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CH_2Cl_2 as reagent in the synthesis of methylene-bridged 3,3′-bis(oxazolidin-2-one) derivatives under ambient conditions†

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This paper describes a highly efficient and facile transformation of substituted oxazolidin-2-ones to methylene-bridged 3,3′-bis(oxazolidin-2-one) derivatives in a mixture solvent of CH_2Cl_2 (DCM) and *N*,*N*-dimethylformamide (DMF) in the presence of NaH at ambient temperature. Isotopic labeling experiments indicated that the C of the bridged methylene group was derived from CH_2Cl_2 instead of DMF and other unknown substances in the NaH reagent (60% dispersion in mineral oil).

Typically, inert DCM is chosen as a solvent for its versatility in a variety of organic applications. The activation of DCM has been studied because of an interest in the construction of methylene-bridged bisamines, which are usually used as various ligands,[1] N-heterocyclic carbenes.[2] DCM has been reported to react with aliphatic amines,[3–6] *i.e.* the nitrogen-containing heterocyclic compounds, such as imidazole,[2,7] pyrrolidine,[8] pyrrole,[9] pyrazole,[10] pyridine,[11] and 1,2,3-triazole,[12] to form the corresponding methylene-bridged compounds with moderate to high yields. However, due to their low reactivity, the reaction of oxazolidin-2-ones with DCM to form methylene-bridged bis(2-oxazolidinone) derivatives has not been realized yet.

2-Oxazolidinones have been widely utilized in asymmetric reactions, such as aldol condensation,[13] alkylation,[14] halogenation,[15] amination,[16] radical addition,[17] and Diels–Alder reactions,[18] and as intermediates for the asymmetric synthesis of bioactive compounds.[13c,19] Moreover, a relatively large number of naturally occurring and synthetic molecules with antibacterial, antiallergenic, immunosuppressants, or monoamine oxidase inhibition activities contain the amino alcohol functionality.[20] Recently, we designed a series of chiral compounds that can be prepared from the intermediate methylene-bridged 3,3′-bis((*S*)-4-benzyloxazolidin-2-one) (**2a**, Table 1) to evaluate their antitumor activity. For the preparation of the key intermediate **2a**, we first attempted to follow the reported methods,[7–12] which were successfully applied to prepare other methylene-bridged bis(N-heterocycle)s *via* the reactions of DCM with imidazole,[2,7] pyrrolidine,[8] pyrrole,[9] pyrazole,[10] pyridine,[11] and 1,2,3-triazole.[12] To our disappointment, these methods did not work to prepare **2a**. A few synthetic examples of methylene-bridged 3,3′-bis(oxazolidin-2-one) derivatives have been reported to date. Ingleby[21] reported an efficient approach to 3,3′-bis(oxazolidin-2-one) methanes *via* the reaction of oxazolidin-2-ones with paraformaldehyde in the presence of *p*-$MeC_6H_4SO_3H$ at 100 °C; Zinner[22] demonstrated two procedures to prepare bis(benzoxazolidinon-3-yl)methane by treating benzoxazolidinone with benzoxazolon-3-ylchloromethane and metal sodium in EtOH under refluxing, and with CH_2Br_2 catalyzed by KOH in EtOH in a water bath in yields of 60%, and 9%, respectively. Seebach[23] treated 4-isopropyl-5,5-diphenyloxazolidinone with BuLi, NaI and chloromethyl methyl sulfide in DME at 0 °C to obtain the dimer 3,3′-bis((*S*)-4-isopropyl-5,5-diphenyl-2-oxazolidinon-3-yl)methane as a side product in a yield of 13%. To the best of our knowledge, there is no detailed investigation on the synthesis of bis(2-oxazolidinon-3-yl) methanes, particularly under mild conditions. Herein, we report a mild and efficient approach to bis(2-oxazolidinon-3-yl) methanes by treating 2-oxazolones with NaH in mixture solvents of DCM and DMF under ambient temperature, in which DCM is disclosed as a C source.

During the course of our ongoing work on the synthesis of oxazolidinone derivatives, we performed a reaction of (*S*)-4-benzyloxazolidin-2-one (**1a**) with an alkynyl bromide mediated by NaH in DMF. The reaction was conducted by stirring a mixture of (*S*)-4-benzyloxazolidin-2-one and NaH in DMF for a certain time. Subsequently, the alkynyl bromide, which was dissolved in a small amount of DCM, was added to the mixture, and the resulting reaction mixture was then stirred for a certain

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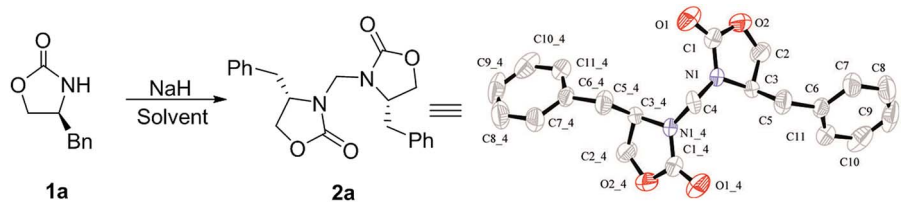
† Electronic supplementary information (ESI) available. CCDC [997065]. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra03248a

Table 1 Survey of reaction conditions[a]



Entry	Solvent	Time (h)	Yield[b] (%)
1	DCM	48	0
2	DMF	48	0
3	DCM/DMF (1 : 5)	33	46
4	DCM/DMF (1 : 2)	33	28
5	DCM/EtOAc (1 : 5)	48	0
6	DCM/THF (1 : 5)	48	0
7	DCM/Et_2O (1 : 5)	48	0
8	DCM/DMF (1 : 5)	27	61[c]
9	DCM/DMF (1 : 5)	9	98[d]

[a] Unless otherwise indicated, all the reactions were carried out with **1a** (1 mmol) and NaH (1 equiv.) in a solvent (3 mL) at ambient temperature (25–30 °C). [b] Isolated yield of **2a**. [c] 1.5 equiv. of NaH was used. [d] 1.8 equiv. of NaH was used.

time under ambient temperature. During the work-up of the reaction mixture, a small amount of an unexpected byproduct was accidentally separated, which was subsequently characterized as a methylene-bridged 3,3′-bis(oxazolidin-2-one) derivate **2a** by ^{1}H NMR, ^{13}C NMR, HRMS and X-ray diffraction (XRD) analysis. Because of the mild and basic condition, this unexpected finding is worthy of further evaluation as an alternative and efficient approach to 3,3′-bis(oxazolidin-2-one)methanes **2**. This finding suggested that DCM should be a reagent to form **2a**. Therefore, to optimize this reaction, a reaction of **1a** in pure DCM was first performed (Table 1, entry 1), to our surprise, no reaction occurred. This result raises doubt as to whether DMF would provide the bridged carbon of **2a** because DMF can also serve as a carbon source.[24] However, the reaction of **1a** in pure DMF also did not work (Table 1, entry 2). Subsequently, some mixed solvents, such as DCM/DMF, DCM/THF, and DCM/Et_2O, were screened (Table 1, entries 3–7), and the results indicated that both DCM and DMF are necessary for the reaction. Using this result, a detailed screening of the reaction conditions was conducted using the model compound of **1a**. After several attempts, the optimal condensation condition was developed, which is listed in Table 1 (entry 8): the reaction of **1a** (1.0 mmol) and NaH (1.8 equiv.) in DCM/DMF (v/v 1 : 5, 3 mL) under ambient conditions gave the desired product **2a** with an excellent yield of 98%.

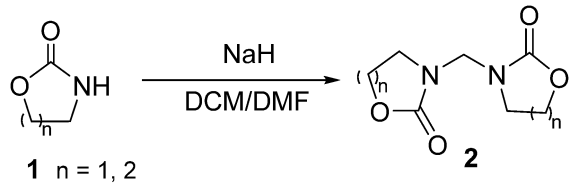
Under the optimized conditions, we explored the scope of the NaH-mediated reaction of DCM with various 2-oxazolidinones **1**, and the results are shown in Table 2. It was found that the reactions of 2-oxazolidinones (including 2-oxazolidinone **1f**, 4-substituted 2-oxazolidinones **1a–e**, and benzoxazolidinone **1g**) proceeded smoothly to afford the desired products in excellent yields. The reactivity of six-numbered cyclic carbamates, such as 1,3-oxazinan-2-one **1h** and 1,4-dihydro-2*H*-benzo[*d*][1,3]oxazin-2-one **1i**, was similar to oxazolidinones **1a-g** and gave the corresponding methylene-bridged products **2h** and **2i** in 89% and 84% yields, respectively. Note that the reactions could not proceed when acyclic carbamates **1j–l** were employed.

Considering that both the DCM and DMF can act as single carbon source,[2–12,24] a labeling experiment was performed (Scheme 1) to elucidate the carbon source of the bridged methylene. The result of the reaction with ^{13}C-labeled DCM indicated that the bridged methylene of compound **2** originated entirely from CH_2Cl_2 (99.1% incorporation) instead of DMF and other unknown substances from the NaH reagent (60% dispersion in mineral oil).[25]

Because DCM serves as a reagent in the transformation of **1** to **2**, we propose that the ability of DMF, a strong polar aprotic solvent, in playing important role in the transformation is a result of the polar solvent's solvating certain reactant intermediate species, thereby decreasing the intermediate energy relative to the starting material. A series of control experiments supported this proposal to some extent (Table 3). It was found that the reactions proceeded smoothly to afford the desired product **2a** in good to excellent yields, when different polar solvents, including strong polar DMSO, and other amides, such as *N,N*-diethylformamide, *N,N*-dimethylbutyramide, *N,N*-diethylbutyramide, and *N,N*-diethylbenzamide were employed. In DMSO (Table 3, entry 1), **1a** reacted with DCM in the presence of NaH at ambient conditions to give **2a** in a yield of 95%, although it took a longer time than in DMF (Table 2, entry 1).

To our delight, a reactant intermediate was detected by LC-MS in small amounts in the control experiment, in which *N,N*-diethylformamide was employed as a solvent (Table 3, entry 2). The presence of a 3-methylene-4-benzyl-2-oxazolidinonium nucleus was strongly indicated by observing the peak at *m*/*z* 190. After enrichment and purification, the intermediate was

Table 2 Synthesis of bis(oxazolidin-2-one) methane derivatives catalyzed by NaH[a]



1 n = 1, 2 2

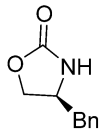
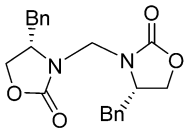
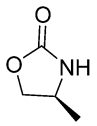
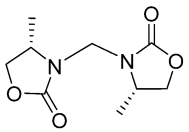
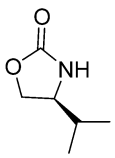
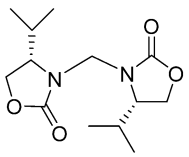
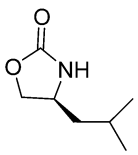
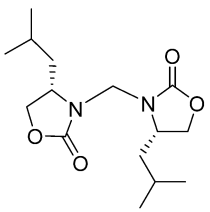
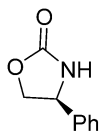
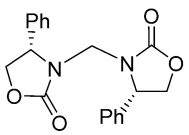
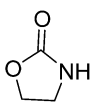
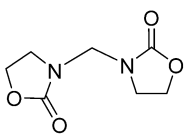
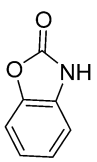
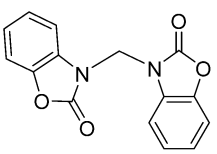
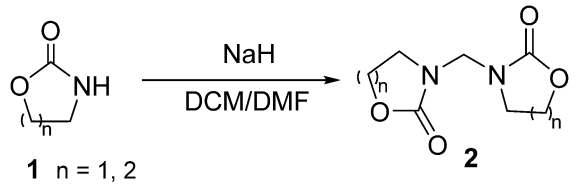
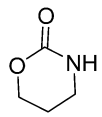
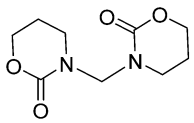
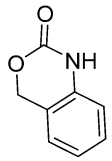
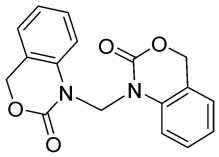
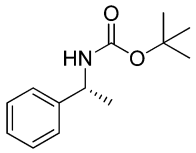
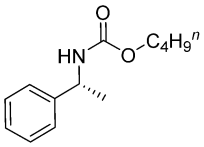
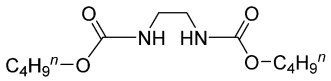
No.	Substance	Time (h)	Product	Yield[b] (%)
1	 1a	9	 2a	98
2	 1b	16	 2b	89
3	 1c	13	 2c	95
4	 1d	17	 2d	91
5	 1e	13	 2e	90
6	 1f	16	 2f	83
7	 1g	16	 2g	87

Table 2 (*Contd.*)

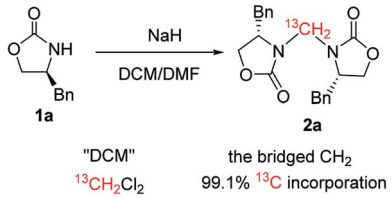


No.	Substance	Time (h)	Product	Yield[b] (%)
8	 **1h**	19	 **2h**	89
9	 **1i**	19	 **2i**	84
10	 **1j**	24	—	—[c]
11	 **1k**	24	—	—[c]
12	 **1l**	24	—	—[c]

[a] All the reactions were carried out with **1** (1 mmol) and NaH (1.8 equiv.) in DCM/solvent (1 : 5, 3 mL) at ambient temperature (25–30 °C). [b] Isolated yield of **2**. [c] The desired product was not observed.

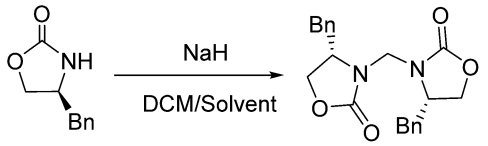
characterized as 3-chloromethyl-4-benzyl-2-oxazolidinone **A** (Scheme 2) by ^{1}H NMR and ^{13}C NMR. ^{1}H NMR in $CDCl_3$ of the intermediate showed a doublet at 4.86 ppm and 4.70 ppm, and ^{13}C NMR showed a resonance at 56.1 ppm. Both the sets of NMR data are consistent with **A** as the major species in the reaction solvent. Added 2-oxazolidinone **1a** to pure intermediate **A** which was obtained from the experiment (Table 3, entry 2), under standard condition showed that intermediate **A** fast loss the resonances at 4.86 ppm and 4.70 ppm with the formation of a broad singlet at 4.98 ppm in the ^{1}H NMR. This result indicated that the formation step of aminal **2** from the reaction intermediates is rapid.

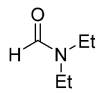
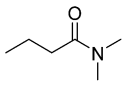
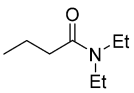
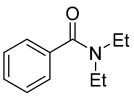
On the basis of the abovementioned results and literature,[26] a plausible mechanism for the reaction is illustrated in Scheme 2. Although the detailed mechanism of the present reaction is still not very clear, the following speculation is reasonable. Cyclic carbamate **1** undergoes *N*-alkylation with dichloromethane in the presence of NaH to chloromethyl analogue **A**. Then, the transient acyliminium intermediate **B** (from the balance between species **A** and **B**) rapidly undergoes a fast reaction with another nucleophile **1** present in the reaction to form the product **2**. The condensation of DCM with **1** is the rate-determining step. The strong polar solvent DMF probably plays an important role by stabilizing the formation of the



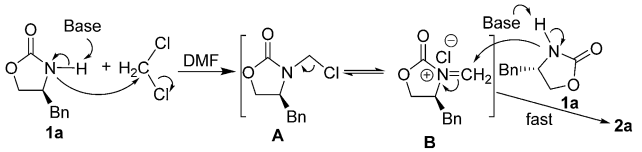
Scheme 1 Isotope incorporation experiment.

Table 3 Transformations using other polar aprotic solvents[a]



Entry	Solvent	Time (h)	Yield[b] (%)
1	DMSO	24	95
2		11	80
3		24	81[c]
4		10	85[c]
5		8[d]	68[c]

[a] Unless otherwise indicated, all the reactions were carried out with **1a** (1 mmol) and NaH (1.8 equiv.) in DCM/solvent (1 : 5, 3 mL) at ambient temperature (25–30 °C). [b] Isolated yield of **2a**. [c] Yield is determined by LC-MS. [d] The reaction was performed at 45 °C.



Scheme 2 The plausible mechanism.

acyliminium ion intermediate B, which makes DCM more available to react with the nucleophile **1**. However, why the reaction of acyclic carbamate does not work is not yet clear.

In conclusion, we have demonstrated a highly efficient and facile NaH-catalyzed condensation of DCM with cyclic carbamates to form corresponding aminal derivatives in a mixture solvent of DCM and DMF under ambient temperature. Isotopic labeling experiments indicated that the bridged methylene group was derived from DCM instead of DMF and other unknown substances in NaH reagent (60% dispersion in mineral oil). This protocol not only extends the application of DCM in organic synthesis but also provides an alternative method for preparing methylene-bridged bis(oxazolidin-2-one) derivatives. However, it is currently limited in scope to acyclic carbamates. Further studies to discover synthetic applications are ongoing.

Experimental section

General information

All the reagents were obtained from commercial sources and used without further purification. NaH (60% dispersion in mineral oil) was purchased from Aladdin Industrial Corporation. The reactions were monitored by TLC on silica gel 60 F_{254}. Column chromatography was performed on silica gel 60 (200–300 mesh). The ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. Chemical shifts were reported in ppm using tetramethylsilane (TMS) as an internal standard in $CDCl_3$ solutions, and coupling constants (J) are given in Hz. High-resolution mass spectra were measured on a MicroTOF mass spectrometer.

General procedure for the preparation of compound 2

A mixture of carbamate **1** (1.0 mmol) and NaH (1.8 equiv., 60% dispersion in mineral oil) in DMF/DCM (5/1, 3 mL) was stirred at room temperature for an appropriate duration, and the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with brine. The organic layer was separated and evaporated, the residue was added to H_2O (10 mL) and washed with CH_2Cl_2, and the combined organics were then concentrated *in vacuo*. The crude product was purified by silica-gel column chromatography and characterized.

3,3′-Bis((*S*)-4-benzyl-2-oxazolidinon-3-yl)methane (2a)

^1H NMR ($CDCl_3$, 400 MHz) δ 7.31–7.19 (m, 10H), 4.99 (s, 2H), 4.20–4.08 (m, 6H), 3.56–3.55 (d, J = 3.2 Hz, 2H), 2.67–2.61 (dd, J = 9.6 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 158.7, 135.0, 129.2, 129.0, 127.2, 67.7, 55.3, 48.4, 37.8. HRMS (ESI), m/z calcd. for $C_{21}H_{22}N_2NaO_4$ ($[M + Na]^+$) 389.1472, found: 389.1474.

3,3′-Bis((*S*)-4-methyl-2-oxazolidinon-3-yl)methane (2b)

^1H NMR ($CDCl_3$, 400 MHz) δ 4.78 (s, 2H), 4.35 (t, J = 8.0 Hz, 2H), 3.94–3.84 (m, 4H), 1.39 (d, J = 6.0 Hz, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 158.4, 69.4, 50.0, 47.7, 17.7. HRMS (ESI), m/z calcd. for $C_9H_{14}N_2NaO_4$ ($[M + Na]^+$) 237.0846, found: 237.0842.

3,3′-Bis((*S*)-4-isopropyl-2-oxazolidinon-3-yl)methane (2c)

^1H NMR ($CDCl_3$, 400 MHz) δ 4.77 (s, 2H), 4.26 (t, J = 9.2 Hz, 2H), 4.11 (dd, J = 6.0 Hz, J = 9.2 Hz, 2H), 3.85–3.81 (m, 2H), 2.46–2.39 (m, 2H), 0.89 (d, J = 7.2 Hz, 6H), 0.85 (d, J = 7.2 Hz, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 158.9, 63.3, 57.8, 48.1, 26.4, 17.8, 13.9.

HRMS (ESI), *m*/*z* calcd. for $C_{13}H_{22}N_2NaO_4$ ($[M + Na]^+$) 293.1472, found: 293.1475.

3,3′-Bis((*S*)-4-isobutyl-2-oxazolidinon-3-yl)methane (2d)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.77 (s, 2H), 4.44 (t, J = 8.4 Hz, 2H), 3.98 (q, J = 8.4 Hz, 2H), 3.88–3.81 (m, 2H), 2.03–1.96 (m, 2H), 1.58–1.57 (m, 2H), 1.40–1.33 (m, 2H), 0.97–0.92 (m, 12H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 158.4, 68.5, 52.6, 47.9, 40.5, 24.4, 23.7, 21.5. HRMS (ESI), *m*/*z* calcd. for $C_{15}H_{26}N_2NaO_4$ ($[M + Na]^+$) 321.1785, found: 321.1789.

3,3′-Bis((*S*)-4-phenzyl-2-oxazolidinon-3-yl)methane (2e)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.19 (m, 10H), 4.99 (s, 2H), 4.11–4.02 (m, 4H), 3.56–3.53 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 158.8, 135.0, 129.3, 129.0, 127.3, 67.7, 55.4, 48.4. HRMS (ESI), *m*/*z* calcd. for $C_{19}H_{18}N_2NaO_4$ ($[M + Na]^+$) 361.1159, found: 361.1160.

3,3′-Bis(2-oxazolidinon-3-yl)methane (2f)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.77 (s, 2H), 4.35 (t, J = 8.0 Hz, 2H), 3.68 (t, J = 8.0 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 158.6, 62.3, 53.5, 44.1. HRMS (ESI), *m*/*z* calcd. for $C_7H_{10}N_2NaO_4$ ($[M + Na]^+$) 209.0533, found: 209.0530.

3,3′-Bis(benz-2-oxazolidinon-3-yl)methane (2g)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (s, 2H), 7.26 (s, 2H), 7.21 (s, 4H), 5.89 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 154.4, 142.4, 128.9, 124.8, 123.9, 110.3, 110.2, 48.5, 29.7. HRMS (ESI), *m*/*z* calcd. for $C_{15}H_{10}N_2NaO_4$ ($[M + Na]^+$) 305.0533, found: 305.0534.

3,3′-bis(1,3-oxazinan-2-on-3-yl)methane (2h)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.90 (s, 2H), 4.20 (t, J = 5.2 Hz, 4H), 3.44 (t, J = 6.0 Hz, 4H), 1.98–1.92 (m, 4H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 154.3, 67.0, 62.1, 45.1, 22.1. HRMS (ESI), *m*/*z* calcd. for $C_9H_{14}N_2NaO_4$ ($[M + Na]^+$) 237.0846, found: 237.0848.

3,3′-Bis(1,4-dihydro-2*H*-benz[*d*][1,3]-oxazinan-2-on-3-yl)-methane (2i)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (s, 2H), 7.32 (s, 2H), 7.11 (s, 4H), 6.36 (s, 2H), 4.97 (s, 4H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 153.5, 134.9, 129.7, 124.9, 124.1, 121.6, 114.2, 67.2, 51.2. HRMS (ESI), *m*/*z* calcd. for $C_{17}H_{14}N_2NaO_4$ ($[M + Na]^+$) 333.0846, found: 333.0841.

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