

Article

## The Effects of Solvent and Added Bases on the Protection of Benzylamines with Carbon Dioxide

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**Abstract:** The introduction and removal of protecting groups is ubiquitous in multi-step synthetic schemes. From a green chemistry standpoint, however, alternative strategies that employ *in situ* and reversible protection and deprotection sequences would be attractive. The reversible reactions of CO<sub>2</sub> with amines could provide a possible vehicle for realizing this strategy. Herein, we present (1) the products of reaction of benzylamines with CO<sub>2</sub> in a variety of solvents with and without the presence of basic additives; (2) new adducts associated with CO<sub>2</sub> protected benzylamine in acetonitrile containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); and (3) the intermolecular competitive acylation of benzylamine and benzyl alcohol and the intramolecular competitive acylation of

(4-aminomethyl)phenyl) methanol with isopropenyl acetate in acetonitrile containing DBU in the absence and presence of CO<sub>2</sub>.

**Keywords:** carbamate; amine; protection; carbon dioxide; sustainable

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## 1. Introduction

The construction of structurally complex molecules in the organic synthesis relies heavily on the use of protecting groups. Protection/deprotection sequences enable reaction at specific sites in a multi-step synthetic sequence, without interference or competitive reactions at other sites within the same molecules. In principle, protecting groups must be first introduced and subsequently eliminated. Both of these steps must be as near quantitative as possible. A wide variety of protecting groups have been developed to address the many requirements for efficient processes. From a sustainable point of view, the introduction and removal of protecting groups is not ideal because (i) it adds steps to the intended synthetic transformation; (ii) it adds to the product and process cost; and (iii) it increases the amount of generated waste. A preferred approach would be to develop direct synthetic methodologies that circumvent the use of a protecting/deprotecting sequence altogether. One approach is to use, when possible, an *in situ* and reversible protection and deprotection sequence that is selective to specific functional groups.

CO<sub>2</sub> is known to react with primary and secondary amines to form the corresponding carbamic acid or ammonium carbamate ion pair [1–11]. The CO<sub>2</sub>-amine reaction can be reversed thermally under relatively mild conditions—a key to developing “*in situ*, reversible” protection schemes. This could be an advantage from a process standpoint since the gaseous CO<sub>2</sub> can be easily recovered and recycled. Supercritical CO<sub>2</sub> (scCO<sub>2</sub>) has been reported as a solvent, reactant and protecting agent for Heck coupling reactions [12–16]. Improved yields were attributed to specific interactions of CO<sub>2</sub> with amino groups, preventing deactivation of the palladium catalyst [17]. Peeters *et al.* further reported the successful use of CO<sub>2</sub> at atmospheric pressure for *in situ*, reversible protection of primary amines in a series of competitive Michael addition and acylation reactions in acetonitrile in the presence of either an unprotected secondary amine or an alcohol [18]. Both inter- and intra-molecular competitions were reported. Based upon an NMR analysis conducted in DMSO, they proposed that the protected species in solution (*i.e.*, acetonitrile) was carbamic acid. It has been well documented however that the particular species formed in the reaction of amines with CO<sub>2</sub> depends on the solvent and any additives that may be present [7,19]. Since synthetic transformations are conducted in a wide variety of solvent systems it is important to accurately know the structures of the protected species in the specific reaction medium. Herein, we present (1) the products of reactions of several benzylamines with CO<sub>2</sub> in a variety of solvents with and without the presence of basic additives; (2) a new adduct associated with CO<sub>2</sub> protected benzylamine in acetonitrile containing 1,8-diazabicycloundec-7-ene (DBU) and (3) two model reactions in acetonitrile with defined protected species. The reactions reported are the intermolecular competitive acylation of benzylamine and benzyl alcohol and the intramolecular competitive acylation of 4-(aminomethyl) benzyl alcohol with isopropenyl acetate in acetonitrile containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the absence and presence of CO<sub>2</sub>.

## 2. Experimental Section

All Chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) and used as received unless otherwise noted. Chemicals used were: benzylamine (>99.5%); 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 98%, purified by distillation); 1,1,3,3-tetramethyl guanidine (TMG, 99%); acetonitrile (ACN, anhydrous); tetrahydrofuran (THF, anhydrous); dichloromethane; Celite<sup>®</sup> 545 (filter aid, treated with sodium carbonate, flux calcined); 4-(aminomethyl)benzoic acid (97%); lithium aluminum hydride (powder, reagent grade, 95%); 1,2,4-triazole (98%); isopropenyl acetate (VWR, 99%); dimethyl sulfoxide (DMSO, >99.5%); dimethylsulfoxide-*d*<sub>6</sub> (99.96 atom % D); *N,N*-dimethylformamide (DMF, anhydrous); *N,N*-dimethylformamide-*d*<sub>7</sub> (99.5 atom % D); acetonitrile-*d*<sub>3</sub> (100%, 99.96 atom % D). <sup>13</sup>C labeled carbon dioxide used was SFE grade from Airgas (99.999%) (Atlanta, GA, USA).

### 2.1. Reactions with 1-(4-Bromophenyl)ethan-1-Amine (1) and Carbon Dioxide to Form 1-(4-Bromophenyl)ethan-1-Aminium (1-(4-Bromophenyl)Ethyl)Carbamate (Ammonium Carbamate Salt (2))

General Procedure: 1-(4-bromophenyl)ethan-1-amine (**1**) added to a round bottom flask. Various organic solvents (aprotic—ACN, THF, ethyl acetate, acetone, 1,4 dioxane and chloroform) was then added to flask to make up dilute solutions of the amine. CO<sub>2</sub> was bubbled through (rotometer flowrate: 200 mL·min<sup>-1</sup>) at 25 °C for 15 min, while stirring, to afford insoluble precipitate (ion pair (**2**)). NMR analysis of (**2**) was carried out using NMR tubes as reaction vessels and isotopically labeled <sup>13</sup>C CO<sub>2</sub> as the sparging gas. 0.04 g (0.2 mmol) of 1-(4-bromophenyl)ethan-1-amine (**1**) and 0.5 mL of d-THF was added to an NMR tube to make a 0.4 molar solution of the amine. Isotopically labeled <sup>13</sup>C CO<sub>2</sub> was bubbled through the solution at 25 °C for 15 min using a stainless steel needle, resulting in the insoluble white precipitate. The NMR tube was then flame sealed and analyzed via NMR at 50 °C to ensure solubility of the precipitate and negligible solvent losses. <sup>13</sup>C NMR (400 Mhz, d-THF) δ<sub>c</sub> 157.4, 149.3, 132.1, 128.8, 120.8, 51.8, 24.9.

### 2.2. Reaction with 1-(4-Bromophenyl)ethan-1-Amine and Carbon Dioxide to Form 1-(4-Bromophenyl)ethan-1-Aminium Methyl Carbonate (Ammonium Carbamate Salt (3))

0.04 g (0.2 mmol) of 1-(4-bromophenyl)ethan-1-amine (**1**) was reacted with isotopically labeled <sup>13</sup>C CO<sub>2</sub> at 25 °C by bubbling through a solution of (**1**) in 0.5 mL of deuterated methanol (MeOD). At 25 °C the resulting carbamate species formed are completely soluble in the MeOH. The reaction solution then added to an NMR tube, flame sealed and analyzed via NMR spectrometry at both 25 °C and 50 °C. <sup>13</sup>C NMR (400 Mhz, MeOD) δ<sub>c</sub> 164.7, 161.6, 146.8, 131.9, 129.1, 121.8, 24.9.

### 2.3. Synthesis of Benzylcarbamic Acid (5)

Benzylamine (**4**) (0.02 g, 2 mmol) was added to an NMR tube along with anhydrous DMSO or DMF (0.5 mL) to make a 0.4 M solutions.  $^{13}\text{C}$   $\text{CO}_2$  (rotometer flowrate:  $200\text{ mL}\cdot\text{min}^{-1}$ ) at  $25\text{ }^\circ\text{C}$  and 1 bar was bubbled through the amine solutions for 30 min using a stainless steel needle to ensure complete conversion of (**4**) to benzylcarbamic acid (**5**). Samples analyzed via  $^{13}\text{C}$  NMR at room temperature and pressure.  $^{13}\text{C}$  NMR (400 Mhz, d-DMSO)  $\delta_c$  158.5, 140.7, 128.4, 127.1, 126.7, 44.0.

### 2.4. Synthesis of the DBU Salt of Benzylcarbamic Acid (7)

Benzylamine (**4**) (0.86 g, 8 mmol) was added to anhydrous acetonitrile (8 mL) to make a 1 M solution. The sample was stirred while adding 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (**6**) (1.34 g, 8.8 mmol) under nitrogen. For 0.5 molar equivalents of DBU, 0.67 g (4.4 mmol) of DBU is added to the flask. The sample was sparged with  $\text{CO}_2$  via a stainless steel needle (rotometer flowrate:  $200\text{ mL}\cdot\text{min}^{-1}$ ) at  $25\text{ }^\circ\text{C}$  and 1 bar for 30 min to ensure complete conversion to the salt. The reaction solution is then analyzed via proton and carbon NMR and discussed in detail in the results below.

### 2.5. Synthesis of (4-(Aminomethyl)Phenyl)Methanol (14)

The model compound, (4-(aminomethyl)phenyl)methanol (**14**) was prepared from 4-aminomethylbenzoic acid by reduction with  $\text{LiAlH}_4$  following as described in literature [20]. Briefly, 4-aminomethylbenzoic acid (2.0 g; 1 eq) was added to a round bottom flask equipped with a stir bar and condenser. The flask was purged with argon and 20 mL of anhydrous tetrahydrofuran (THF) was added. The solution was cooled to near  $0\text{ }^\circ\text{C}$  using an ice bath.  $\text{LiAlH}_4$  (2.0 g, 4 eq) was slowly added in portions. Then, the solution was heated to reflux ( $66\text{ }^\circ\text{C}$ ). After 12 h, the reaction mixture was cooled to  $0\text{ }^\circ\text{C}$  and slowly quenched with water (2.5 mL), aqueous sodium hydroxide 15% (2 mL) and then diluted with 6 mL of water. The aqueous layer extracted with dichloromethane, dried over magnesium sulfate, filtered and the solvent evaporated under reduced pressure to yield (**14**) as a white solid in 30% isolated yield.  $^{13}\text{C}$  NMR (400 Mhz, d-ACN)  $\delta_c$  142.9, 140.4, 127.0, 126.8, 63.5, 45.7.  $^1\text{H}$  NMR (400 Mhz, d-ACN)  $\delta_h$  3.8 (s, 2H), 4.6 (s, 2H), 7.3(s, 4H).

### 2.6. Procedure for the Acylation Reactions

(4-(aminomethyl)phenyl)methanol (**14**) (0.22 g, 1.6 mmol) was weighed into a 10 mL round bottom flask, and placed under a nitrogen atmosphere. Anhydrous acetonitrile (4 mL) was added and the resulting solution was stirred. DBU (**6**) (0.27 g, 1.8 mmol) was added under stirring. The sample was sparged with  $\text{CO}_2$  (rotometer flowrate:  $200\text{ mL}\cdot\text{min}^{-1}$ ) or  $\text{N}_2$  via a stainless steel needle at  $25\text{ }^\circ\text{C}$  and 1 bar for 30 min. A stock solution was prepared by dissolving 1,2,4-triazole (0.11 g, 1.60 mmol) in anhydrous acetonitrile (10 mL). One milliliter of the stock solution was added to the solution of (**14**) in acetonitrile. Isopropenyl acetate ((0.161 g, 1.60 mmol) or (0.321 g, 3.20 mmol)) was added to the reaction mixture for the two reaction conditions (1 or 2 equivalents of acylating species, respectively). Aliquots of samples were taken and analyzed with  $^1\text{H}$  and  $^{13}\text{C}$  NMR.

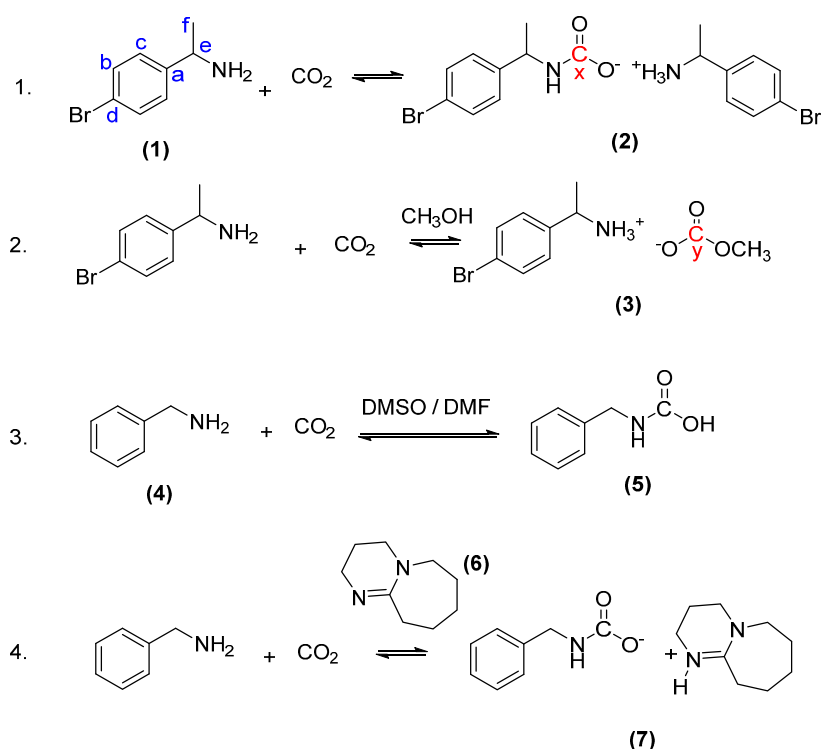
## 2.7. NMR Analyses

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were collected on a Bruker AMX-400 (Billerica, MA, USA). To conduct quantitative  $^{13}\text{C}$  NMR, a complete relaxation was determined by performing an inversion recovery  $T_1$  experiment. The carbonyl peak at 159.14 ppm had the longest  $T_1$  time of 23 s. The recommended delay time is 5 times the longest  $T_1$  time and therefore a delay time of 125 s was used. A full  $90^\circ$  pulse was used to insure complete excitation of the nucleus, and proton decoupling was done only during the acquisition period to avoid a false and disproportional signal build-up.

## 3. Results and Discussion

### 3.1. Reactions of Benzylamines and $\text{CO}_2$ —the Protection Step

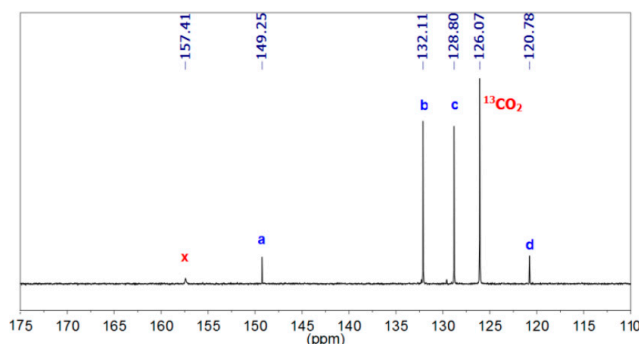
Primary and secondary amines are known to react rapidly and reversibly with  $\text{CO}_2$ . The reaction products, however, are highly dependent on the reaction conditions (e.g., neat amine, aprotic or protic solvents, dipolar protophilic solvents, presence of additional base and the stoichiometry of the additional base). The reactions of benzylamines under four distinct reaction conditions are presented in Figure 1.



**Figure 1.** Reactions of primary amines with  $\text{CO}_2$  as a function of environment.

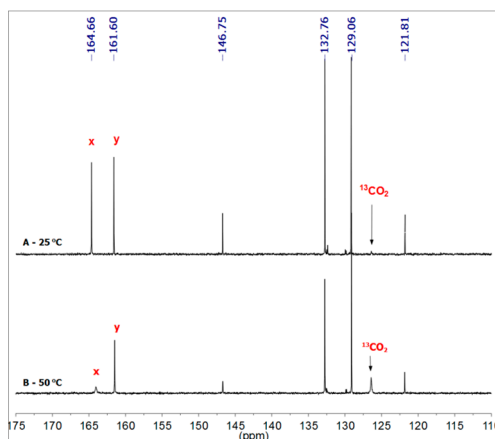
Neat 1-(4-bromophenyl)ethan-1-amine (1) and solutions of (1) dissolved in an aprotic solvent such as acetonitrile, tetrahydrofuran, ethyl acetate, acetone, dichloromethane, or 1,4-dioxane, were reacted with  $\text{CO}_2$  to produce the corresponding ammonium carbamate as an insoluble white solid [21–23]. Attempts to dissolve the carbamate salt in these solvents by raising the temperature to  $50^\circ\text{C}$  resulted in significant reversal back to the starting amine. This is clearly shown in

the  $^{13}\text{C}$  NMR (Figure 2) of the carbamate salt (**2**) formed by reaction of  $^{13}\text{C}$ -labeled  $\text{CO}_2$  with (**1**) in THF at 50 °C. The relatively small size of the carbamate peak at 157.41 ppm is indicative of the protected carbamate-containing species is only present in solution in small concentration. Since isotopically labeled  $^{13}\text{CO}_2$  was used to form the protected salt, it should appear much larger than the rest of the non-isotopically labeled peaks. The relative larger  $^{13}\text{CO}_2$  peak at 126.07 ppm suggests that the free  $^{13}\text{CO}_2$  is present in much higher concentration than the carbamate species. It is important to note that this  $^{13}\text{C}$  NMR experiment is only semi-quantitative; however peak heights are often at least qualitatively indicative of concentration.



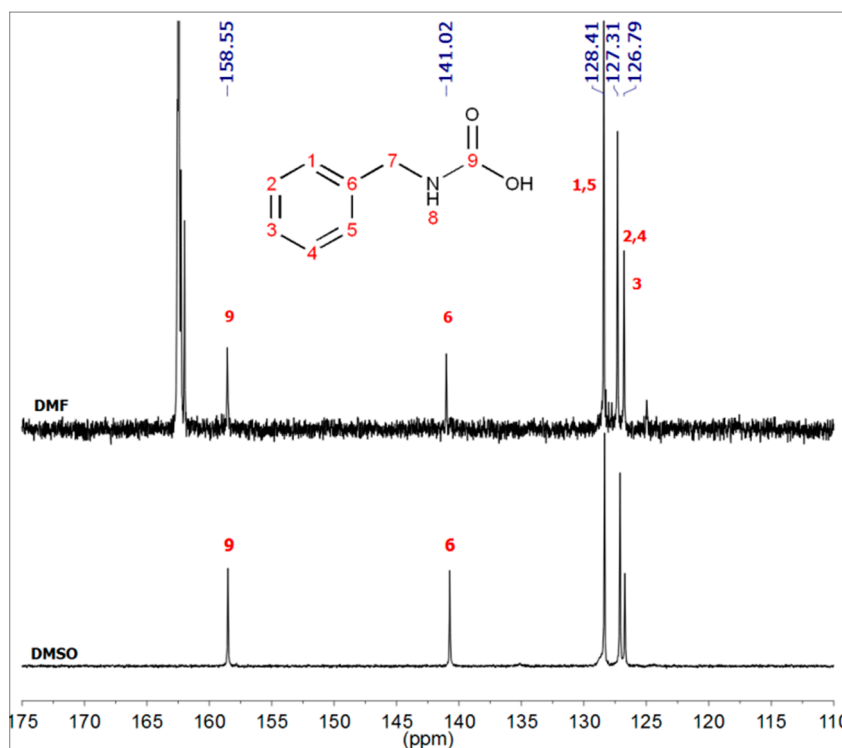
**Figure 2.**  $^{13}\text{C}$  NMR of the reaction of  $^{13}\text{C}$ -labeled  $\text{CO}_2$  with 1-(4-bromophenyl)ethan-1-amine in THF at 50 °C.

In a protic solvent such as methanol, (**1**) reacts with  $^{13}\text{C}$ -labeled  $\text{CO}_2$  to produce both the corresponding ammonium carbamate (**2**) and the ammonium methylcarbonate (**3**) in approximately equal amounts. The  $^{13}\text{C}$  NMR spectrum at 25 °C is in Figure 3. The peak at 164.66 ppm has been assigned to the carbonyl carbon of the carbamate species and the peak at 161.60 ppm has been assigned to the carbonyl carbon of the carbonate species. Figure 3 also highlights the effect of temperature; when raised to 50 °C a significant decrease in the carbamate carbonyl absorption is observed while the  $^{13}\text{CO}_2$  peak at 126.40 ppm increases. It appears that the ammonium carbamate (**2**) reverses to the amine (**1**) to a greater extent than the ammonium methylcarbonate (**3**) suggesting that the latter species has a greater stability. Full  $^{13}\text{C}$  NMR spectra are included in the ESI (Figures S1–S3).



**Figure 3.**  $^{13}\text{C}$  NMR for the reactions of 1-(4-bromophenyl)ethan-1-amine (**1**) with  $^{13}\text{C}$ -labeled  $\text{CO}_2$  at 25 °C (**top**) and 50 °C (**bottom**) in MeOH.

Reaction of benzylamine (**4**) with CO<sub>2</sub> in strong hydrogen bonding (protophilic) solvents such as DMSO and DMF leads exclusively to the carbamic acid (**5**). The strong hydrogen bonding properties of these solvents appear to be sufficient to stabilize the carbamic acid. This is substantiated by both <sup>13</sup>C NMR spectra in DMSO and DMF (Figure 4) exhibiting an absorbance at 158.55 ppm associated with the carbonyl of the acid. This peak is not observed in the unreacted benzylamine (Figure S4). These results are consistent with similar systems reported in the literature [4].

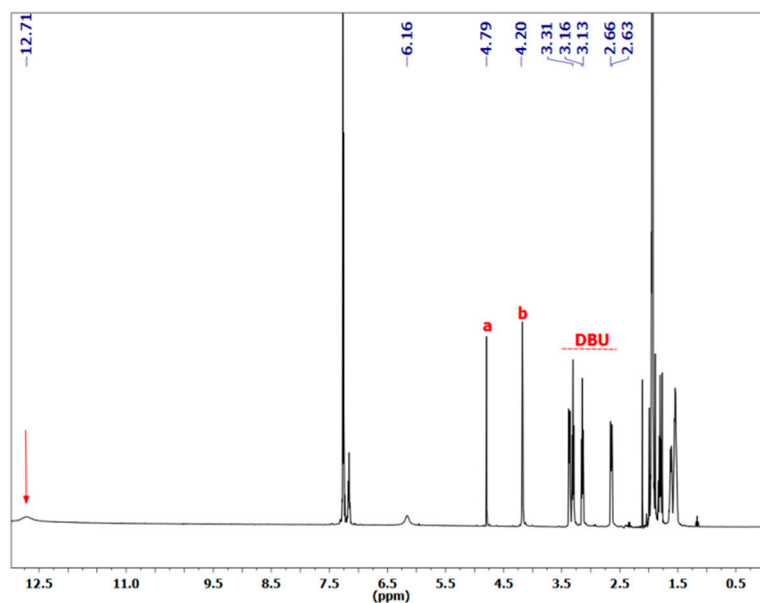


**Figure 4.** <sup>13</sup>C NMR spectrums for the reaction of benzylamine (**4**) with <sup>13</sup>C-labeled CO<sub>2</sub> in DMSO (**bottom**) and DMF (**top**).

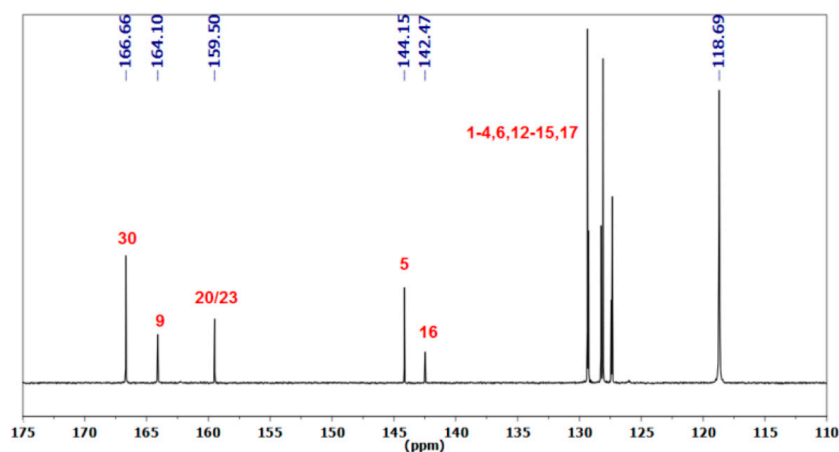
DBU and TMG are strong organic bases which have been shown not to react directly with CO<sub>2</sub>. [24] In the presence of DBU or *N,N,N',N'*-tetramethylguanidine (TMG), the reaction of a solution of benzylamine with CO<sub>2</sub> at atmospheric pressure and ambient temperature exclusively forms as counter cation the protonated form of the added base. However, weaker bases, such as triethylamine, diisopropylethylamine, butylamine, and sodium carbonate do not effectively compete with the benzylamine in the deprotonation of the benzylcarbamic acid.

### 3.1.1. Reaction of Benzylamine with 1 Equivalent of DBU

It was discovered that the reaction of benzylamine (**4**) with CO<sub>2</sub> in acetonitrile in the presence of one equivalent of DBU (**6**) at room temperature is more complex than the Equation (4) in Figure 1. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of the reaction products are shown in Figures 5 and 6, respectively.



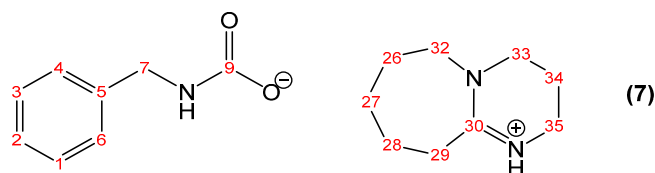
**Figure 5.**  $^1\text{H}$  NMR of reaction of benzylamine with  $\text{CO}_2$  in acetonitrile in the presence of one equivalent of DBU.



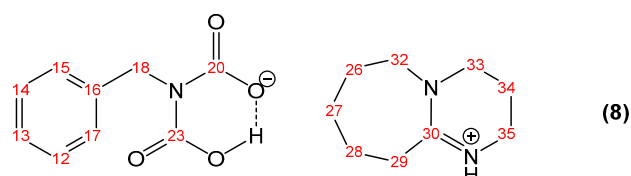
**Figure 6.**  $^{13}\text{C}$  NMR of reaction of benzylamine with  $\text{CO}_2$  in acetonitrile in the presence of one equivalent of DBU.

While it is clear that the expected ion pair species (Figure 1, Equation (4)) is present, additional absorptions are also observed. For instance, the  $^{13}\text{C}$  NMR spectrum shows three distinct absorptions between 159.1 and 166.3 ppm. The absorption at 163.67 ppm is consistent with the C-9 (the carbamate carbon) of the carbamate ion and the peak at 166.23 ppm is consistent with the C-30 of the protonated DBU (Figure 7). The peak at 159.07 ppm, however, does not fit any structural component of the  $\text{DBUH}^+$  carbamate ion pair. In the  $^1\text{H}$  NMR spectrum, the peak labeled “b” is consistent with the  $\text{CH}_2$  hydrogens of the expected carbamate. The peak labeled “a”, however, is not. It is concluded that, in addition to the expected DBU salt of the carbamate (7), an additional species is also present in the reaction mixture. Employing additional NMR experiments, the structure of this species was postulated to be the DBU salt of benzylbicarbamate (8) shown in Figure 8.





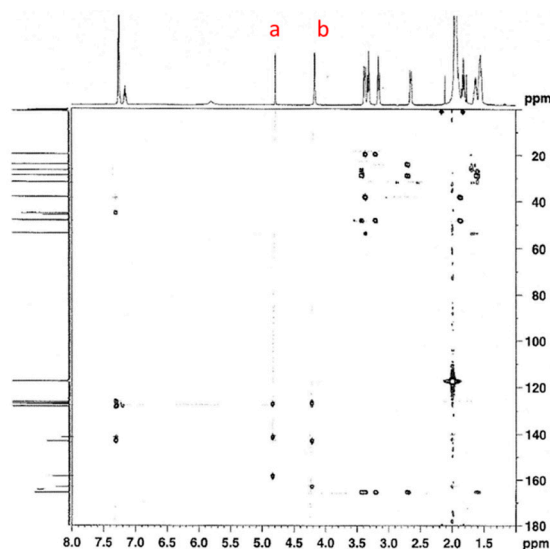
**Figure 7.** Amidinium benzylcarbamate (“mono-adduct”) formed upon reaction of benzylamine with CO<sub>2</sub> in acetonitrile in the presence of DBU.



**Figure 8.** Amidinium benzylcarbamate (“di-adduct”) formed upon reaction of benzylamine with CO<sub>2</sub> in acetonitrile in the presence of DBU.

The experimental details and accompanying interpretation are presented as follows.

(1) Figure 9 shows the <sup>1</sup>H, <sup>13</sup>C HMBC spectrum of the reaction mixture. This NMR experiment correlates chemical shifts of the proton and carbon nuclei separated from each other by two or more bonds. It is clear that the <sup>1</sup>H NMR absorption labeled “b” at 4.20 ppm (the benzyl hydrogens of the carbamate) correlates with the <sup>13</sup>C absorptions at 163.67, 143.72, and 127 ppm corresponding to the carboxylate carbon, the benzyl carbon, and the *ipso*-carbon of the aromatic ring, respectively. In contrast, the absorption labeled “a” at 4.79 ppm in the <sup>1</sup>H NMR spectrum correlates with the <sup>13</sup>C absorptions at 159.14, 142.12, and 127.02 ppm corresponding the carboxylate carbons, the benzyl carbon, and the *ipso* carbon of the ammonium bicarbamate structure shown in Figure 8.



**Figure 9.** <sup>1</sup>H-<sup>13</sup>C HMBC NMR experiment of protected benzylamine with DBU.

(2) Quantitative <sup>13</sup>C NMR provided further support for the proposed bicarbamate (8) structure. Table 1 shows the pertinent absorptions and the quantitative peak integrations for the reaction of benzylamine with one equivalent of DBU. All peak intensities reported in Table 1 were normalized with

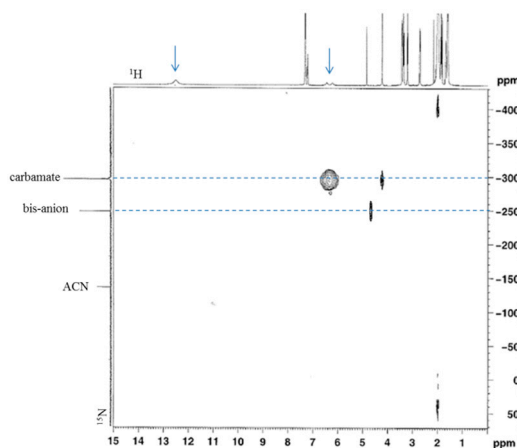
respect to the quaternary carbon in the DBU cationic species (C-30), which was given a value of unity. The benzylcarbamate salt (Figure 7) showed the expected 1:1:1 ratio of carbonyl carbon (163.67 ppm) to *ipso* carbon (143.72 ppm) to CH<sub>2</sub> carbon (46.54 ppm) and the benzylbicarbonate showed the expected 2:1:1 ratio of carbonyl carbon (159.07 ppm) to the *ipso* carbon (142.04 ppm) to the CH<sub>2</sub> (45.87 ppm) providing additional evidence for the proposed structure.

**Table 1.** Quantitative peak integrations for the reaction of benzylamine with one equivalent of DBU.

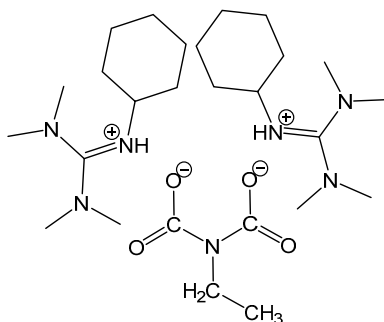
Peak Assignment	Species	Integration
30	DBUH <sup>+</sup>	1
9	Carbamate	0.54
20/23	Bicarbamate	0.57
5	Carbamate	0.48
16	Bicarbamate	0.23
7	Carbamate	0.49
18	Bicarbamate	0.21

(3) The <sup>1</sup>H NMR spectrum (Figure 5) indicates an absorption at 12.71 ppm. This was postulated to be the proton bonded to the two carboxylates in the benzylbicarbamate (**8**) as opposed to a proton attached to the amine nitrogen. In order to provide evidence to support this postulate a <sup>1</sup>H <sup>15</sup>N HSQC NMR experiment was conducted at −30 °C with <sup>15</sup>N-labeled benzylamine. The low temperature (−30 °C) was employed in order to minimize proton exchange. The results are shown in Figure 10. It is clear that there is no correlation between the proton at 12.71 ppm and the <sup>15</sup>N-nitrogen and is therefore concluded that this proton is bonded between the two carboxylate anions as shown in Figure 9.

An analogous adduct has been reported in literature for the reaction of ethylamine with CO<sub>2</sub> in the presence of two equivalents of *N*-cyclohexyl-*N'*,*N'*,*N''*,*N''*-tetramethylguanidine in acetonitrile at −30 °C (Figure 11).[25] It is suggested that the driving force for the reaction of two CO<sub>2</sub> molecules is the presence of enough base to neutralize the bis-carbamic acid to form the structure in Figure 11. In the present report, however, only one equivalent of base was employed (not enough to form the bis-anion) at room temperature and the adduct shown in Figure 8 was approximately 50% of the resulting products. Full <sup>13</sup>C NMR spectra are included in the ESI (Figures S4–S8).



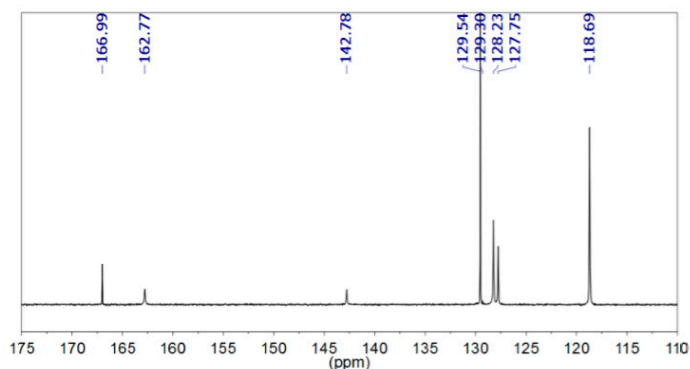
**Figure 10.** <sup>1</sup>H-<sup>15</sup>N HSQC NMR experiment of protected <sup>15</sup>N benzylamine at −30 °C.



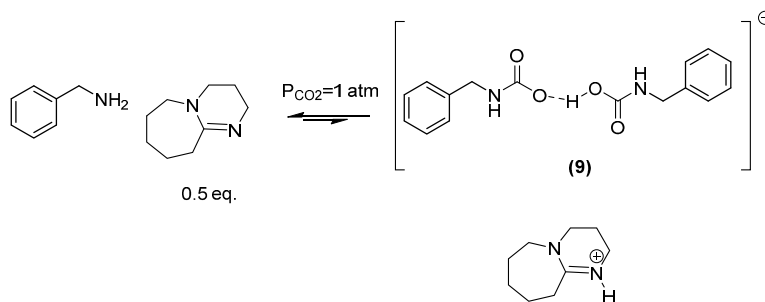
**Figure 11.** Adduct reported for the reaction of ethylamine with CO<sub>2</sub> in the presence of two equivalents of *N*-cyclohexyl-*N*',*N*'',*N*''',*N*''''-tetramethyl guanidine in acetonitrile at −30 °C.

### 3.1.2. Reaction of Benzylamine with 0.5 Equivalent of DBU

Addition of CO<sub>2</sub> to an acetonitrile solution of benzylamine results in the precipitation of benzylammonium benzylcarbamate (**1**). It has already been shown that this salt has little solubility in acetonitrile. It was surprising, therefore, to find that with the addition of only 0.5 equivalent of DBU no precipitate was formed. It was anticipated that the DBU salt of benzylcarbamate (**7**) would form along with the insoluble benzylammonium benzylcarbamate (**1**). This, however, was not observed. The <sup>13</sup>C NMR spectrum clearly shows only one carbonyl peak, one benzyl carbon peak, one *ipso* carbon peak, a single peak attributed to the quaternary carbon of the DBU cationic salt (Figure 12). These data are consistent with the structure of the DBU salt of bis-benzylbicarbamate (**9**) shown in Figure 13.



**Figure 12.** <sup>13</sup>C NMR spectrum of the reaction CO<sub>2</sub> with benzylamine in presence of 0.5 equivalent of DBU in acetonitrile at 25 °C.



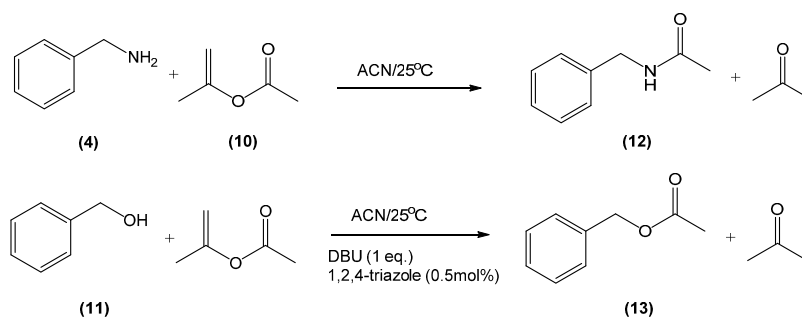
**Figure 13.** Equilibrium for the reaction of CO<sub>2</sub> with benzylamine in presence of 0.5 equivalent of DBU in acetonitrile at 25 °C.

### 3.2. In situ Protection of Amines with CO<sub>2</sub>

It has been shown that amines readily react with CO<sub>2</sub> to form a variety of products depending on the solvent and/or the presence of strong organic bases [4,5,9,25]. These CO<sub>2</sub> adducts are, in principle, protected amines. In DMSO or DMF the carbamic acid is the primary product. In a solvent such as acetonitrile and an equivalent amount of strong organic base such as DBU, the amidinium benzylcarbamate (7) is the major product along with the amidinium benzylbicarbamate (8). In contrast, if only 0.5 equivalent of DBU is present the major species appears to be the DBU salt of bis-benzylbicarbamate. From a sustainability point of view, the question remains as to the efficacy of these types of protected amines. The following preliminary experiments were therefore conducted to explore the reactivity of benzylamine models in the absence and in the presence of “CO<sub>2</sub> protection”. Both inter- and intramolecular acylation competition reactions between amino and hydroxyl functional groups were investigated. The following summarizes the results of these experiments.

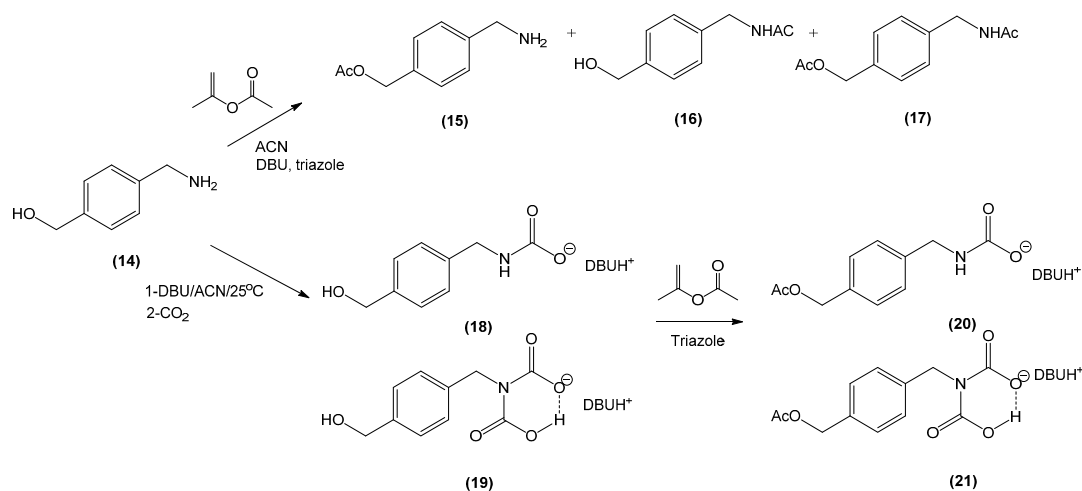
(1) Reaction of benzylamine with isopropenyl acetate (10) in acetonitrile proceeds to *N*-benzylacetamide (12) in approximately 50% yield in six hours (Figures S9–S11) [26,27]. In the presence of CO<sub>2</sub> and 1.1 equivalents of DBU, however, no detectable product was observed during the same time period as analyzed by <sup>13</sup>C NMR. The amine remained protected; this is further discussed and highlighted in Figure S12.

(2) In a competitive experiment, one equivalent of isopropenyl acetate (10) was reacted with an equimolar mixture of benzylamine (4) and benzyl alcohol (11) and 1.1 equivalents of DBU (6). In the presence of CO<sub>2</sub> no reaction of the benzylamine was observed over a period of six hours. The amine was successfully protected as the absorptions at ~170 ppm and ~140 ppm associated to the *N*-acylation are not observed (Figure S16). Only a small amount of benzyl acetate (13), however, was produced. The acetylation of the alcohol under these conditions was very slow. It is conjectured that the reduced reactivity of the alcohol was due to the unavailability of sufficient amounts of unprotonated DBU which acts as a catalyst for the acetylation process. Indeed, in control experiments it was demonstrated that the reactivity of benzyl alcohol toward isopropenyl acetate was greatly enhanced in the presence of unprotonated DBU (Figures 14, S13–S15). As a consequence 1,2,4-triazole anion, which has been successfully used as an acyl transfer catalyst was employed. In the reaction of benzyl alcohol with isopropenyl acetate, 0.5 mol % triazole was shown to effectively catalyze the reaction; the acylation reaction was completed in 6 h as monitored by <sup>13</sup>C NMR.



**Figure 14.** Control reactions of benzylamine and benzyl alcohol with isopropenyl acetate conducted independently under an inert atmosphere of N<sub>2</sub> to form *N*-benzylacetamide (12) and benzyl acetate (13) respectively.

(3) (4-(aminomethyl)phenyl)methanol (**14**) was chosen as a model to explore the intramolecular competitive acylation process (Figure 15). The results in the absence and presence of CO<sub>2</sub> are summarized in Table 2. In the absence of CO<sub>2</sub> and in the presence of 1 equivalent of isopropenyl acetate and 1 equivalent of DBU for 6 h, the product composition consisted of 60% *N*-acylation and 40% *O*-acylation (Table 2, Entry 1). When the equivalents of isopropenyl acetate and DBU were increased to 1.7 and 1.2, respectively, the *N*-acylation reaction was quantitative (100%) while the *O*-acylation amounted to 70% (Table 2, Entry 2). In contrast, with *in situ* CO<sub>2</sub> protection of the amine the reaction proceeded with complete chemoselectivity for the *O*-acylation. The DBU salts (**18**) and (**19**) rendered the amine functionality protected. In fact, no *N*-acylated product could be detected (Table 2, Entries 3 and 4, Figures S18–S20). Only the alcohol reacted with 15% and 30% yield of the *O*-acylated product after 6 h. It is noted that the *O*-acylation appeared to proceed slower with the carbamate species than with its free amine analog. However, in presence of 1% triazole catalyst over a period of 24 h, 80% of the *O*-acylated product (**20**) and (**21**) was obtained (Table 2, Entry 5). Only traces of the *N*-acylated product could be detected.



**Figure 15.** Competitive intermolecular acylation of benzylamine and benzyl alcohol with isopropenyl acetate.

**Table 2.** Experimental conversions of *N*-acylation and *O*-acylation with and without CO<sub>2</sub> protection.

Entry	CO <sub>2</sub>	DBU (eq)	Iso-PA (eq)	Time (h)	<i>O</i> -Product <sup>b</sup> (%)	<i>N</i> -Product <sup>b</sup> (%)
1	No	1	1	6	40	60
2	No	1.2	1.7	6	70	100
3	Yes	1	1	6	15	0
4	Yes	1.2	1.7	6	30	0
5 <sup>a</sup>	Yes	1.2	1.7	24	80	0

<sup>a</sup> 1 mol % triazole; <sup>b</sup> Yield determined by <sup>1</sup>H NMR.

### 3.3. Thermal Treatment of the Carbamate-Amidinium Species—the Reversal Step

The effective protection of benzylamine models with CO<sub>2</sub> is one part of a sustainable process. The facile removal of the protecting group is essential for the entire process to be valuable. As

a consequence, the following series of experiments were conducted in order to determine the optimum conditions for the removal of the CO<sub>2</sub> protection. It was previously pointed out that the addition of CO<sub>2</sub> to benzylamine dissolved in acetonitrile containing at least one equivalent of DBU produced two species—the DBU salt of benzylcarbamate (**7**) (Figure 7) and the DBU salt of benzylbicarbamate (**8**) (Figure 8). Heating this solution to 60 °C over a period of 15–20 min with the system open to the atmosphere resulted in the disappearance of the benzylbicarbamate salt; the benzylcarbamate salt remained unchanged. Interestingly, when the solution was heated to 60 °C in a sealed NMR tube, a 40% reduction of the benzylbicarbamate was observed using <sup>1</sup>H NMR. When the temperature was reduced back to 25 °C, the benzylbicarbamate species reformed; the ratio of the two protected species (benzylcarbamate and benzylbicarbamate) returned to their original ratio. These experiments clearly demonstrate the reversibility of the bicarbamate formation. Experiments dealing with the complete reversal of both the carbamate and the bicarbamate species are summarized in Table 3. At 60 °C, sparging with nitrogen, resulted in 81% recovery of the unprotected benzylamine after 2 h. At 70 °C, however, recovery of benzylamine (**4**) was complete within one hour.

**Table 3.** Reversal of CO<sub>2</sub> protection: effects of temperature and time experiment via sparging with N<sub>2</sub>.

Temperature (°C)	Time (h)	Amount of Reversal by NMR Integration (%)
60	1	63
60	2	81
70	0.5	75
70	1	100

#### 4. Conclusions

The products formed in the reaction of CO<sub>2</sub> with amines are strongly dependent on the solvent employed, the absence or presence of a strong organic base, and the temperature. In acetonitrile, NMR studies indicated that benzylamine reversibly reacted with CO<sub>2</sub> to form two products in the presence of a strong base like DBU. The major product is the DBU salt of benzylcarbamate along with a minor product, the DBU salt of dibenzylbicarbamate. The competitive intramolecular acylation of 4-(aminomethyl)-benzyl alcohol with isopropenyl acetate, producing exclusively *O*-acylation, demonstrated the effective protection of benzylamine as carbamate and bicarbamate amidinium species. Finally, the recovery of (un-protected) benzylamine was achieved upon mild heating. These results demonstrate that under specific and controlled conditions “*in situ*, reversible” protection of amine functionalities can be successful.

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#### Author Contributions

The reported work is a collaboration between researchers at Dow Chemical Company and the Research Teams of Charles L. Liotta (chemistry, Chem), Charles. A. Eckert (chemical engineering,

Chem. E.) and Pamela Pollet (Chem). A.L.E. and J.R.S. contributed equally: experimentally determined, conducted and interpreted the bulk of the data on the reaction of benzylamines and CO<sub>2</sub> in presence and absence of bases, neat and in solution NMR studies of protected species, *in-situ* protection of amines with CO<sub>2</sub> and competitive experiment and the reversal experiment. L.G. designed and reviewed NMR data, A.C.R. conducted preliminary reactions of benzylamine with isopropenyl acetate, W.M. conducted initial screening of bases and Z.L. optimized competitive experiments along with purification, isolation and quantification of reaction products. J.F. B.H. and C.A.E. contributed to the design of experiments while P.P. and C.L.L. oversaw the entire research study and coordinated the redaction of the manuscript.

### Conflicts of Interest

The authors declare no conflict of interest.

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