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An efficient and convenient aldol addition of acyldiazomethane with aldehydes promoted by MgI_2 etherate

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Abstract: The aldol addition of acyldiazomethane with aromatic aldehydes, vinyl aldehyde and aliphatic aldehydes was carried out efficiently in the presence of MgI_2 etherate and $^{i}Pr_2EtN$ (DIPEA) using untreated reagent-grade CH_2Cl_2 under atmospheric conditions in good to excellent yields. Iodide counterion and a non-coordinating reaction media (i.e. CH_2Cl_2) are among the critical factors for the unique reactivity of this reaction system.

Keywords: acyldiazomethane; aldehydes; aldol addition; MgI_2 etherate.

Introduction

α-Diazo carbonyl compounds are a potential source of amino alcohols and acids (Doyle et al., 1998). α-Diazo carbonyl compounds are generally prepared by the azido transfer reaction of carbonyl compounds (Moody and Morfitt, 1998; Yao and Wang, 2003). Recently, the synthesis of α-diazo carbonyl compounds has been widely explored, such as α-diazo-β-hydroxy esters which are involved in many reactions in organic chemistry. The most straightforward synthesis of α-diazo carbonyl compounds involves the condensation of aldehydes and acyldiazomethanes. This is generally carried out by using strong bases, such as butylithium (Schöllkopf et al., 1970), lithium diisopropylamide (Moody and Taylor, 1987), sodium hydride (NaH) (Jiang et al., 2001), potassium hydroxide (KOH) (Woolsey and Khalil, 1972), tert-BuOK (Sreedhar et al., 2005), tetrabutylammonium hydroxide (Varala et al., 2006), 1,8-diazabicyclo[5.4.0]undec-7-ene (Jiang and Wang, 2002), Mg/La mixed oxide (Kantham et al., 2007a,b), NAP-MgO (Kantham et al., 2007a,b) and Bu_2Mg (Trost et al., 2009, 2012). Also, some Lewis and Bronsted acids, such as Et_2Zn (Cui et al., 2011), Me_2Zn (Benfatti et al., 2009), PhCOOH (Krishna et al., 2011), $Ti(O^{i}Pr)_4$ (Wang et al., 2009a,b), $Zr(O^{t}Bu)_4$ (Yao and Wang, 2003) and $Sc(OTf)_3$ (Wang et al., 2009a,b) are utilized into this coupling as catalysts. However, some of these methods involve the use of very strong bases, expensive catalysts, prolonged reaction time and vigorous reaction conditions, which afford the low yields of the products. Moreover, the use of strong bases may not be compatible with certain functional groups in the substrates. From the viewpoints above, the development of less expensive, environmentally benign, and easily handled promoters for aldol reaction of acyldiazomethane with aldehydes to form α-diazo-β-hydroxy esters is still highly desirable.

Magnesium is an abundant, cheap and benign element which exists in nature, and many reactions using magnesium salts have been developed recently in organic synthesis (Zhang and Li, 2003). In our previous paper, we have demonstrated that MgI_2 etherate could efficiently catalyze Mukaiyama-type aldol reaction of aldehydes with trimethylsilyl enolates and allylation of aldehydes with allylstannane (Li and Zhang, 2002; Zhang, 2008). We have also found that MgI_2 etherate-promoted direct aldol addition of methyl ketone with aldehydes in the presence of Et_3N under mild reaction conditions (Liu et al., 2012). Herein, we wish to report an efficient and facile method for the synthesis of α-diazo-β-hydroxy esters by the coupling of aldehydes with acyldiazomethane promoted by $MgI_2 \cdot (Et_2O)_n$ in the presence of diisopropylethylamine (DIPEA) at room temperature under atmospheric conditions.

Results and discussion

At the onset of this work, we investigated a variety of conditions with a model reaction of benzaldehyde with ethyl diazoacetate (EDA) using MgI_2 etherate as promoter in the presence of DIPEA, and the results are summarized in Table 1. No product formation was observed by using only $MgI_2 \cdot (Et_2O)_n$ or DIPEA, respectively. The reaction

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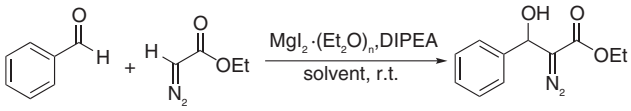
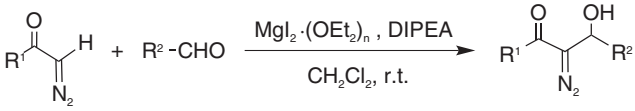
Table 1: Screening reaction conditions for the condensation of benzaldehyde with EDA[a].



Entry	MgI_2·$(Et_2O)_n$ (mol%)[b]	DIPEA (mol%)[b]	Solvent	Time (h)	Yield (%)[c]
1	15	200	CH_2Cl_2	8	16
2	30	200	CH_2Cl_2	8	31
3	50	200	CH_2Cl_2	3	46
4	60	200	CH_2Cl_2	3	59
5	70	200	CH_2Cl_2	2	71
6	80	200	CH_2Cl_2	1	82
7	100	200	CH_2Cl_2	0.35	96
8	100	100	CH_2Cl_2	1	85
9	100	300	CH_2Cl_2	0.25	94
10	100	200	$CHCl_3$	5	92
11	100	200	Toluene	4	87
12	100	200	THF	7	78
13	100	200	Et_2O	7	74
14	100	200	CH_3CN	12	60
15	100	200	DMSO	12	61
16	100	200	DMF	12	NR[d]
17	100	200	MeOH	12	NR

[a]To a solution of benzaldehyde (1.0 mmol) and EDA (1.2 mmol) in solvents was added $MgI_2 \cdot (Et_2O)_n$ and DIPEA at room temperature.
[b]Relative to the benzaldehyde.
[c]Yields after silica gel column chromatography purification.
[d]NR = No reaction.

Table 2: $MgI_2 \cdot (OEt_2)_n$-promoted aldol addition of acyldiazomethane with various aldehydes[a].



Entry	R^1	R^2	Time (min)	Product	Yield (%)[b]
1	OEt	C_6H_5-	20	**1a**	96
2	OEt	4-ClC_6H_4-	15	**1b**	97
3	OEt	4-FC_6H_4-	15	**1c**	96
4	OEt	4-BrC_6H_4-	15	**1d**	96
5	OEt	4-$NO_2C_6H_4$-	15	**1e**	99
6	OEt	4-$CF_3C_6H_4$-	15	**1f**	98
7	OEt	3,4-$F_2C_6H_3$-	15	**1g**	95
8	OEt	2-ClC_6H_4-	15	**1h**	94
9	OEt	3-$NO_2C_6H_4$-	15	**1i**	93
10	OEt	3-$MeOC_6H_4$-	15	**1j**	93
11	OEt	4-$MeOC_6H_4$-	30	**1k**	92
12	OEt	2-MeC_6H_4-	30	**1l**	93
13	OEt	3,4-$Me_2C_6H_3$-	30	**1m**	90
14	OEt	2-Thienyl-	15	**1n**	93
15	OEt	$C_6H_5CH=CH$-	15	**1o**	89
16	OEt	*i*-Pr-	20	**1p**	88
17	OEt	*t*-Bu-	20	**1q**	90
18	OEt	Cyclohexanone	60	–	NR[c]
19	C_6H_5-	C_6H_5-	30	**1r**	94
20	C_6H_5-	4-$MeOC_6H_4$-	45	**1s**	91
21	C_6H_5-	4-$NO_2C_6H_4$-	20	**1t**	98

[a]To a solution of aldehyde (1.0 mmol) and acyldiazomethane (1.2 mmol) in CH_2Cl_2 was added 1.0 mmol of $MgI_2 \cdot (Et_2O)_n$ and 2.0 mmol of DIPEA at room temperature.
[b]Yields after silica gel column chromatography purification.
[c]NR = No reaction.

stoichiometry was checked by varying the amounts of $MgI_2 \cdot (Et_2O)_n$. As shown in Table 1, the yields of ethyl 3-hydroxy-2-diazo-3-phenyl propionate are improved by increasing the amount of $MgI_2 \cdot (Et_2O)_n$ (Table 1, entries 2–7). 1.0 equivalent of $MgI_2 \cdot (Et_2O)_n$ was sufficient. In addition, the amount of DIPEA has also effects on the reaction conversion and yield. 2.0 equivalent of DIPEA was enough, although good yield was also afforded with 3.0 equivalent of DIPEA (Table 1, entries eight and nine). Of various untreated solvents screened, excellent yield was obtained in non-coordinating reaction media CH_2Cl_2, and good yields are afforded in $CHCl_3$ and toluene, respectively (Table 1, entries 10 and 11). Moderate yields of the product were isolated in tetrahydrofuran (THF) and Et_2O (Table 1, entries 12 and 13), while low yields were given in CH_3CN and dimethylsulfoxide (DMSO) (Table 1, entries 14 and 15). No reactions were carried out in dimethylformamide (DMF) and MeOH (Table 1, entries 16 and 17). To examine the halide anion effect, halogen analogs of MgI_2 etherate, $MgBr_2$ etherate and $MgCl_2$ etherate were compared under parallel reaction conditions (1.0 equivalent of promoters). $MgCl_2$ etherate and $MgBr_2$ etherate was almost inactive in terms of substrate conversion and yield.

With these optimal conditions in hand, we explored the scope and limitation of this simple process by the reaction of electronically and functionally diverse aldehydes under the same conditions. There is no need to exclude moisture and oxygen from the reaction system. The experimental results are summarized in Table 2. MgI_2 etherate-DIPEA could promote the direct aldol coupling of acyldiazomethane with various aldehydes in good to excellent yields in a short period. Interestingly enough, the nucleophilic addition of acyldiazomethane with aldehydes in the presence of MgI_2 etherate and DIPEA was processed efficiently without removal of diazo group. Moreover, the aromatic aldehydes bearing electron-donating and electron-withdrawing groups in the aromatic ring were reacted smoothly to afford the desired aldol adducts in good to excellent yields (Table 2, entries 2–14). Furthermore, we have observed the following

delicate electronic effects: (1) Aromatic aldehydes with an electron-withdrawing substituent (i.e. Cl, F and NO_2) reacted faster than benzaldehyde and provided the corresponding adducts in excellent yields (Table 2, entries 2–9). (2) Aromatic aldehydes with an electron-donating substituent (i.e. OMe, Me) afforded the corresponding adducts in lower yields than benzaldehyde (Table 2, entries 10–13). Seemingly, this reactivity of aromatic aldehydes is principally dependent on the inherent electrophilicity of the carbonyl group. Heteroaromatic aldehyde, such as 2-thiophenealdehyde, was a good substrate as well (Table 2, entry 14). Acid-sensitive aldehyde, such as cinnamaldehyde, reacted with EDA to afford the 1,2-adduct in good yield without any decomposition or polymerization under the present reaction conditions (Table 2, entry 15). Also, the aliphatic aldehydes with the bulkier substituents such as isopropyl and tert-butyl groups gave good yields (Table 2, entries 16 and 17). Gratifyingly, the reactivity of benzoyldiazomethane (R = Ph) toward the aromatic aldehydes bearing electron-withdrawing groups and electron-donating groups is similar compared to that of EDA under the identical condition (Table 2, entries 19–21), which afforded the desired products in excellent yields. In general, aromatic, heteroaromatic, and α,β-unsaturated aldehydes underwent the conversion efficiently in a short period, whereas aliphatic and aromatic ketones, such as cyclohexanone and acetophenone, with EDA did not yield any product even prolonging the reaction time in the presence of MgI_2 etherate and DIPEA.

In summary, we have demonstrated the unique reactivity of MgI_2 etherate in aldol coupling of aldehydes with acyldiazomethane. This magnesium-promoted aldol addition is mild, efficient and operationally simple. Iodide counterion and a non-coordinating reaction medium are critical factors for the unique reactivity of this reaction system. Further investigation on the reactivity of MgI_2 etherate in other C-C bond constructing reactions is ongoing in our laboratory.

Experimental section

General methods

For product purification by flash column chromatography, silica gel (200 ~ 300 mesh) and light petroleum ether (b.p. 60 ~ 90°C) were used. ^{1}H NMR and ^{13}C NMR were recorded with Bruker AVANCE III instrument at 500 MHz and trimethylsilyl was used as internal standard. High resolution mass spectrometry (electrospray ionization) [HRMS (ESI)] were determined on a Therm LCQ TM Deca XP plus spectrometer.

Typical procedure of MgI_2 etherate-promoted aldol reaction of aldehyde with acyldiazomethane

To a stirred mixture solution of benzaldehyde (105 mg, 1.0 mmol) and EDA (137 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) was added a freshly prepared MgI_2 etherate (Arkley et al., 1962) (1.0 mmol) at room temperature, followed by addition of DIPEA (258 mg, 2.0 mmol). The resulting reaction mixture was stirred at room temperature for 20 min and quenched with saturated aqueous Na_2SO_3. Extractive workup with ether and chromatographic purification of the crude product on silica gel gave the desired aldol adduct in 96% yield.

Ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (Varala et al., 2006): Yellow liquid. ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7.2 Hz, 3H), 3.26 (br s, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 5.93 (s, 1H), 7.28–7.45 (m, 5H).

Ethyl 3-(4-chlorophenyl)-2-diazo-3-hydroxypropanoate (Varala et al., 2006): Yellow liquid. ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3H), 3.69 (br s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 5.87 (s, 1H), 7.34–7.38 (m, 4 H).

Ethyl 2-diazo-3-(4-fluorophenyl)-3-hydroxypropanoate (Varala et al., 2006): Yellow liquid. ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3H), 3.52 (br s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 5.89 (s, 1H), 7.06–7.09 (m, 2H), 7.40–7.43 (m, 2H).

Ethyl 3-(4-bromophenyl)-2-diazo-3-hydroxypropanoate (Varala et al., 2006): Yellow liquid. ^{1}H NMR ($CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 3H), 3.40 (br s, 1 H), 4.27 (q, *J* = 7.1 Hz, 2H), 5.87 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.50–7.53 (m, 2H).

Ethyl 2-diazo-3-hydroxy-3-(4-nitrophenyl)propanoate (Varala et al., 2006): Yellow liquid. ^{1}H NMR ($CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3H), 3.90 (br s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 5.99 (s, 1H), 7.63 (d, *J* = 8.6 Hz, 2H), 8.21–8.24 (m, 2H).

Ethyl 2-diazo-3-hydroxy-3-(4-(trifluoromethyl)phenyl) propanoate (Hasegawa et al., 2006): Yellow solid. m.p. 52.3–53.1°C; ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3H), 3.65 (br s, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 5.96 (s, 1H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H).

Ethyl 2-diazo-3-(3,4-difluorophenyl)-3-hydroxypropanoate: Yellow liquid. FT-IR (KBr) (cm^{-1}): 3439, 2101, 1671, 1613, 1520, 1474, 1433, 1343, 1285, 1110, 1037, 787; ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3H), 3.70 (br s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 5.87 (s, 1H), 7.15–7.18 (m, 2H), 7.28–7.32 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 166.1, 151.3 (dd, *J* = 12.7 Hz, *J* = 25.4 Hz), 149.3 (dd, *J* = 12.7 Hz, *J* = 25.3 Hz), 136.3, 121.8 (dd, *J* = 3.6, 6.4 Hz), 117.6 (d, *J* = 17.4 Hz), 115.1 (d, *J* = 18.4), 67.7, 61.4, 14.4; HRMS (ESI): calcd. for $C_{11}H_{10}F_2N_2NaO_3$ $[M+Na]^+$ 279.0552; found 279.0552.

Ethyl 3-(2-chlorophenyl)-2-diazo-3-hydroxypropanoate (Trost et al., 2012): Yellow solid. ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3H), 3.89 (br s, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 6.13 (d, *J* = 3.7 Hz, 1H), 7.25–7.28 (m, 1H), 7.31–7.33 (m, 1H), 7.34–7.39 (m, 1H), 7.70–7.72 (m, 1H).

Ethyl 2-diazo-3-hydroxy-3-(3-nitrophenyl)propanoate (Kantham et al., 2007a,b): Yellow liquid. ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3H), 3.90 (br s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 6.00 (s, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 8.17 (dd, *J* = 1.6, 8.1 Hz, 1H), 8.33 (s, 1H).

Ethyl 2-diazo-3-hydroxy-3-(3-methoxyphenyl)propanoate (Trost et al., 2012): Yellow liquid. ^{1}H NMR ($CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3H), 3.65 (br s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 5.87 (s, 1H), 6.83–6.85 (m, 1H), 6.98 (s, 1H), 6.99 (s, 1H), 7.28 (dd, *J* = 7.5, 12.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 166.5, 159.9, 140.9, 129.8, 117.9, 113.8, 111.1, 68.4, 61.2, 55.2, 14.4.

Ethyl 2-diazo-3-hydroxy-3-(4-methoxyphenyl)propanoate (Varala et al., 2006): Yellow liquid. ^{1}H NMR ($CDCl_3$): δ = 1.33 (t, *J* = 7.3 Hz, 3H), 3.00 (br s, 1H), 3.83 (s, 3H), 4.29 (q, *J* = 7.3 Hz, 2H), 5.88 (s, 1H), 6.93 (dd, *J* = 2.0, 6.8 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H).

Ethyl 2-diazo-3-hydroxy-3-(o-tolyl)propanoate (Xiao et al., 2007): Yellow liquid. ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3H), 3.75 (br s, 1H), 3.84 (s, 3H), 4.25 (q, *J* = 7.1 Hz, 2H), 5.96 (s, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 7.00 (m, 1H), 7.31 (m, 1H), 7.47 (d, *J* = 7.3 Hz, 1H).

Ethyl 2-diazo-3-(3,4-dimethylphenyl)-3-hydroxypropanoate: Yellow liquid. FT-IR (KBr) (cm^{-1}): 3444, 2097, 1671, 1503, 1450, 1398, 1373, 1341, 1291, 1108, 1026, 780; ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 3H), 2.27 (s, 3H), 2.28 (s, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 5.86 (s, 1H), 7.15 (s, 2H), 7.20 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 166.4, 136.9, 136.6, 136.5, 129.9, 126.9, 123.0, 68.5, 61.0, 19.7, 19.3, 14.4; HRMS (ESI): calcd. for $C_{13}H_{16}N_2NaO_3$ $[M+Na]^+$ 271.1053; found 271.1054.

Ethyl 2-diazo-3-hydroxy-3-(thiophen-2-yl)propanoate (Kanemasa et al., 1999): Yellow liquid. ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7.2 Hz, 3H), 3.39 (br s, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 6.12 (s, 1H), 7.02 (dd, *J* = 3.5, 5.0 Hz, 1H), 7.03–7.07 (m, 1H), 7.31 (dd, *J* = 1.2, 5.0 Hz, 1H).

(E)-Ethyl 2-diazo-3-hydroxy-5-phenylpent-4-enoate (Varala et al., 2006): Yellow liquid. ^{1}H NMR ($CDCl_3$): δ = 1.32 (t, *J* = 7.2 Hz, 3H), 2.87 (br s, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 5.46 (s, 1H), 6.28 (dd, *J* = 5.6, 16.0 Hz, 1H), 6.82 (d, *J* = 15.6 Hz, 1H), 7.29–7.42 (m, 5H).

Ethyl 2-diazo-3-hydroxy-4-methylpentanoate (Arai et al., 2004): ^{1}H NMR ($CDCl_3$): δ = 0.94 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.85–1.92 (m, 1H), 2.79 (br s, 1H), 4.21–4.30 (m, 3H).

Ethyl 2-diazo-3-hydroxy-4,4-dimethylpentanoate (Hasegawa et al., 2006): Yellow liquid. ^{1}H NMR ($CDCl_3$): δ = 0.97 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H), 2.94 (br s, 1H), 4.19–4.23 (m, 3H).

2-Diazo-3-hydroxy-1,3-diphenylpropan-1-one (Jiang and Wang, 2002): Yellow liquid. ^{1}H NMR ($CDCl_3$): δ = 4.22 (br s, 1H), 6.22 (s, 1H), 7.33–7.36 (m, 1H), 7.40–7.44 (m, 4H), 7.49–7.53 (m, 3H), 7.62–7.63 (d, *J* = 7.3 Hz, 2H).

2-Diazo-3-hydroxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one: Yellow solid. m.p. 98–99°C; FT-IR (KBr) (cm^{-1}): 3425, 2067, 1598, 1569, 1513, 1444, 1349, 1236, 1173, 1037, 772, 702; ^{1}H NMR ($CDCl_3$): δ = 3.82 (s, 3H), 3.89 (s, 1H), 6.16 (s, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 7.40–7.45 (m, 4H), 7.50–7.53 (m, 1H), 7.62–7.63 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 189.2, 159.6, 137.3, 132.0, 131.7, 128.7, 127.3, 127.2, 114.2, 68.9, 55.3; HRMS (ESI): calcd. for $C_{16}H_{14}N_2NaO_3$ $[M+Na]^+$ 305.0897; found 305.0902.

2-Diazo-3-hydroxy-3-(4-nitrophenyl)-1-phenylpropan-1-one (Miyauchi et al., 1981): Yellow solid. m.p. 113–114°C; ^{1}H NMR ($CDCl_3$): δ = 4.17 (s, 1H), 6.31 (s, 1H), 7.45 (m, 2H), 7.53–7.56 (m, 1H), 7.60–7.62 (m, 2H), 7.69 (d, *J* = 8.7 Hz, 2H), 8.26 (d, *J* = 8.8 Hz, 2H).

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