Preparation of Secondary Alkyl and Benzylic Zinc Bromides Using Activated Zinc Metal Deposited on Titanium Oxide

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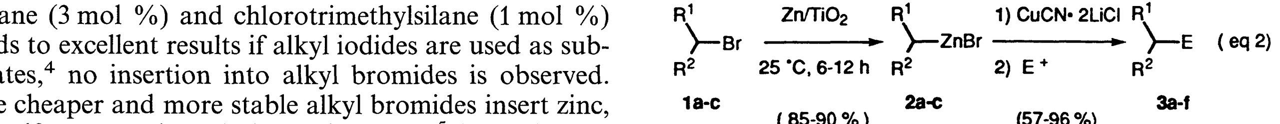
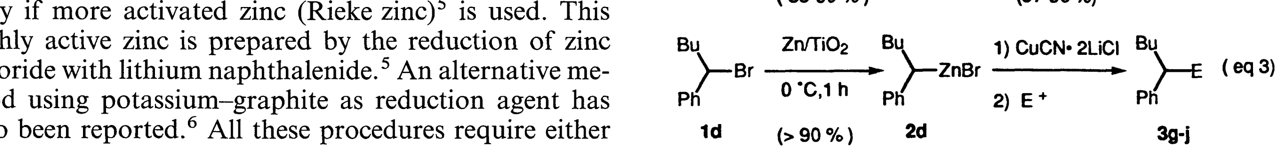
Sodium dispersed on titanium oxide readily reduces zinc chloride leading to a highly active zinc powder which inserts into secondary alkyl and benzylic bromides under mild conditions, producing the corresponding zinc reagents in high yields. Compared to zinc dust, this activated zinc allows the preparation of secondary benzylic zinc bromides with significantly less Wurtz-coupling products.

Organozinc halides are useful organometallic intermediates in organic synthesis because of their high functional group tolerance.[1] They are prepared by the insertion of zinc metal into alkyl iodides.[2] The insertion rate strongly depends on the reaction conditions (solvent, concentration) and on the zinc activation.[3] Whereas zinc powder (− 325 mesh), activated successively with 1,2-dibromoethane (3 mol %) and chlorotrimethylsilane (1 mol %) leads to excellent results if alkyl iodides are used as substrates,[4] no insertion into alkyl bromides is observed. The cheaper and more stable alkyl bromides insert zinc, only if more activated zinc (Rieke zinc)[5] is used. This highly active zinc is prepared by the reduction of zinc chloride with lithium naphthalenide.[5] An alternative method using potassium–graphite as reduction agent has also been reported.[6] All these procedures require either the use of expensive reagents or costly experimental conditions. We report a simple and convenient method using a sodium dispersion on titanium oxide for preparing highly reactive zinc and its use for the preparation of secondary benzylic and alkylzinc bromides starting from the corresponding organic bromides. Sodium is a cheap and powerful reducing agent and it has been shown that its deposition on dry alumina furnishes a high-surface sodium catalyst which is effective for performing the isomerization of small olefins.[7] We envisioned that the reduction of zinc chloride with sodium on a solid support would lead to an activated zinc powder. Furthermore, interactions between the zinc powder and the support would avoid clustering, which is responsible for a lower activity. It was observed that a residual water content in the support had a detrimental effect. For this reason solid supports such as barium, tin or aluminum oxide, as well as silica, could not be used. Thermogravimetric analyses of a range of these commercially available oxides confirm the presence of significant amounts of water.[8] On the other hand, commercial titanium oxide is almost water free and constitutes the best support for our purpose. Thus, the addition of sodium (ca. 8 g/100 g TiO_2) to titanium dioxide[9] (dried at 150 °C for 2 hours) at 150 °C, produces a homogenous, gray powder after 15 min. Interestingly, this powder is not pyrophoric but its exposure to air and moisture results in a slow decomposition (2–3 min). After cooling, the addition of a THF solution of zinc chloride at 0 °C leads to a reactive zinc powder which is ready to use after 15 min of stirring (eq 1). Remarkably, the addition of a THF solution of a secondary alkyl bromide affords the corresponding organozinc reagent of type **2** in 85–90 % yield (25 °C, 6 h). After transmetalation with CuCN · 2 LiCl,[1] the resulting organocopper–zinc species reacts with several electrophiles (allylic halides,[1] acid chlorides,[1] nitroolefins[10]) affording the expected products **3** in satisfactory yields (eq 2; Table 1). Zinc dust which has been activated with 1,2-dibromoethane and chlorotrimethylsilane[1] does not react significantly under these conditions (only 23 % insertion is observed).

$$\mathrm{Na} \xrightarrow{\mathrm{TiO_2}} \mathrm{Na/TiO_2} \xrightarrow[0\ ^\circ\mathrm{C},\ 15\ \mathrm{min}]{\mathrm{ZnCl_2}} \mathrm{Zn/TiO_2} \qquad (\text{eq } 1)$$



(eq 2)



(eq 3)

1 and **2**	**a**	**b**	**c**	**d**
R^1	$-(CH_2)_5-$	$-(CH_2)_6-$	Me	Ph
R^2	-	-	C_6H_{13}	Bu

Whereas the preparation of secondary benzylic zinc bromides is possible by using regular zinc powder,[11] the formation of up to 20 % Wurtz-coupling products is always observed. By using the new activated zinc dispersed on titanium oxide, the secondary benzylic zinc bromide is formed reproducibly in over 90 % yield and with less than 1 % of the Wurtz-coupling side product (eq 3). After transmetalation with CuCN · 2 LiCl (− 20 °C, 5 min), a benzylic zinc–copper reagent is produced which reacts with electrophiles such as 3-iodo-2-cyclohexen-1-one,[12] nitrostyrene,[10] diethyl benzylidenemalonate[13] and tosyl cyanide[14] affording the desired products **3a–j** in good yields (Table 1).

In summary, we have shown that activated zinc deposited on titanium oxide can be conveniently prepared by reducing zinc chloride with sodium dispersed on titanium. This activated nonphyrophoric zinc powder allows the preparation of secondary alkylzinc bromides directly from the corresponding alkyl bromides under very mild conditions, a reaction which was only possible previously by using highly activated Rieke zinc.[5] Furthermore, the use of activated zinc on titanium oxide allows a unique high yielding preparation of secondary benzylic bromides without the formation of appreciable amounts of Wurtz-

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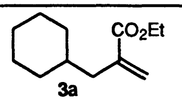
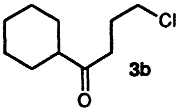
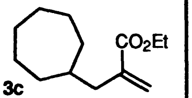
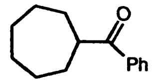
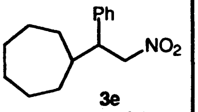
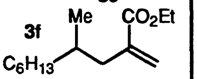
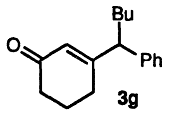
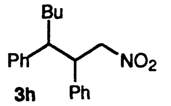
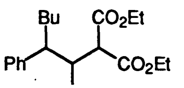
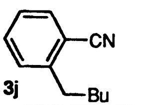
Table 1. Products **3a-j** Obtained by the Reaction of Secondary Organozinc Bromides with Electrophiles After Transmetalation with CuCN•2LiCl.

Zinc reagent	Electrophile	Product 3	Yield (%)[a]
2a	ethyl 2-(bromomethyl)acrylate	 **3a**	88
2a	4-chlorobutyryl chloride	 **3b**	93[b]
2b	ethyl 2-(bromomethyl)acrylate	 **3c**	96
2b	benzoyl chloride	 **3d**	72
2b	nitrostyrene	 **3e**	57
2c	ethyl 2-(bromomethyl)acrylate	 **3f**	95
2d	3-iodo-2-cyclohexen-1-one	 **3g**	83
2d	nitrostyrene	 **3h**	76
2d	diethyl benzylidenemalonate	 **3i**	71
2d	tosyl cyanide	 **3j**	78[c]

[a] All yields are isolated yields of analytically pure products. [b] Iriodin 121 (E. Merck - Darmstadt) was used as a solid support. [c] No transmetalation with CuCN•2LiCl was performed.

coupling products. We anticipated that the simple preparation of zinc on titanium oxide using cheap starting materials will lead to further synthetic applications since this cheap and powerful reducing agent may be used for the reduction of other metallic salts.[15]

All reactions were carried out under a positive pressure of Ar. Solvents (THF and Et_2O) were dried and freshly distilled from sodium/benzophenone. Flash chromatography with E. Merck silica gel (Kieselgel 60, 230–400 mesh) was used. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker WM-200 (200 MHz) or WM-300 (300 MHz) nuclear magnetic resonance spectrometer using TMS as an internal standard. Fourier transform infrared spectra (FT-IR) were recorded under N_2 on NaCl plates on a Nicolet 512 FT-IR spectrophotometer. Satisfactory microanalyses or HRMS were obtained for all compounds.

Titanium oxide was purchased from Bayer (Anatas). Cyclohexyl bromide **1a**, cycloheptyl bromide **1b**, 2-bromoheptane **1c** and 1-bromo-1-phenylpentane **1d** were purchased form Aldrich or Lancaster.

Preparation of Activated Zinc Deposited on Titanium Oxide.

A three-necked 100 mL flask equipped with an Ar inlet, a glass stopper and a septum cap was charged with TiO_2 (18 g, 380 mmol) and heated for 2 h at 150 °C under vacuum (0.1 mmHg). The glass stopper was replaced by a mechanical stirrer, the reaction flask was flushed with Ar and Na (1.50 g, 65 mmol) was added at once. Alternatively, the Na could be added at 25 °C to the dry TiO_2 (TiO_2 can be stored for several weeks after drying, as described above, without noticeable changes). The reaction mixture was vigorously stirred at 150 °C for 15 min and cooled to 0 °C leading to a gray homogenous powder. A solution of dry $ZnCl_2$ (4.57 g, 35.5 mmol) in THF (20 mL) was added with stirring. After 15 min, the activated Zn on TiO_2 was ready to use. Storage of the Zn powder leads to a loss of activity.

Preparation of a Secondary Alkylzinc Bromide; Typical Procedure: Ethyl 2-(Cyclohexylmethyl)acrylate (3a):

A THF solution (10 mL) of cyclohexyl bromide (1.71 g, 10.5 mmol) was rapidly added to the above prepared suspension of Zn on TiO_2 at 25 °C. The formation of cyclohexylzinc bromide was complete after 6 h, as indicated by GC analysis of hydrolyzed reaction aliquots. The gray solution of the alkylzinc reagent was filtered over a pad of Celite under Ar and added at 0 °C to a THF solution (10 mL) of CuCN (0.93 g, 10 mmol) and LiCl (0.90 g, 21 mmol). After 5 min of stirring, the reaction mixture was cooled to − 78 °C and a THF solution (2 mL) of ethyl 2-(bromomethyl)acrylate (1.43 g, 7.4 mmol) was added. The reaction mixture was allowed to warm to 0 °C, poured into a solution of sat. aq NH_4Cl (200 mL) after 5 min and extracted with Et_2O (3×100 mL). The combined organic phases were washed with brine (2×25 mL), dried ($MgSO_4$), filtered and concentrated. The residual oil was purified by flash chromatography (hexanes/Et_2O, 9 : 1) providing **3a** as a clear oil (1.27 g, 88 %).

Preparation of Secondary Benzylic Zinc Bromides; Typical Procedure: 3-(1-Phenylpentyl)-2-cyclohexen-1-one (3g):

A THF solution (10 mL) of 1-bromo-1-phenylpentane **1d** (2.37 g, 10.5 mmol) was slowly added (1 drop every 5 s) at 0 °C to the above prepared suspension of Zn on TiO_2. Formation of the benzylic zinc reagent was complete after 1 h, as indicated by GC analysis of hydrolyzed reaction aliquots. Less than 1 % of the homo-coupling product (5,6-diphenyldecane) was formed. A control experiment performed under the same conditions, but using Zn dust (− 325 mesh, Riedel-de Haen) activated by 1,2-dibromoethane (3 mol %) and TMSCl (1 mol %) produces up to 20 % of 5,6-diphenyldecane as shown by GC analysis. The solution of the Zn reagent was filtered under Ar over Celite providing a clear solution of the benzylic reagent. This was added at − 60 °C to a THF solution (10 mL) of CuCN (0.93 g, 10 mmol) and LiCl (0.90 g, 21 mmol). The reaction mixture was warmed to −20 °C, stirred for 5 min and cooled back down to − 78 °C. A THF solution (2 mL) of iodo-2-cyclohexen-1-one (1.63 g, 7.35 mmol) was added and the reaction mixture was warmed to − 30 °C and stirred for 8 h at this temperature. The reaction mixture was worked up, as above, leading to a crude oil which was purified by flash chromatography (hexanes/Et_2O, 20 : 1) giving the product **3g** as a clear oil (1.48 g, 6.1 mmol, 83 % yield.).

Analytical Data of Products 3a–j in Table 1

Ethyl 2-(Cyclohexylmethyl)acrylate (**3a**):

^1HNMR ($CDCl_3$, 300 MHz): $\delta = 6.07$ (d, $J = 1.7$ Hz, 1 H), 5.40–5.39 (m, 1 H), 4.12 (q, $J = 7.1$ Hz, 2 H), 2.11 (d, $J = 7.0$ Hz, 2 H), 1.64–1.56 (m, 6 H), 1.41–1.34 (m, 1 H), 1.23 (t, $J = 7.1$ Hz, 3 H), 1.18–1.04 (m, 2 H), 0.86–0.79 (m, 2 H).

^{13}CNMR ($CDCl_3$, 75 MHz): $\delta = 167.5$, 139.6, 125.3, 60.5, 39.9, 36.7, 33.1, 26.5, 26.2, 14.2.

IR (neat): $\nu = 2982$ (m), 2924 (vs), 2850 (s), 1717 (vs), 1628 (m), 1450 (s).

MS (EI, 70 eV): $m/z = 196$ (M^+, 13), 168 (3), 151 (7), 115 (20), 114 (100), 86 (77), 83 (35), 81 (11), 69 (10), 67 (15), 55 (50), 41 (30), 29 (18), 27 (10).

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4-Chloro-1-cyclohexyl-1-butanone **(3b)**:

Compound **3b** (1.3 g, 93.5 % yield) was obtained using cyclohexyl bromide (1.71 g, 10.5 mmol) and 4-chlorobutyl chloride (1.04 g, 7.4 mmol). The product was purified by chromatography (hexanes/Et_2O, 4:1).

^1H NMR ($CDCl_3$, 300 MHz): $\delta = 4.06$ (t, 2 H, $J = 6.0$ Hz), 3.48 (t, 2 H, $J = 6.3$ Hz), 2.02–1.92 (m, 1 H), 1.82–1.56 (m, 6 H), 1.36–1.04 (m, 6 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 212.6$, 50.8, 44.4, 36.9, 28.3, 26.2, 25.7, 25.5.

IR (neat): $\nu = 2925$ (vs), 2854 (s), 1702 (vs).

MS (EI): $m/z = 188$ (M^+, 6), 111 (30), 83 (100).

Ethyl 2-(Cycloheptylmethyl)acrylate **(3c)**:

Compound **3c** (510 mg, 97 % yield) was obtained using cycloheptyl bromide (620 mg, 3.5 mmol) and ethyl 2-(bromomethyl)acrylate (480 mg, 2.5 mmol). The Zn reagent was prepared within 12 h at 25 °C. The product **3c** was purified by flash chromatography (hexanes/Et_2O, 9:1).

^1H NMR ($CDCl_3$, 300 MHz): $\delta = 6.26$ (d, $J = 2$ Hz, 1 H), 5.39–5.38 (m, 1 H), 4.14 (q, $J = 7$ Hz, 2 H), 2.13 (d, $J = 6$ Hz, 2), 1.62–1.25 (m, 11 H), 1.23 (t, $J = 7$ Hz, 3 H), 0.80–0.78 (m, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 167.4$, 140.0, 125.1, 60.3, 40.2, 38.0, 34.1, 28.3, 26.2, 14.1.

IR (neat): $\nu = 2922$ (s), 2853 (m), 1717 (s), 1629 (m).

MS (EI): $m/z = 210$ (M^+, 2), 165 (3), 121 (2), 115 (15), 114 (85), 97 (25), 86 (38), 55 (100), 41 (26), 29 (21).

Cycloheptyl Phenyl Ketone **(3d)**:

Compound **3d** (1.03 g, 72 % yield) was obtained using cycloheptyl bromide (1.86 g, 10.5 mmol) and benzoyl chloride (1.04 g, 7.4 mmol). The Zn reagent was prepared within 12 h at 25 °C. The product **3d** was purified by flash chromatography (hexanes/Et_2O, 9:1).

^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.94$–7.91 (m, 2 H), 7.52–7.41 (m, 3 H), 3.47–3.38 (m, 1 H), 2.02–1.38 (m, 12 H).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 204.0$, 136.4, 132.5, 128.5, 128.1, 46.5, 30.7, 28.2, 26.7.

IR (neat): $\nu = 2922$ (s), 2856 (m), 1679 (vs).

MS (EI): $m/z = 203$ ($M + 1$, 2), 202 (M^+, 13), 120 (11), 105 (100), 77 (38), 55 (26), 51 (11), 41 (13), 18 (15).

2-Cycloheptyl-1-nitro-2-phenylethane **(3e)**:

Compound **3e** (1.03 g, 57 % yield) was obtained using cycloheptyl bromide (1.86 g, 10.5 mmol) and nitrostyrene (1.10 g, 7.4 mmol). The product **3e** was purified by flash chromatography (hexanes/Et_2O, 4:1).

^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.28$–7.19 (m, 3 H), 7.13–7.10 (m, 2 H), 4.74–4.56 (m, 3 H), 3.37–3.29 (m, 1 H), 1.79–1.72 (m, 2 H), 1.59–1.13 (m, 12 H).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 139.2$, 128.6, 128.3, 127.4, 79.0, 50.4, 42.2, 32.3, 31.4, 28.4, 28.0, 26.4, 26.3.

IR (neat): $\nu = 2925$ (s), 2856 (s), 1553 (vs), 1496 (m), 1455 (m), 1433 (m), 1380 (s).

MS (EI): $m/z =$ 200 (6), 129 (2), 117 (5), 105 (14), 104 (99), 97 (39), 91 (20), 55 (100), 43 (13), 41 (20), 32 (19), 29 (14), 28 (88).

Ethyl 2-(Methyloctyl)acrylate **(3f)**:

Compound **3f** (460 mg, 95 % yield) was obtained using 2-bromooctane (680 mg, 3.5 mmol) and ethyl 2-(bromomethyl)acrylate (480 mg, 2.5 mmol). The Zn reagent was prepared within 1 h at 50 °C. The product **3f** was purified by flash chromatography (hexanes/Et_2O, 9:1).

^1H NMR ($CDCl_3$, 300 MHz): $\delta = 6.13$ (d, $J = 1.7$ Hz, 1 H), 5.45 (dd, $J = 1.4$, 1.1 Hz, 1 H), 4.17 (q, $J = 7.1$ Hz, 2 H), 2.37–2.31 (m, 1 H), 2.04–1.97 (m, 1 H), 1.30–1.24 (m, 14 H), 0.88–0.81 (m, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 167.5$, 140.1, 125.3, 60.4, 39.7, 36.8, 31.9, 29.5, 26.9, 22.6, 1913, 14.2, 14.0.

IR (neat): $\nu = 2960$ (s), 2924 (s), 2853 (s), 1717 (s), 1627 (m).

MS (EI): $m/z = 226$ (M^+, 1), 181 (5), 115 (23), 114 (100), 86 (53), 71 (27), 69 (15), 57 (48), 55 (20), 43 (56), 41 (37), 29 (3), 27 (15).

3-(1-Phenylpentyl)-2-cyclohexen-1-one **(3g)**:

^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.28$–7.18 (m, 5 H), 6.04 (d, 1 H, $J = 1$ Hz), 3.30 (t, 1 H, $J = 7.6$ Hz), 2.32–2.27 (m, 2 H), 2.10 (t, 2 H, $J = 6.1$ Hz), 1.87–1.74 (m, 4 H), 1.29–1.14 (m, 4 H), 0.82 (t, 3 H, $J = 7.1$ Hz).

^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 200.2$, 168.0, 141.7, 128.7, 128.0, 127.0, 125.4, 120.9, 53.3, 37.6, 32.2, 29.9, 28.4, 22.9, 22.7, 14.0.

IR (neat): $\nu = 2956$ (s), 1673 (vs), 1622 (s).

MS (EI): $m/z = 242$ (M^+, 30), 185 (100), 129 (43), 91 (47).

1-Nitro-2,3-diphenylheptane **(3h)**:

Compound **3h** (1.66 g, 71 % yield) was obtained as a white solid (mp 93 °C) from 1-bromo-1-phenylpentane (2.37 g, 10.5 mmol) and nitrostyrene (1.10 g, 7.35 mmol). The product **3h** was purified by flash chromatography (hexanes/Et_2O, 20:1) and obtained as a mixture of 2 diastereomers in a ratio of 67:33.

^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.32$–6.77 (m, 10 H), 4.36 (dd, 1 H, $J_1 = 12.3$ Hz, $J_2 = 1.2$ Hz), 4.14 (dd, 1 H, $J_1 = 12.4$ Hz, $J_2 = 3.4$ Hz), 3.61–3.52 Hz (m, 1 H), 2.75–2.70 (m, 1 H), 1.74–1.54 (m, 1 H), 1.50–0.74 (m, 6 H), 0.62 (t, 3 H, $J = 7.2$ Hz).

^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 141.9$, 139.0, 129.1, 128.9, 128.1, 127.9, 127.7, 127.3, 80.2, 50.7, 49.4, 33.7, 29.4, 22.3, 13.7.

IR (neat): $\nu = 2954$ (s), 1698 (m), 1552 (vs).

MS (EI): $m/z = 297$ (M^+, 1), 251 (3), 147 (73), 91 (100).

Diethyl 1,2-Diphenylhexylmalonate **(3i)**:

Compound **3i** (2.06 g, 71 % yield) was obtained as a clear oil from 1-bromo-1-phenylpentane (2.37 g, 10.5 mmol) and diethyl benzylidenemalonate (1.82 g, 7.35 mmol). The product **3i** was purified by flash chromatography (hexenes/Et_2O, 20:1).

^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.12$–6.65 (m, 8 H), 4.35–4.23 (m, 2 H), 3.79–3.69 (m, 4 H), 2.97–2.93 (m, 1 H), 1.66–1.63 (m, 1 H), 1.58–1.44 (m, 1 H), 1.32 (t, 3 H, $J = 7.1$ Hz), 1.24–0.98 (m, 6 H), 0.86–0.72 (m, 6 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 168.8$, 167.6, 140.3, 137.4, 130.2, 129.8, 127.9, 127.6, 126.8, 126.5, 61.7, 61.1, 56.0, 50.0, 47.6, 33.3, 29.8, 22.7, 14.2, 14.0, 13.5.

IR (neat): $\nu = 2960$ (s), 1733 (vs), 1630 (m).

MS (EI): $m/z = 396$ (M^+, 1), 305 (5), 250 (34), 147 (54), 91 (100).

2-Pentylbenzonitrile **(3j)**:

Compound **3j** (0.99 g, 78 % yield) was obtained from TsCN (1.33 g, 7.35 mmol) and 1-bromo-1-phenylpentane (2.37 g, 10.5 mmol). The product **3j** was purified by flash chromatography (hexanes/Et_2O, 4:1).

^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.43$–7.13 (m, 4 H), 2.70 (t, 2 H, $J = 8.1$ Hz), 1.63–1.50 (m, 2 H), 1.27–1.21 (m, 4 H), 0.78 (t, 3 H, $J = 2.8$ Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 145.7$, 131.6, 188.4, 125.2, 117.1, 111.3, 34.9, 31.7, 29.9, 21.6, 12.9.

IR (neat): $\nu = 2958$ (s), 2224 (s), 1602 (m).

MS (EI): $m/z = 173$ (M^+, 5), 145 (31), 117 (100).

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