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N-Heterocyclic Carbene-Catalyzed Michael Additions of 1,3-Dicarbonyl Compounds

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Abstract: A study of the organocatalytic activity of N-heterocyclic carbenes (NHCs) in the Michael addition of 1,3-dicarbonyl compounds has allowed us to identify 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) as an excellent catalyst for this transformation (up to 99% yield with a 2.5 mol% catalyst loading), and the reaction was found to be of broad scope. Two early applications of this unprecedented catalytic activity of NHCs are described, that is, the domino carbocyclization reactions of simple cyclic 1,3-dicarbonyl and malonic acid derivatives, which allow stereoselective access to bridged bicyclic compounds, and the stereoselective synthesis of cyclohexanols (or cyclohexene). Early mechanistic investigations are also reported.

Keywords: carbenes · dicarbonyl compounds · domino reactions · Michael addition · organocatalysis

Introduction

The Michael addition is one of the most important reactions for the creation of carbon–carbon bonds.[1] The two essential features of this reaction are its reliability for the still-challenging creation of all-carbon chiral quaternary centers, and its potency in anionic domino reactions[2] for the construction of several covalent chemical bonds in a single operation.[3] In the laboratory, these reactions are traditionally performed by simple treatment of a pronucleophile containing at least one enolizable or related position with a stoichiometric amount of base in the presence of an α,β-unsaturated carbonyl group or related stabilizing, electron-withdrawing group. With the advancements in the science of synthesis, several catalytic systems have been made available to perform efficient Michael addition reactions,[4] and in recent years, the Michael addition has become the cornerstone of many enantioselective organocatalytic processes.[5]

The discovery of new classes of catalyst for Michael addition reactions and related domino reactions is of considerable importance. In the past decade, catalysis by N-heterocyclic carbenes (NHCs) has received considerable attention,[6] and we have recently reported the serendipitous discovery of the excellent organocatalytic activity of *N,N*-diaryl-1,3-imidazol(in)-2-ylidenes in intramolecular Michael additions of 1,3-dicarbonyl compounds, and its application to the stereoselective synthesis of spiro compounds (Scheme 1).[7] Herein, we report our studies on the scope of the NHC-catalyzed Michael addition[8] of 1,3-dicarbonyl derivatives and related compounds, some applications to stereoselective organocatalytic domino carbocyclization reactions, and the results of early mechanistic investigations.

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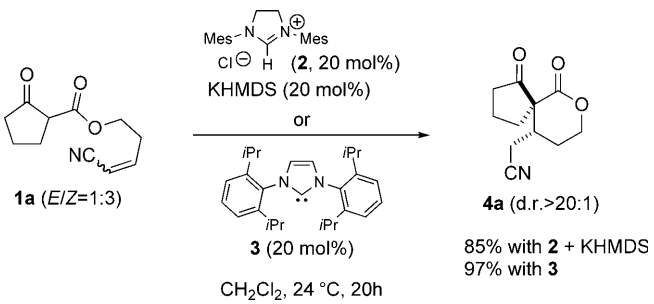
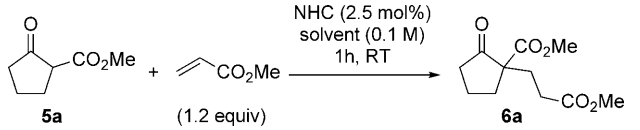


Scheme 1. The NHC-catalyzed Michael-based spirocyclization; HMDS = 1,1,1,3,3,3-hexamethyldisilazane; Mes = mesityl (2,4,6-trimethylphenyl).

Results and Discussion

The work started with a brief optimization study of the archetypal intermolecular NHC-catalyzed Michael addition of methyl 2-oxocyclopentanecarboxylate (**5a**) to methyl acrylate (Table 1), which indicated that IPr (**3**, 2.5 mol%) in di-

Table 1. Optimization study of the NHC-catalyzed Michael addition reaction.



5a (1.2 equiv) **6a**

	Solvent	NHC[a]	Yield [%][b]
1	CH_2Cl_2	IPr (**3**)	98
2	toluene	IPr (**3**)	42
3	THF	IPr (**3**)	68
4	Et_2O	IPr (**3**)	34
5	DMF	IPr (**3**)	96
6	CH_3CN	IPr (**3**)	71
7	$CHCl_3$	IPr (**3**)	47
8	MeOH	IPr (**3**)	6
9	pentane	IPr (**3**)	<5
10	CH_2Cl_2	IMes	95
11	CH_2Cl_2	SIMes	75

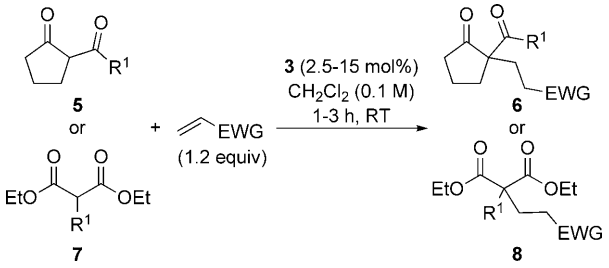
[a] IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; SIMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene. [b] Yields were determined by GC using naphthalene as the internal standard.

chloromethane or DMF gave the best results (Table 1, entries 1 and 5, respectively). Alternatively, IMes and SIMes (generated in situ by treatment of their respective chlorohydrates with KHMDS) were also efficient catalysts, leading to Michael adduct **6a** in 95 and 75% yield, respectively (Table 1, entries 10 and 11).[9] The scope of the reaction with various 1,3-dicarbonyl compounds and representative acrylic derivatives was examined next (Table 2). The reaction proved to be very general and proceeded in good to excellent yields, with either cyclic or acyclic pronucleophiles (**5** and **7**, respectively), such as 1,3-ketoesters, 1,3-diketones, 1,3-ketoamides, and 1,3-diesters (Table 2, entries 1–4, 5, 6, and 7–9, respectively) in combination with methyl acrylate, acrylamide, phenyl vinyl sulfone, acrylonitrile, methyl vinyl ketone, or acrolein (Table 2, entries 1 and 5, 2, 3, 4 and 6, 8 and 9, and 7, respectively).

Interestingly, for the reaction of cyclic 1,3-ketoester **5a** (as the pronucleophile) with acrolein, the reaction evolved through the known domino Michael–aldol sequence,[10] leading to bicyclo[3.2.1]octanol[11] **9a** as a 4:1 mixture of two diastereomers (Table 3, entry 1). This transformation proved equally efficient with 1,3-diketone **5c** and ketoamide **5d** (Table 3, entries 2 and 3, respectively), and was successfully extrapolated to the formation of the corresponding bicyclo-[3.3.1]nonanol (**11**)[12] from six-membered cyclic β-keto ester **10** (Table 3, entries 4 and 5).

Encouraged by these results, we examined the possibility of preparing cycloheptanol **13** from β-keto ester **5a**, croton-

Table 2. Scope of the NHC-catalyzed Michael addition reaction.

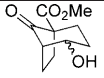
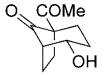
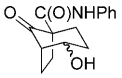
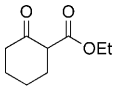
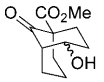


5 or **7** **6** or **8**

	Substrate	R^1	EWG	IPr (**3**) [mol%]	Product	Yield [%][a]
1	**5a**	OMe	CO_2Me	2.5	**6a**	96
2	**5a**	OMe	$CONH_2$	15	**6b**	82
3	**5a**	OMe	SO_2Ph	5	**6c**	97
4	**5b**	O*t*Bu	CN	10	**6d**	74
5	**5c**	Me	CO_2Me	5	**6e**	94
6	**5d**	NHPh	CN	5	**6f**	99
7	**7a**	Me	CHO	2.5	**8a**	99
8	**7a**	Me	COMe	2.5	**8b**	95
9[b]	**7b**	H	COMe	2.5	**8c**	78

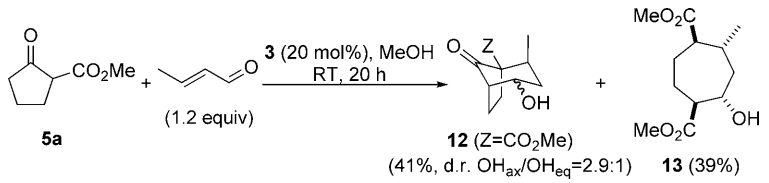
[a] Yields for isolated products obtained after silica gel flash column chromatography. [b] Reaction performed with 1.0 equivalent of the acrylic derivative.

Table 3. The NHC-catalyzed domino Michael–aldol reaction.

	Substrate	Conditions[a]	Product (Yield, d.r. OH_{ax}/OH_{eq})[b]
1	**5a**	**3** (20 mol%) CH_2Cl_2, 4 h	 **9a** (92%, d.r.=4:1)
2	**5c**	**3** (10 mol%) CH_2Cl_2, 20 h	 **9b** (66%, d.r.>1:20)
3	**5d**	**3** (5 mol%) CH_2Cl_2, 20 h	 **9c** (78%, d.r.=1:1)
4	 **10**	**3** (10 mol%) CH_2Cl_2, 20 h	 **11** (53%, d.r.=5:1)
5	**10**	**3** (10 mol%) MeOH, 20 h	**11** (90%, d.r. = 1:1)

[a] All reactions performed with acrolein (1.2 equiv) at room temperature; reaction times and catalyst loading were not optimized. [b] Yields for isolated products obtained after silica gel flash column chromatography; the diastereomeric ratios were determined from ^1H and ^{13}C NMR data of the crude material.

aldehyde, and methanol by following the Michael–aldol–retro-Dieckmann three-component domino reaction (MARDi cascade) previously developed in our laboratory (Scheme 2).[13] Thus, **5a** was allowed to react with crotonaldehyde in methanol in the presence of IPr (**3**; 20 mol%), which provided bicyclo[3.2.1]octanols **12** (41%, d.r. OH_{ax}/OH_{eq} = 2.9:1) and the expected cycloheptanol **13** (39%, only a single diastereomer was detected). In a separate experiment, the diastereomeric mixture of bicyclo[3.2.1]octanols **12** (d.r. = 2.9:1) was placed back under the reaction condi-



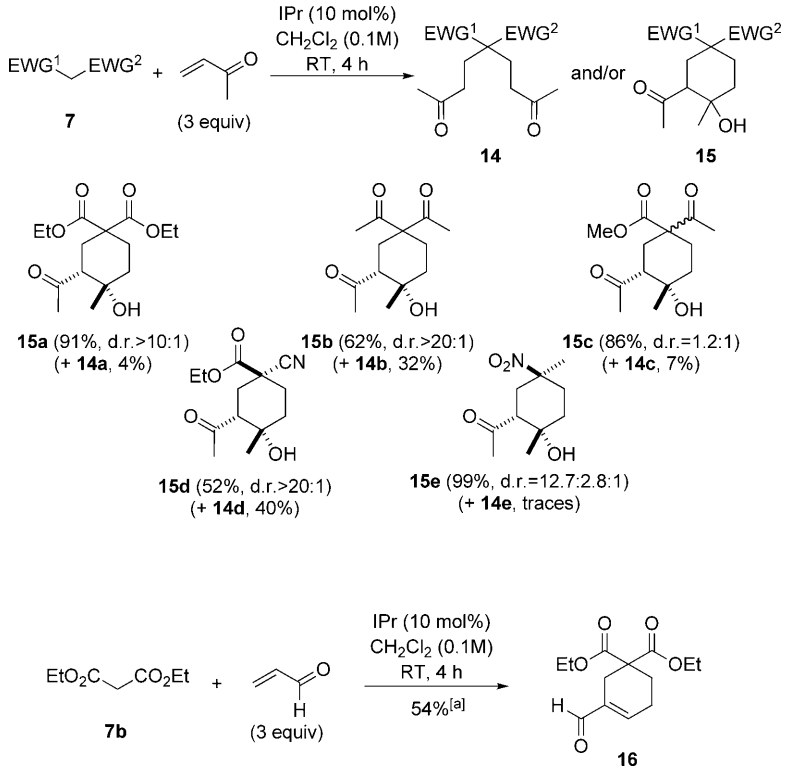
Scheme 2. The NHC-catalyzed three-component domino Michael–aldol–retro-Dieckmann reaction.

tions (MeOH, **3** (20 mol%)) without any detectable change in the diastereomeric ratio. These two experiments indicate, by comparison with the mechanism of the base-promoted MARDi cascade reaction,[13c] which involves a fully reversible Michael–aldol sequence and the selective retro-Dieckmann fragmentation of only the bicyclo[3.2.1]octanol that has both methyl and hydroxyl substituents in equatorial positions, that the NHC-catalyzed domino Michael–aldol reaction is not reversible (or is reversible at a very slow rate), under the conditions studied.

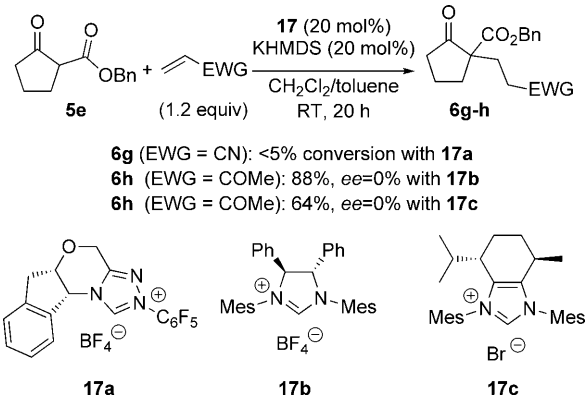
During our studies on NHC-catalyzed Michael addition reactions with 1,3-dicarbonyl pronucleophiles containing an activated methylene reaction site (e.g., **7b** in Table 2), we observed minor amounts of double Michael-addition products **14** (Scheme 3). In light of this precedent, we surmized that this reactivity could be exploited for the preparation of cyclohexanols by following an organocatalytic, domino Michael–Michael–aldol reaction if the reaction is performed in the presence of an excess of methyl vinyl ketone (Scheme 3). It is worth noting that comparable domino double-Michael–aldolization sequences have only been reported to proceed efficiently with organometallic catalysts for 1,3-dicarbonyl derivatives[14] or with a stoichiometric amount of base for nitroalkanes.[15] The domino reaction proceeded well with a variety of pseudoacids, yielding minor amounts of double Michael adducts **14** and the expected cyclohexanols **15** with generally good to excellent diastereoselectivities (Scheme 3). If acrolein is used as the Michael acceptor, the domino Michael–Michael–aldol sequence is extended by a dehydration step to give α,β-unsaturated aldehyde **16**. Importantly, in a separate experiment, the reaction of double Michael adduct **14e** with IPr (**3**, 10 mol%) at room temperature for 48 h yielded aldolization product **15e** (93%, d.r. = 3:1:1:ε). This experiment demonstrates that IPr (**3**) is not only an excellent catalyst for the Michael addition, but also for the intramolecular aldol reaction, although at a slower rate due to a higher pK_a value of the pronucleophile.

With few exceptions, the NHC-catalyzed Michael addition reactions described herein have allowed the formation of chiral, all-carbon quaternary centers. Logically, we have examined the possibility of an asymmetric version of these reactions by using some known chiral NHCs (Scheme 4). The triazolylidene NHC derived from **17a**[16] did not promote a Michael addition in the model reaction between benzyl 2-oxocyclopentane carboxylate (**5e**) and acrylonitrile, and no enantioselectivity was observed on using the C_2-symmetric chiral imidazolin-2-ylidene NHC derived from **17b**[17] or the imidazol-2-ylidene NHC derived from **17c**[18] in the reaction between **5e** and methyl vinyl ketone to give adduct **6h** (Scheme 4).

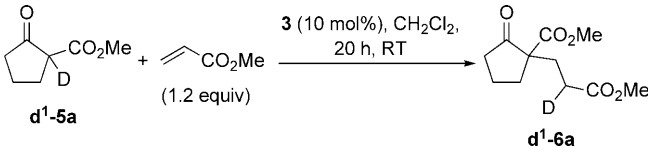
These results raise questions about the origin of the excellent catalytic activity of the NHCs in Michael addition reactions. A deuterium labeling experiment confirmed that, in the catalytic cycle, the acidic deuterium atom in **d^1-5a** is quantitatively transferred to the α position of the Michael acceptor in the adduct **d^1-6a** (Scheme 5). To better understand the role of the NHC catalyst in these Michael additions, a series of



Scheme 3. The NHC-catalyzed domino Michael–Michael–aldol reaction. Only the major diastereomer is depicted. [a] The crude mixture contained **16** (≈90% yield) but the product, not surprisingly, partially decomposed upon silica gel purification.



Scheme 4. NHC-catalyzed Michael addition reactions with chiral NHCs.



Scheme 5. A deuterium labeling experiment (ca. 80% deuterium incorporation in both **d^1-5a** and **d^1-6a**).

control experiments was performed. We have examined the intramolecular Michael addition of substrates **1a** and **b**[19] to give spiro products **4a** and **b**, first with a representative set of bases (Table 4, entries 1–8), and then with a set of nucleophilic additives known to catalyze Michael addition reactions (Table 4, entries 9–15). Surprisingly, under none of these conditions could the desired spiro products **4** be obtained efficiently (very minor amounts of **4** were detected in some cases), whereas NHC **3** afforded both spiro products **4a** and **b** in high yields and diastereoselectivities (Table 4, entries 16 and 17, respectively). Although *N,N*-dialkylimidazol(in)-2-ylidene NHCs have been described as strong Brønsted bases (ca. p$K_{a,DMSO}$ = 21–24),[20] the *N,N*-diaryl analogues are somewhat less basic (ca. p$K_{a,DMSO}$ = 16–17).[21] From the results in Table 4, entries 1–8, it seems that, in these reactions, NHC catalyst **3** is not acting as a "classic" Brønsted base. From the results of Table 4, entries 9–15, a mechanism initiated by conjugate nucleophilic addition of NHC **3** to the activated olefin to generate a basic imidazolium enolate appears unlikely.[22] Plausible alternative mechanisms have been considered. Among these, a mechanism involving NHC **3** as a simple Brønsted base initiator of the reaction could not be totally ruled out, although it is unlikely considering its potency in the catalyzation of aldol reactions (e.g., **14e**→**15e**). A non-coordinating counterion effect of the protonated NHC may also be envisioned by analogy to the chemistry of quaternary ammonium ions.[23] The purely carbenic properties of the NHC could also be involved, with a catalytic cycle initiated by an insertion reaction of the carbene into the activated C–H bond of the pseudoacid, as described by Arduengo,[24] but in this case, some enantioselectivity would be expected with optically active chiral NHCs.

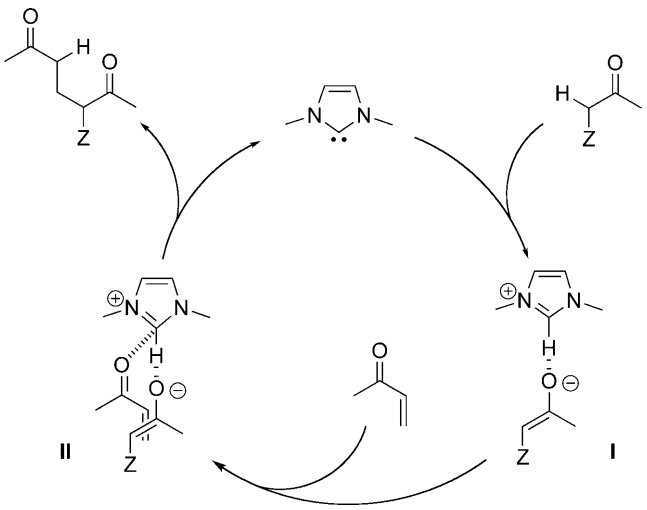
Table 4. Control experiments.[a]

1a: R = H, X = O, EWG = CN (*E*/*Z*=1:3) **4a** (d.r.>20:1)
1b: R = Me, X = NBn, EWG = CO_2Me (*E*/*Z*>10:1) **4b** (d.r.>20:1)

	Substrate	Conditions	Yield [%][b]
1	**1a**	basic Al_2O_3 (excess), MeOH, 50 °C, 24 h	<5
2	**1a**	KHMDS (1 equiv), THF, RT, 6 h	<5
3	**1a**	*t*BuOK (1 equiv), THF, RT, 6 h	<5
4	**1a**	*i*PrNEt$_2$ (1 equiv), CH_3CN, RT, 6 h	<5
5	**1a**	K_2CO_3 (1 equiv), acetone, RT, 6 h	<5
6	**1a**	DBU (1 equiv), CH_2Cl_2, RT, 6 h	degradation
7	**1a**	DBU (20 mol%), CH_2Cl_2, RT, 6 h	degradation
8	**1b**	basic Al_2O_3 (excess), MeOH, 50 °C, 24 h	<5
9	**1a**	*n*Bu$_3$P (20 mol%), CH_2Cl_2, RT, 6 h	<5
10	**1a**	*n*Bu$_3$P (1 equiv), CH_2Cl_2, 100 °C, 20 min[c]	<5
11	**1a**	Cy$_3$P (1 equiv), CH_2Cl_2, 100 °C, 20 min[c]	<5
12	**1a**	DABCO (20 mol%), CH_2Cl_2, RT, 6 h	<5
13	**1b**	*n*Bu$_3$P (1 equiv), CH_2Cl_2, 100 °C, 20 min[c]	<5
14	**1b**	DMAP (20 mol%), CH_2Cl_2, RT, 48 h	<5
15	**1b**	PhNC (20 mol%), CH_2Cl_2, RT, 48 h	<5
16	**1a**	**3** (20 mol%), CH_2Cl_2, RT, 20 h	97
17	**1b**	**3** (20 mol%), CH_2Cl_2, RT, 3 h	93

[a] DBU = 1,8-diazabicycloundec-7ene; DABCO = 1,4-diazabicyclo-[2.2.2]octane; DMAP = 4-dimethylaminopyridine. [b] Yields determined by ^{1}H NMR spectroscopy of the crude reaction mixture for entries 1–15, and for isolated products obtained after silica gel flash column chromatography for entries 16 and 17. [c] Reaction performed in a sealed vessel under microwave irradiation.

Based on the above set of data, we propose that in these Michael additions the NHC is acting as a unique and optimal combination of a catalytic Brønsted base and Lewis acid on the same carbon atom, as illustrated in Scheme 6.[25] The catalytic cycle would be initiated by the formation of enolate–imidazolium complex **I** in which the carbene plays



Scheme 6. The proposed catalytic cycle.

the role of a Brønsted base in a similar manner to the methyl acetoacetate–IAd (IAd = 1,3-bis(1-adamantyl)imidazol-2-ylidene) complex reported by Nolan.[26] Complex **I** would then behave as a Lewis acid and activate the electrophile, as depicted in complex **II**, which would evolve to afford the Michael adduct and regenerate the NHC.

Conclusion

In summary, the unprecedented organocatalytic activity of *N,N*-diaryl-1,3-imidazol(in)-2-ylidene NHCs in the Michael addition of 1,3-dicarbonyl compounds and their analogues has been studied. IPr (**3**) was identified as the most potent catalyst for this transformation (up to 99% yield with a 2.5 mol% catalyst loading), and the reaction was found to be broad in scope. Some applications of this catalytic reaction are described, that is, the domino carbocyclization reactions of simple cyclic 1,3-dicarbonyl compounds and malonic acid derivatives, which allow, respectively, a stereoselective route to bridged bicyclic compounds or cycloheptanols, and the stereoselective synthesis of cyclohexanols (or cyclohexene). The excellent catalytic activity of NHCs in these Michael addition reactions appears to entail a dual activation mode, in which both the σ-donor and π-acceptor properties of the NHC are involved. We surmise that other applications of the unique reactivity of NHCs with pseudoacids described herein will soon be discovered.

Experimental Section

Representative procedure: the synthesis of 6c (Table 2, entry 3): Phenyl vinyl sulfone (50 mg, 0.30 mmol) and IPr (**3**, 5 mg, 0.013 mmol) were successively added to a solution of **5a** (31 μL, 0.25 mmol) in dichloromethane (2.5 mL), and the resulting mixture was stirred for 3 h at room temperature, whereupon the reaction mixture was concentrated under vacuum. The resulting crude product was directly purified by silica gel flash column chromatography eluted with EtOAc/petroleum ether (3:2) to afford pure **6c** (75 mg, 97%) as a colorless oil. $R_f = 0.14$ (EtOAc/petroleum ether, 3:7); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.83$ (d, $J = 7.6$ Hz, 2H), 7.60 (d, $J = 8.1$ Hz, 1H), 7.52 (dd, $J = 7.6$, 8.1 Hz, 2H), 3.58 (s, 3H), 3.26–3.41 (m, 1H), 3.02–3.16 (m, 1H), 2.45–1.74 ppm (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 213.5$ (C), 170.8 (C), 138.5 (C), 133.6 (CH), 129.1 (2CH), 127.7 (2CH), 57.8 (C), 52.5 (CH_3), 51.7 (CH_2), 37.6 (CH_2), 33.9 (CH_2), 26.1 (CH_2), 19.3 ppm (CH_2); HRMS (ESI+): *m/z* calcd for $C_{15}H_{19}O_5S^+$: 311.0948; found: 311.0953 $[M+H]^+$; *m/z* calcd for $C_{15}H_{22}NO_5S^+$: 328.1213; found: 328.1214 $[M+NH_4]^+$.

Acknowledgements

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