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Some reactions of 2-(4-substitutedphenyl)-2-(N-methyl-N-4-substitutedbenzamido) acetic acids

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ABSTRACT
In situ generated 2,4-diaryl substituted munchnones from 2-(4-substitutedphenyl)-2-(N-methyl-N-4-substitutedbenzamido)acetic acids react with acetic anhydride in the presence of 2-nitromethylene thiazolidine, which is most likely acting as a base, and unexpectedly undergo a Dakin–West type reaction and a concurrent autoxidation reaction leading to the formation of (E)-1-(N,4-dimethylbenzamido)-1-(4-fluorophenyl)prop-1-en-2-yl acetate, 4-substitutedphenyl-N-methyl-N-(4-substitutedbenzoyl) benzamides and p-substituted benzoic acids. In addition, a novel and efficient access to N-acyl urea derivatives is described by the reaction between 2-(4-substitutedphenyl)-2-(N-methyl-N-4-substitutedbenzamido)acetic acids and cyclohexyl, isopropyl carbodiimides in the presence of a base. The structures of all new products were identified on the basis of NMR and IR spectra, along with X-ray diffraction data and HRMS measurements.

GRAPHICAL ABSTRACT

Introduction
Munchnones, so-called, 1,3-oxazolium-5-olates, are among the five-membered mesoionic compounds which can be easily prepared by cyclodehydration of N-substituted-N-acyl-\(\alpha\)-amino acids with acetic anhydride, N,N\textsuperscript{0}-dicyclohexylcarbodiimide,
N,N\textsuperscript{0}-diisopropylcarbodiimide and they are utilized in the synthesis of many valuable heterocycles such as substituted pyrroles through 1,3-dipolar cycloaddition with a wide range of doubly or triply bonded electron-deficient dipolarophilic reagents.\textsuperscript{[1–8]} There are many examples regarding the munchnones\textsuperscript{€} as 1,3-dipoles in cycloaddition reactions, but other reactions of these ring systems have not been fully explored.

Imides in general are one of the most important structural motif for natural and pharmaceutical compounds such as palau’imide,\textsuperscript{[12]} coniothyriomycin,\textsuperscript{[13]} ethosuximide,\textsuperscript{[14]} fumaramidmycin,\textsuperscript{[15]} and berkeleyamide B and C.\textsuperscript{[16]} The N-acyl urea derivatives are an important sub-class of such substrates especially for medicinal and agrochemical applications. In addition, N-acylurea derivatives are used as inhibitors of the reproduction and growth for the house fly and fall army worm (Figure 1).\textsuperscript{[17]}

There are various methods to synthesize N-acylurea derivatives from the reactions of carboxylic acids with carbodiimides.\textsuperscript{[18–20]} Soeta and Ukaji have reported oxidative coupling reaction of various kind of aldehydes with N,N\textsuperscript{0}-disubstituted carbodiimides catalyzed by N-heterocyclic carbene under aerobic conditions to furnish N-acyl derivatives.

Taking account of the above considerations and literature-based knowledge of munchnones,\textsuperscript{€} Dakin–West reaction which can be realized as a reaction pathway for our work, we have focused on some reactions of the munchnone\textsuperscript{€} precursors which have turned out to be a practical one-pot protocol for the synthesis of N-acyl urea derivatives.

**Results and discussion**

Recently, we have reported some chemistry incorporating mesoionic 1,3-dipoles; namely sydnones, nitrile oxides, nitrile imines and electron-deficient alkenes, alkynes,\textsuperscript{[22]}
2-nitromethylenethiazolidine and benzothiophene 1,1-dioxide.\[23–28] Herein, we report a study of munchnones\(E\) generated from 2-(4-substitutedphenyl)-2-(N-methyl-N-4-substitutedbenzamido)acetic acids 3 and acetic anhydride, DCC and DIPC in the presence of 2-nitromethylenethiazolidine 4 and diisopropylamine. In this regard, the products were one enol ester, five imides and seven benzoic acid derivatives obtained by the autoxidation reaction between munchnone\(E\) precursors (amino acids) and acetic anhydride in the presence of 2-nitromethylenethiazolidine. To the best of our knowledge, 2-nitromethylenethiazolidine has not been reported so far as a base in such reactions, but in our case, it might have behaved as a base through its imine tautomeric form. On the other hand, N-acylureas derivatives have also been generated through a substitution reaction in which 2-(4-substitutedphenyl)-2-(N-methyl-N-4-substitutedbenzamido)acetic acids 3 were interacted with dehydrating agents, DCC and DIPC in the presence of diisopropyl-amine under reflux conditions in acetonitrile. There is no reported example for the synthesis of N-acylureas from munchnone\(E\) precursors by means of N,N\(^0\)-disubstituted carbodiimides in the presence of a base.

4-Substituted N-methylglycine hydrochloride 1a and 1b play a key role in the synthesis of unsymmetrical munchnone\(E\) derivatives which were generated in situ from C-(4-substitutedphenyl)-N-(benzoyl)-N-methylglycines 3a-k which were synthesized according to the literature procedures\[1–3\] and used in the subsequent steps without further purification.

2-(N,4-Dimethylbenzamido)-2-(4-fluorophenyl)acetic acid 3b underwent a reaction affording an enol ester 5 through a Dakin–West type transformation both in the presence of pyridine and 2-nitromethylene thiazolidine 4, but no reaction occurred under microwave heating (Scheme 1). IR spectrum showed two carbonyl absorptions and proton NMR gave four singlet peaks between 3.31-1.98 ppm, one of them was of \(p\)-tolyl methyl protons.

After obtaining a fine crystal of the compound 5, we were able to establish full structural characterization by means of X-ray diffraction data.

Other substituted amino acids 3 were tried under the same conditions for obtaining derivatives of enol ester 5, but, amino acids 3a, 3ck have been found to be transformed into imides 6d, 6f, 6i-k and 4-substituted benzoic acids 7a-g through sequential Dakin–West and autoxidation reactions (Scheme 2). Huisgen and co-workers were first to report the autooxidation of munchnone\(E\) generated from N-benzoyl-N-methyl phenylglycine.\[29\] Also, Kawase investigated the autooxidation reaction of munchnones\(E\) derived from cyclic \(\alpha\)-amino acids.\[30\] Although, in some cases, both structures (6 and 7) were obtained, some of the reactions gave only one product (i.e. imides 6 or carboxylic acids 7) and also no 2-nitromethylenethiazolidine residue was detected along with the products.

We began the reaction using amino acid 3b (1 mmol): after addition of acetic anhydride (3 mmol) and heated the mixture at 55 C for 15 min 2-nitromethylenethiazolidine 4 was added and the resulting mixture heated at 90 C overnight. Only enol ester 5 was obtained, possibly through a Dakin–West type reaction pathway at which a tautomeric form of 2-nitromethylenethiazolidine might behaved as a base (Scheme 3). A similar product obtained through a rearrangement process with N-acyl prolines in the presence of inorganic bases such as K\(\text{2CO}_3\), Na\(\text{2CO}_3\) was reported by the Kawase group.\[31\]
Scheme 1. Reactions between 3b and acetic anhydride in the presence of 2-nitromethylene-thiazoline 4 and pyridine to afford enol ester 5.

We have utilized the same reaction conditions for other amino acids (3a-k) to obtain a variety of enol esters 5, but all the attempts failed, that is, no ester products were formed.

In order to provide a full characterization of the structure, an X-ray ORTEP view for enol ester 5 was obtained (Figure 2). However, when the compounds 3d, 3f, 3i-k were used as starting aminoacids, some new benzoyl, methyl substituted benzamides 6d, 6f, 6i-k were obtained as the only products. IR spectra of the products showed two carbonyl absorption bands. Since proton NMR spectra did not give four singlet peaks as in compound 5 and only one singlet peak appeared at approximately 3.50 ppm (N-CH₃), we concluded that these products were the imides 6. A possible reaction mechanism can be proposed in which, after münchnone formation, the ketene is likely attacked by a water molecule and a subsequent release of carbon dioxide may be considered (Scheme 4).

Formation of similar imides, but not exactly the same, through peroxidation of C-H bonds in amides, via the reaction of nitrones with aroyl chlorides; imidoyl chlorides with phenols and by thermal transformations of oxazole endoperoxides has been reported. [32–37] We used the amino acids (3d, 3f, 3i-k) and obtained similar proton and carbon NMR resonances for the products.

We were able to establish exact structure of 6d by X-ray diffraction data (Figure 3). In some cases, the carboxylic acids 7 were obtained possibly via a mechanism depicted below (Scheme 5).

In order to identify the carboxylic acid formed above reaction exactly, X-Ray diffraction data of 4-trifluoromethylbenzoic acid 7f was obtained using a fine crystal of it
Scheme 2. The reaction between munchnone precursors 3 and acetic anhydride in the presence of 2-nitromethylenethiazolidine 4.

(Figure 4). Finger print region in the IR spectrum of 7f is exactly same with the one of euthentic sample.

In order to rationalize whether aromatic substituent on nitrogen affects the product formation, we used N-acetyl substituted amino acid 3h both under classical and microwave heating conditions and observed no reaction at all, confirming that aromatic group has the major impact on this reaction.

Then, munchnone precursors 3 were reacted both with cyclohexyl and isopropyl carbodiimides in the presence of diisopropyl amine and a series of urea derivatives 9, 11 have been obtained. Their IR spectra showed two carbonyl absorptions between 1720
and 1690 cm$^{-1}$. Also, proton NMR spectra showed one singlet signal between 6.70 and 6.00 ppm, two multiplet peaks between 4.50 and 3.75 ppm (Figure 5). These spectral data were not enough for full structural characterization of these compounds. But, however, we were able to obtain fine crystals of the compound 11e. X-ray diffraction ORTEP view which confirmed the structures is shown (Scheme 6, Figure 6). On the basis of these results, we were able to write a Dakin–West type reaction mechanism for the formation of N-acylurea products. Thus, initially, N-acylamino acids 3 reacted with carbodiimides to give a mesoionic 1,3-oxazolium-5-olate form which may be in equilibrium with ketene whose formation could be facilitated by the elevated temperature of refluxing acetonitrile.
Scheme 4. Possible reaction mechanism involving an autoxidation pathway leading to N-acyl amides 6d, 6f, 6i-k.

Figure 3. X-Ray ORTEP view of 6d.
Scheme 5. Possible reaction mechanism leading to 4-substituted benzoic acids 7a-g.

Figure 4. X-Ray ORTEP view of 7f.

Figure 5. $^1$H NMR spectra of 9d and 11g.
Scheme 6. Reactions of munchnone precursors 3 with diisopropyl carbodiimide (DIPC) 8 and dicy-clohexyl carbodiimide (DCC) 10 in the presence of diisopropyl amine (DIPA) to afford 9a-f and 11a-g. Reagents and solvent: 3 (0.47 mmol), 8 (3.0 mL), 10 (1.91 mmol), DIPA (0.2 mL), CH$_3$CN (10.0 mL).

![Scheme 6](image)

Then, amide carbonyl was attacked by OH$^-$ later converted to carboxylic acid 7 and formyl imine which could not be detected or isolated. Finally, excess carbodiimide underwent a reaction with carboxylic acid 7, namely, acyl transfer leads to the corresponding N-acylureas 9 and 11 (Scheme 7).

![Figure 6](image)

Figure 6. X-Ray ORTEP view of 11e.
Conclusion

In summary, we demonstrated that a Dakin–West type transformation and autoxidation reaction occur in the interactions between munchnone precursors (amino acids) and acetic anhydride in the presence of 2-nitromethyleneithiazolidine which likely acts as a base through its enamine tautomer to afford an enol ester; (E)-1-(N,4-dimethylbenzamido)-1-(4-fluorophenyl)prop-1-en-2-yl acetate 5, 4-substituted-N-methyl-N-(4-substitutedbenzoyl)benzamides 6 and substituted benzoic acids 7. A plausible mechanism where munchnones are being converted into imides through an autoxidation process was proposed. In addition, we introduced a novel, efficient and one-pot protocol to give N-acylurea derivatives 9 and 11 through the reaction between munchnone precursors with carbodiimides in the presence of a base. This reaction sequence demonstrates the influence of the carbodiimides both as a dehydrating agent and a reactant.

Experimental: Reactions between munchnone precursors 3a-k and acetic anhydride in the presence of 2-nitromethyleneithiazolidine 4

General procedure

Route A

Synthesis of E-1-(N,4-dimethylbenzamido)-1-(4-fluorophenyl)prop-1-en-2-yl acetate 5: 2-(N,4-Dimethylbenzamido)-2-(4-fluorophenyl)acetic acid 3b (2.80 mmol, 806 mg) was
heated in acetic anhydride (8 mL) at 55°C for 30 min. Then, 2-(nitromethylene) thiazolidine 4 (1.00 mmol, 146 mg) was added to the reaction mixture and refluxed overnight at 90°C. After cooling the reaction mixture to room temperature, the solvent was removed under the reduced pressure and the crude residue was purified by flash column chromatography (silica gel, EtOAc/ n-hexane; 1:7) to give 5 as yellow solid. Yield: 1C. IR (KBr): ¼ 2958, 1745, 1647, 1508, 1358, 1217, 1082, 839 cm⁻¹.

H NMR (400 MHz, CDCl₃): d 7.27 (d, J ¼ 8.1 Hz, 2H), 7.13–7.10 (m, 2H), 7.01 (d, J ¼ 7.9 Hz, 2H), 6.90 (t, J ¼ 8.7 Hz, 2H), 3.31 (s, 3H), 2.30 (s, 3H), 1.98 (d, J ¼ 4.8 Hz, 6H). 13 C NMR (100 MHz, CDCl₃): d 171.6, 168.6, 162.0 (d, C-F carbon, J ¼ 247.0 Hz), 144.7, 140.4, 132.6 (d, b-C to C-F, Jmeta= 18.0 Hz), 131.2, 129.4, 129.3, 128.4, 127.5, 115.2 (d, a-C to C-F, Jong= 122.0 Hz), 37.2, 21.4, 20.9, 17.3. LC-MS (ES+) m/z (%): 342.2 [M+H]+. HRMS: m/z (ESI-TOF, [M+H]+) calcd for C20H20FNO3: 342.1505. Found: 342.1500.

Route B

4-Chlorobenzoic acid 7e: 2-(4-Chloro-N-methylbenzamido)-2-(4-fluorophenyl)acetic acid 3e (0.715 mmol, 230 mg) in acetic anhydride (2.23 mL) was irradiated at 0–150 W for 15 min in closed glass vial in a CEM Discover microwave reactor at 55°C. Then, 2-(nitromethylene)thiazolidine 4 (0.255 mmol, 38 mg) was added the reaction mixture and irradiated at 0-150 W for further 45 min at 80°C. After cooling the reaction mixture to room temperature, the solvent was removed under the reduced pressure and the residue was purified by flash column chromatography (silica gel, EtOAc/ n-hexane; 1:18) to give 7e.

4-Fluoro-N-methyl-N-(4-nitrobenzoyl)benzamide 6d (route a): Yellow solid. Yield: 34%; mp 131-133°C. IR (KBr): ¼ 3117, 1701, 1651, 1600, 1519, 1342, 1288, 1041, 852 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): d 8.10 (d, J ¼ 8.0 Hz, 2H), 7.62-7.56 (m, 4H), 7.00 (t, J ¼ 8.0 Hz, 2H), 3.50 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): d 172.9, 171.9, 165.3 (d, C-F carbon, J ¼ 154.0 Hz), 149.2, 141.6, 131.7 (d, b-C to C-F, Jmeta= 9.0 Hz), 131.1, 129.3, 123.7, 116.2 (d, a-C to C-F, Jong= 22.0 Hz), 34.6. LC-MS (ES+) m/z (%): 297 [M+H]+=. Calculated for C₁₅H₁₁FN₂O₄: 302.0703; C, 59.61; H, 3.67; N, 9.27. Found: C, 59.84; H, 3.84; N, 9.22.

4-Chlorobenzoic acid 7e (route a and route B): White solid. Yield: 83%; mp 235-237°C (lit.[38,39] mp 236-237°C). IR (KBr): ¼ 3093, 1685, 1593, 1423, 1280, 1176, 1091, 759 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): d 13.1 (s, 1H), 7.90 (dd, J ¼ 8.0, 4.0 Hz, 2H), 7.53 (d, J ¼ 8.0, 4.0 Hz, 2H). ¹³C NMR (100 MHz, DMSO-d₆): d 169.9, 138.3, 131.7, 130.2, 129.3. LC-MS (ES-) m/z (%): 155 [M-H]⁻.

General procedure

Synthesis of 4-substituted-N-isopropyl-N-(isopropylcarbamoyl)benzamides 9a-f and 4-substituted-N-cyclohexyl-N-(cyclohexylcarbamoyl)benzamides 11a-g

2-(4-Chloro-N-methylbenzamido)-2-(4-fluorophenyl) acetic acid 3e (0.47 mmol, 151 mg) was dissolved in acetonitrile (10 mL) and DIPC (diisopropyl carbodiimide) 8 (0.3 mL) was added. Then, the reaction mixture was heated at 55°C for 30 min. Then, DIPA
(diisopropyl amine) (0.2 mL) was added and refluxed overnight at 90 C. After cooling the reaction to room temperature, the solvent was removed under vacuum and the residue was purified by flash column chromatography (silica gel, EtOAc/n-hexane:1:8) to give 9a-f and when DCC (dicyclohexylcarbodiimide) was used at the same reaction conditions and molar amounts of reagents, the compounds 11a-g were obtained (Scheme 6).

N-isopropyl-N-(isopropylcarbamoyl)-4-chlorobenzamide 9d

White solid. Yield: 50%; mp 154–156 C. IR (KBr): ¼ 3321, 2974, 1705, 1631, 1546, 1373, 1257, 1091, 833 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.46 (d, J ¼ 8.4 Hz, 2H), 7.39 (d, J ¼ 8.5 Hz, 2H), 6.57 (s, 1 H, NH), 4.42–4.32 (m, 1H), 3.88–3.78 (m, 1H), 1.41 (d, J ¼ 6.8 Hz, 6H), 1.00 (d, J ¼ 6.6 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 171.0, 153.9, 136.9, 135.4, 128.9, 127.9, 50.3, 42.8, 22.3, 20.9. LC-MS (ES-) m/z (%): 281.3 [M-H]⁻, 326.9 [M + Na⁺]. HRMS: m/z (ESI-TOF, [M + H]⁺) calcd for C₂₀H₂₀FNO₃: 342.1505. Found: 342.1500.

N-cyclohexyl-N-(cyclohexylcarbamoyl)-4-chlorobenzamide 11d


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Heterocycles in the Presence of Inorganic Bases: Unexpected Formation of (Z)-2-(Nitro((E)-p-


