxyphenyl)bismuthine, carboxylic acids bearing α–hydrogen are readily converted into the corresponding amides or esters in good yields while those without α–hydrogen remain intact.
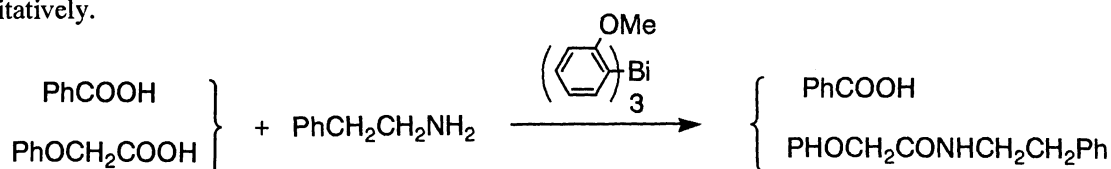
In recent years many mild methods have been developed for the condensation of carboxylic acids with amines and alcohols.[1] To our knowledge, however, no reagents appear to be available for such purpose, which can effectively differentiate carboxylic acids bearing α–hydrogen atom or atoms from those without α–hydrogen. We wish to report herein that carboxylic acid bearing α–hydrogen can be selectively condensed with amines and alcohols in the presence of a tris(methoxyphenyl)bismuthine to afford the corresponding amides and esters in good yields, while carboxylic acids without α–hydrogen remained intact under the same conditions.

$$R^1COOH + R^2XH \xrightarrow[\text{C}_6\text{H}_6, \text{ reflux}]{} R^1CO\text{-}XR^2 + Ar\text{-}H$$

(reagent: $\left(\text{(OMe)}_n\text{-aryl}\right)_3Bi$, $n=1\text{-}3$; $X=O, NH, NEt$)

A typical example is as follows: A benzene solution (3 cm^3) of phenoxyacetic acid (182 mg, 1.2 mmol), 2–phenylethylamine (145 mg, 1.2 mmol), and tris(2–methoxyphenyl)bismuthine (1) (212 mg, 0.4 mmol) was heated under reflux for 12 h. The precipitated inorganic solid was filtered off and the solvent together with anisole formed were evaporated under reduced pressure to leave the crude product, which was recrystallized from CH$_2$Cl$_2$/hexane to give N–(2–phenyl)ethylphenoxyacetamide (239 mg, 76%) as colorless crystals (Table 1, Run 2). When the reaction was performed without using solvent, the yield was improved to 88% after chromatographic separation (Run 6). Tris(4–methoxyphenyl)bismuthine (2) and tris(2,3,4–trimethoxyphenyl)bismuthine (3) showed similar efficiency for the reaction (Runs 3, 4). However, triphenylbismuthine had no effect and the starting materials were recovered completely unchanged (Run 1).[2] Among several triarylbismuthines examined tris(2,6–dimethoxyphenyl)bismuthine (4) was found to be the best to promote the condensation reactions; within reasonable reaction time (ca. 6 h) a high yield (94%) of the product was obtained (Run 5). In the absence of triarylbismuthine, no reaction took place.
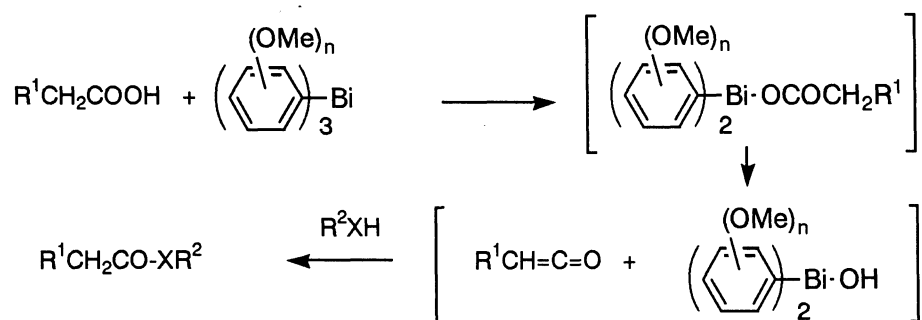
The condensation reaction proceeded not only with aliphatic amine but also with aromatic amine (Run 7, 8, and 10), and alcohols (Runs 14–17). Epoxide group remained intact under the reaction conditions employed; the reaction of epoxyoleic acid with 2-phenylethylamine in the presence of 4 afforded N–(2-phenylethyl)epoxyoleamide in 35% yield (Run 20).

A prominent feature of the present condensation reaction is that only the carboxylic acids bearing α-hydrogen can be condensed with nucleophiles; attempted reactions with tertiary (Run 12) and aromatic (Runs 11 and 13) carboxylic acids failed completely. The unique selectivity of our reaction was demonstrated by a competition experiment: Heating of benzoic acid (1 mmol), phenoxyacetic acid (1 mmol), 2-phenylethylamine (1 mmol), and 1 (1 mmol) in benzene for 21 h followed by acidic work up afforded only N–(2-phenylethyl)phenoxyacetamide (> 95%) as the condensation product and benzoic acid was recovered almost quantitatively.

$$PhCOOH \brace PhOCH_2COOH \quad + \quad PhCH_2CH_2NH_2 \quad \xrightarrow{\text{(o-MeOC}_6H_4\text{)}_3Bi} \quad \left\{ \begin{array}{l} PhCOOH \\ PHOCH_2CONHCH_2CH_2Ph \end{array} \right.$$

Selectivity for the acylation of amino group versus hydroxyl group was also satisfactory: When aminoalcohols were reacted with phenoxyacetic acid in the presence of 4, only the amino acylated products were obtained and the hydroxyl group remained intact (Run 18, 19). However, the reaction could not differentiate primary alcohols from secondary ones; the acylation of butan–1,2–diol with phenoxyacetic acid under the same reaction conditions afforded a mixture of 1–acylated (40%), 2–acylated (19%), and diacylated (8%) products (Run 21).

Reese and coworkers reported the acetylation of amines and alcohols by triacetoxybismuthine at high temperatures (ca. 180 °C).[3] Although acyloxybismuth compound might be formed to some extent, the direct acylation of amines or alcohols by such acyloxybismuth species is less probable in view of mild conditions used here. The reaction mechanism is not clear at present, but a tentative pathway involving the in situ generation of ketene as a possible intermediate is suggested below;

$$R^1CH_2COOH \quad + \quad (\text{C}_6H_4(\text{OMe})_n)_3Bi \quad \longrightarrow \quad \left[(\text{C}_6H_4(\text{OMe})_n)_2Bi\text{-}OCOCH_2R^1 \right]$$

$$R^1CH_2CO\text{-}XR^2 \quad \xleftarrow{R^2XH} \quad \left[R^1CH=C=O \quad + \quad (\text{C}_6H_4(\text{OMe})_n)_2Bi\text{-}OH \right]$$

The present reaction provides a selective and convenient method for the amide and ester formation from aliphatic carboxylic acids bearing α–hydrogen under completely neutral conditions. The procedure is straightforward; simple heating of the starting materials followed by filtration and evaporation of the solvent together with the accompanying aromatic ether gives the condensation product almost in pure form in moderate to good yields.

Table 1.   Transformation of Carboxylic Acids to Amides and Esters[4, a]

$$R^1COOH \quad + \quad R^2XH \quad \xrightarrow{\text{1/3 Ar}_3\text{Bi}} \quad R^1CO\text{-}XR^2 \quad +Ar\text{-}H$$

Run	R^1	R^2	X	Ar	Solv.	Time h	$R^1CO\text{-}XR^2$ Yield[b] %	$R^1CO\text{-}XR^2$ Mp $\theta m/°C$
1	$PhOCH_2$-	$PhCH_2CH_2$-	NH	Ph	C_6H_6	12	$0^{c)}$	-----
2	$PhOCH_2$-	$PhCH_2CH_2$-	NH	2-MeOC_6H_4	C_6H_6	12	78	76–77
3	$PhOCH_2$-	$PhCH_2CH_2$-	NH	4-MeOC_6H_4	C_6H_6	12	76	76–77
4	$PhOCH_2$-	$PhCH_2CH_2$-	NH	$2,3,4\text{-(MeO)}_2C_6H_2$	C_6H_6	12	76	76–77
5	$PhOCH_2$-	$PhCH_2CH_2$-	NH	$2,6\text{-(MeO)}_2C_6H_3$	C_6H_6	6	94	76–77
6	$PhOCH_2$-	$PhCH_2CH_2$-	NH	2-MeOC_6H_4	$neat^{d)}$	12	88	76–77
7	$PhOCH_2$-	Ph-	NH	2-MeOC_6H_4	C_6H_6	12	56	104–106
8	$PhOCH_2$-	Ph-	NH	$2,3,4\text{-(MeO)}_3C_6H_2$	C_6H_6	20	58	104–106
9	$n\text{-C}_7H_{15}$-	$PhCH_2CH_2$-	NH	2-MeOC_6H_4	C_6H_6	12	61	59–61
10	$n\text{-C}_7H_{15}$-	Ph-	NH	2-MeOC_6H_4	C_6H_6	12	44	55–57
11	Ph-	$PhCH_2CH_2$-	NH	2-MeOC_6H_4	C_6H_6	12	$0^{c)}$	-----
12	t-Bu-	$PhCH_2CH_2$-	NH	2-MeOC_6H_4	C_6H_6	12	$0^{c)}$	-----
13	$Mes^{e)}$-	$PhCH_2CH_2$-	NH	2-MeOC_6H_4	C_6H_6	12	$0^{c)}$	-----
14	$PhOCH_2$-	Et-	O	2-MeOC_6H_4	C_6H_6	12	75	oil
15	$PhOCH_2$-	Et-	O	$2,6\text{-(MeO)}_2C_6H_3$	C_6H_6	12	37	oil
16	$PhOCH_2$-	$PhCH_2$-	O	2-MeOC_6H_4	C_6H_6	12	73	oil
17	$n\text{-C}_7H_{15}$-	$PhCH_2$-	O	2-MeOC_6H_4	C_6H_6	12	86	oil
18	$PhOCH_2$-	$HO(CH_2)_2$-	NH	$2,6\text{-(MeO)}_2C_6H_3$	C_6H_6	12	65	52–54
19	$PhOCH_2$-	$HO(CH_2)_2$-	NEt	$2,6\text{-(MeO)}_2C_6H_3$	C_6H_6	12	43	oil
20	$epoxyOL^{f)}$	$PhCH_2CH_2$-	NH	$2,6\text{-(MeO)}_2C_6H_3$	C_6H_6	12	35	65–67
21	$PhOCH_2$-	$EtCH(OH)CH_2$-	O	2-MeOC_6H_4	C_6H_6	12	$40^{g)}$	oil

a) Reactions were performed at reflux temperature under a nitrogen atmosphere.   Products were identified by direct comparison with authentic samples.   b) Isolated yields, not optimized. c) Starting materials were recovered.   d) Bath temperature was 90 °C.   e) Mes = 2,4,6-trimethylphenyl.   f) Epoxyoleic acid.   g) Accompanied by 19% of 2-acylated product and 8% of 1,2-diacylated product.

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4) Spectral and analytical data of some representative products are as follows: N–(2–Phenylethyl)phenoxy acetamide; colorless crystals, mp 76–77 °C. ^{1}H NMR (CDCl$_3$) δ = 2.81 (t, J=6 Hz, 2H), 3.61 (dt, J=6, 6 Hz, 2H), 4.44 (s, 2H), 6.45–7.46 (m, 10H), and 8.06 (bs, 1H). IR (KBr) 3325, 1655, 1595, and 1540 cm^{-1}. Found: C, 75.63; H, 6.79; N, 5.73%. Calcd for C$_{16}$H$_{17}$NO$_2$: C, 75.27; H, 6.71; N, 5.49%. N–Phenylphenoxyacetamide; colorless crystals, mp 104–106 °C (lit. 101.5 °C)[5]. ^{1}H NMR (CDCl$_3$) δ = 4.62 (s, 2H), 6.95–7.55 (m, 10H), and 8.32 (bs, 1H). IR (KBr) 3180, 1660, 1598, and 1555 cm^{-1}. Found: C, 73.92; H, 5.75; N, 6.11%. Calcd for C$_{14}$H$_{13}$NO$_2$: C, 73.99; H, 5.77; N, 6.16%. N–(2–Phenylethyl)octanamide; colorless crystals, mp 59–61 °C. ^{1}H NMR (CDCl$_3$) δ = 0.85–0.90 (m, 3H), 1.26–1.71 (m, 10H), 2.11 (t, J=7 Hz, 2H), 2.81 (t, J=6 Hz, 2H), 3.52 (dt, J=6, 6 Hz, 2H), 5.44 (bs, 1H), and 7.18–7.34 (m, 5H). IR (KBr) 3275, 2895, 1630, and 1535 cm^{-1}. Found: C, 77.39; H, 10.16; N, 5.69%. Calcd for C$_{16}$H$_{25}$NO: C, 77.68; H, 10.19; N, 5.66%. N–Phenyloctanamide; colorless crystals, mp 55–57 °C (lit. 57 °C).[6] ^{1}H NMR (CDCl$_3$) δ = 0.88 (t, J=6 Hz, 3H), 1.29–2.17 (m, 10H), 2.35 (t, J=6 Hz, 2H), 7.05–7.59 (m, 5H), and 7.82 (bs, 1H). IR (KBr) 3295, 2910, 1655, and 1595 cm^{-1}. N–(2–Hydroxyethyl)phenoxyacetamide; colorless crystals, mp 52–54 °C. ^{1}H NMR (CDCl$_3$) δ = 3.03–3.86 (m, 6H), 4.46 (s, 2H), and 6.83–7.32 (m, 5H). IR(NaCl) 3350, 2920, 1650, and 1590 cm^{-1}. Found: C, 61.44; H, 6.58; N, 7.10%. Calcd for C$_{10}$H$_{13}$NO$_3$: C, 61.53; H, 6.71; N, 7.17%. N–Ethyl(2–hydroxyethyl)phenoxyacetamide; oil. ^{1}H NMR (CDCl$_3$) δ = 1.19 (t, J=7 Hz, 3H), 3.24–3.66 (m, 7H), 4.70 (s, 2H), and 6.87–7.40 (m, 5H). IR (NaCl) 3350, 2930, 1645, and 1595 cm^{-1}. N–(2–Phenylethyl)–9,10–epoxyoctadecanamide; colorless crystals, mp 65–67 °C. ^{1}H NMR (CDCl$_3$) δ = 0.86–0.91 (m, 3H), 1.27–1.61 (m, 26H), 2.11 (t, J=7 Hz, 2H), 2.84 (t, J=7 Hz, 2H), 2.89 (bs, 2H), 3.52 (q, J=7 Hz, 2H), 5.41 (bs, 1H), and 7.18–7.34 (m, 5H). IR (KBr) 3300, 2910, 1640, and 1550 cm^{-1}. MS m/z (rel intensity) 402 (M$^+$, 0.8), 383 (5), 292 (8), 274 (13), 176 (15), 163 (23), 155 (8), 122 (24), 105 (37), and 104 (100).

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