Tetrahedron Letters 51 (2010) 4091–4094

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# An unexpected coupling reaction between isocyanides and carboxylic acids: a method for the synthesis of highly stable symmetrical and unsymmetrical alkylamidine and arylamidine carbocations

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ARTICLE INFO

*Article history:*
Received 14 April 2010
Revised 12 May 2010
Accepted 28 May 2010
Available online 1 June 2010

*Keywords:*
Isocyanide
Carboxylic acid
Stable carbocation

ABSTRACT

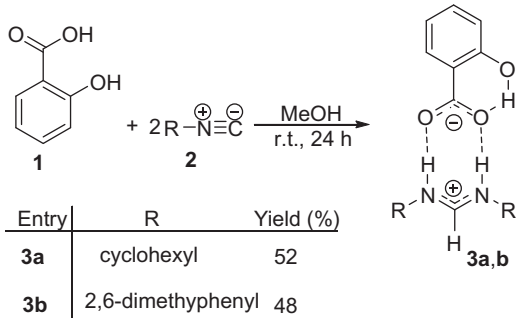
An unexpected coupling reaction between isocyanides and carboxylic acids which led to the synthesis of highly stable symmetrical and unsymmetrical alkylamidine and arylamidine carbocations under mild reaction conditions is described. The structures of these compounds were confirmed by IR, mass, $^{1}H$ NMR, $^{13}C$ NMR, and single-crystal X-ray diffraction studies and a plausible mechanism is proposed.



Carbocations are well known as key reactive intermediates in many organic reactions.[1,2] The generation of carbocations in protic solvents is problematic because they can easily react with protic solvents.[3,4] However, in superacidic media at low temperatures, carbocations are sufficiently long-lived for spectroscopic detection.[1–10] The stability of carbocations is increased by charge delocalization over aromatic rings[1] or when bound to a heteroatom carrying a lone electron pair.[6,7] Such resonance-stabilized carbocations are common intermediates of metabolic and synthetic organic reactions, and the formation of these intermediates and the study of their chemical reactivity are of interest to both organic chemists and biochemists.

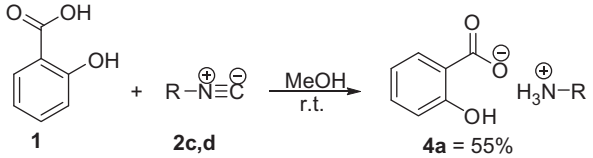
The reaction of carboxylic acids with isocyanides forms the basis of the Passerini and Ugi reactions, which are much admired in combinatorial chemistry. Anthranilic acid provides dibenzo-1,5-diazocine-2,6-dione derivatives by a double Ugi four component reaction. In contrast, the prototypical combination of an acid with an isocyanide is a relatively obscure reaction and poorly represented under ambient conditions.[11–16]

As a part of our ongoing research program on isocyanide chemistry,[17] herein we report a hitherto unknown reaction between 2-hydroxybenzoic acid (**1**) and isocyanides **2**, to give symmetrical alkylamidine- and arylamidine-acid zwitterionic compounds **3a**,**b** (Scheme 1). To the best of our knowledge, this is the first example of isolated and structurally characterized carbocations derived from the reaction of isocyanides and benzoic acid in which not only is the stable carbocation produced at room temperature but also




| Entry | R | Yield (%) |
|---|---|---|
| **3a** | cyclohexyl | 52 |
| **3b** | 2,6-dimethyphenyl | 48 |

**Scheme 1.** Synthesis of symmetrical alkylamidine- and arylamidine-acid zwitterionic compounds.




**2c** = 1,1,3,3-tetramethylbutyl
**2d** = *tert*-butyl

**Scheme 2.** Synthesis of salts **4a** and **4b**.

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doi:10.1016/j.tetlet.2010.05.132

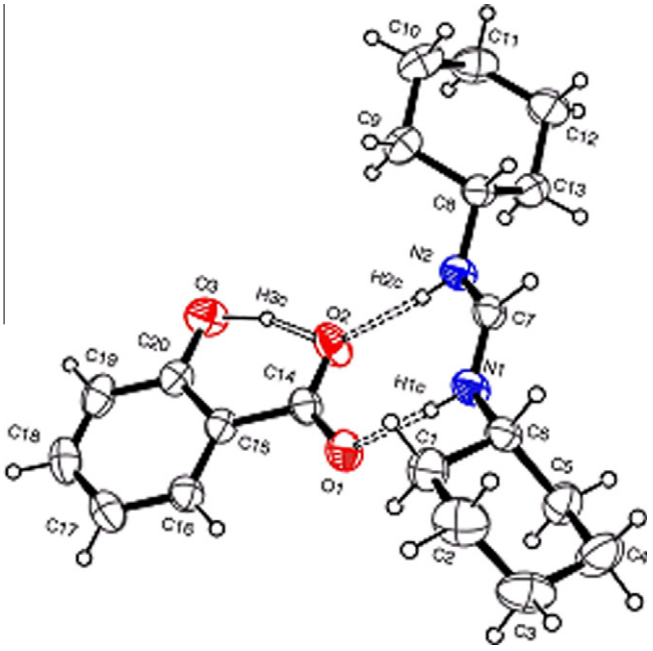



**Figure 1.** ORTEP diagram for **3a**.

**Table 1**
Effect of solvent on the reaction yield[a]

| Entry | Solvent | Yield (%) |
|---|---|---|
| 1 | $H_2O$ | 37 |
| 2 | EtOH | 40 |
| 3 | MeOH | 52 |
| 4 | $CH_3CN$ | 0 |
| 5 | $CH_2Cl_2$ | 0 |
| 6 | $C_6H_5CH_3$ | 0 |
| 7 | *n*-Hexane | 0 |

[a] Cyclohexyl isocyanide (2.0 mmol), 2-hydroxybenzoic acid (1.0 mmol), solvents, rt, 24 h.

does not require a strongly acidic medium for its formation or stabilization.

As indicated in Scheme 1, treatment of cyclohexyl **2a** or 2,6-dimethylphenyl **2b** isocyanide with 2-hydroxybenzoic acid in methanol at room temperature led to the formation of the corresponding 1,3-di(cyclohexyl)amidine- or 1,3-di(2,6-dimethylphenyl)amidine-*ortho* hydroxy benzoic acid zwitterions **3a** and **3b**, respectively. It should be noted that the reaction of 1,1,3,3-tetramethylbutyl and *tert*-butyl isocyanides **2c**,**d** with 2-hydroxybenzoic acid (**1**) under the same reaction conditions led to salts **4a**,**b** (Scheme 2).

It is noteworthy that compounds **3a**,**b** are similar to urea-acid salts which are used as redox-active receptors,[18a] whilst compounds **4a**,**b** are important materials for the synthesis of gelators.[18b]

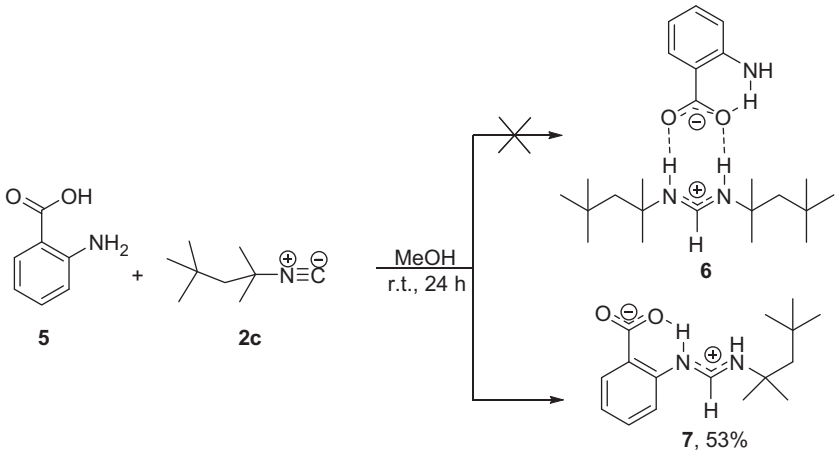
The structures of compounds **3a**,**b** and **4a**,**b** were deduced from their IR, mass, $^1$H NMR, and $^{13}$C NMR spectral data. For example, the $^1$H NMR spectrum of **3a** exhibited a singlet for a phenolic proton at $\delta$ = 15.44, two NH protons at $\delta$ = 9.80 and 9.47, one carbocationic proton at $\delta$ = 7.90, two CH–N cyclohexyl protons at $\delta$ = 3.60 and 3.35, three signals for the aromatic moiety at $\delta$ = 6.65, 7.17 and 7.69, and a multiplet due to the two cyclohexyl rings at $\delta$ = 1.17–1.83 ppm. The $^1$H-decoupled $^{13}$C NMR spectrum of **3a** showed 16 distinct resonances in agreement with the proposed structure. The mass spectra of these compounds displayed amidine fragments of the suggested structures at appropriated *m*/*z* values, for example, for compound **3a**: MS (EI, 70 eV) *m*/*z* (%): 209 ($C_{13}H_{25}N_2^+$) (70).

These crystalline solids are stable at room temperature for months and melt at 175–177 °C (**3a**) and 189–190 °C (**3b**). The $^{13}$C NMR spectrum of **3a** shows a signal due to the N–CH–N carbon atom at 152.2 ppm (on the basis of HMQC and DEPT NMR data). This value is similar to ($\delta$ = 149.4)[6,19a] and indicates significant stabilization of the cationic carbon. The structure of compound **3a** was determined unambiguously by X-ray crystallography.

The general view of the molecular structure is shown in Figure 1. It is interesting to note that interactions between the carbocation and the anion are observed. Hydrogen bonds form between the nitrogen atoms of the carbocation and the oxygen atoms of the anion.[6]

In the crystalline state, the positive charge of compound **3a** is delocalized by the two amine groups. This delocalization was consistent with the observation that the N1–C7 bond length [1.296(2) Å] was similar to the N2–C7 bond length [1.308(2) Å]. These are significantly shorter than the typical N–C bond lengths (N1–C6 and N2–C8 [1.471(2) Å] and [1.466(2) Å], respectively) and longer than imine bond lengths.[19]

In order to find the best solvent, the reaction of cyclohexyl isocyanide (**2**) and 2-hydroxybenzoic acid (**1**) was examined in water and various organic solvents at room temperature. As shown in Table 1, methanol was the best solvent with respect to yield (Table 1, entry 3). It is interesting to note that the reaction proceeded in protic solvents, but not in aprotic solvents (Table 1).




**Scheme 3.** Synthesis of unsymmetrical amidine carbocation **7**.

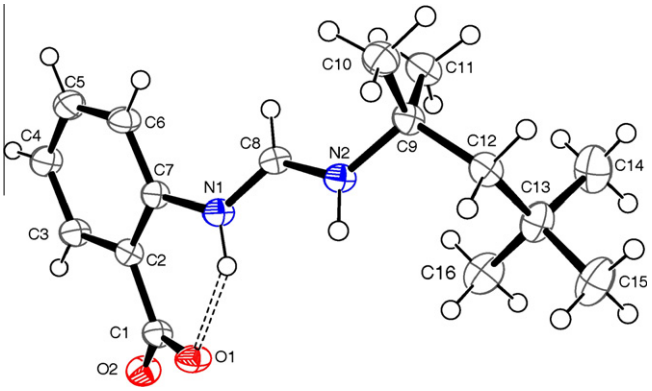



**Figure 2.** ORTEP diagram of **7**: Selected bond lengths [Å]: N1–C8 1.316(4), N2–C8 1.300(4), N1–C7 1.421(4), N2–C9 1.453(4), and selected bond angles [deg]: N1–C8–N2 123.0(2), C7–N1–C8 123.4(2), C8–N2–C9 124.3(3).

In order to further investigate the scope and limitations of this unusual reaction, we applied it to 2-aminobenzoic acid (**5**). In the event, reaction of 2-aminobenzoic acid (**5**) with 1,1,3,3-tetramethylbutyl isocyanide (**2c**) in methanol at room temperature gave highly stable unsymmetrical amidine carbocation **7**. The desired product **6** was not obtained under the given reaction conditions (Scheme 3).

It is worth noting that other isocyanides such as cyclohexyl, 2,6-dimethylphenyl, *tert*-butyl, and benzyl isocyanides failed to give analogous products.

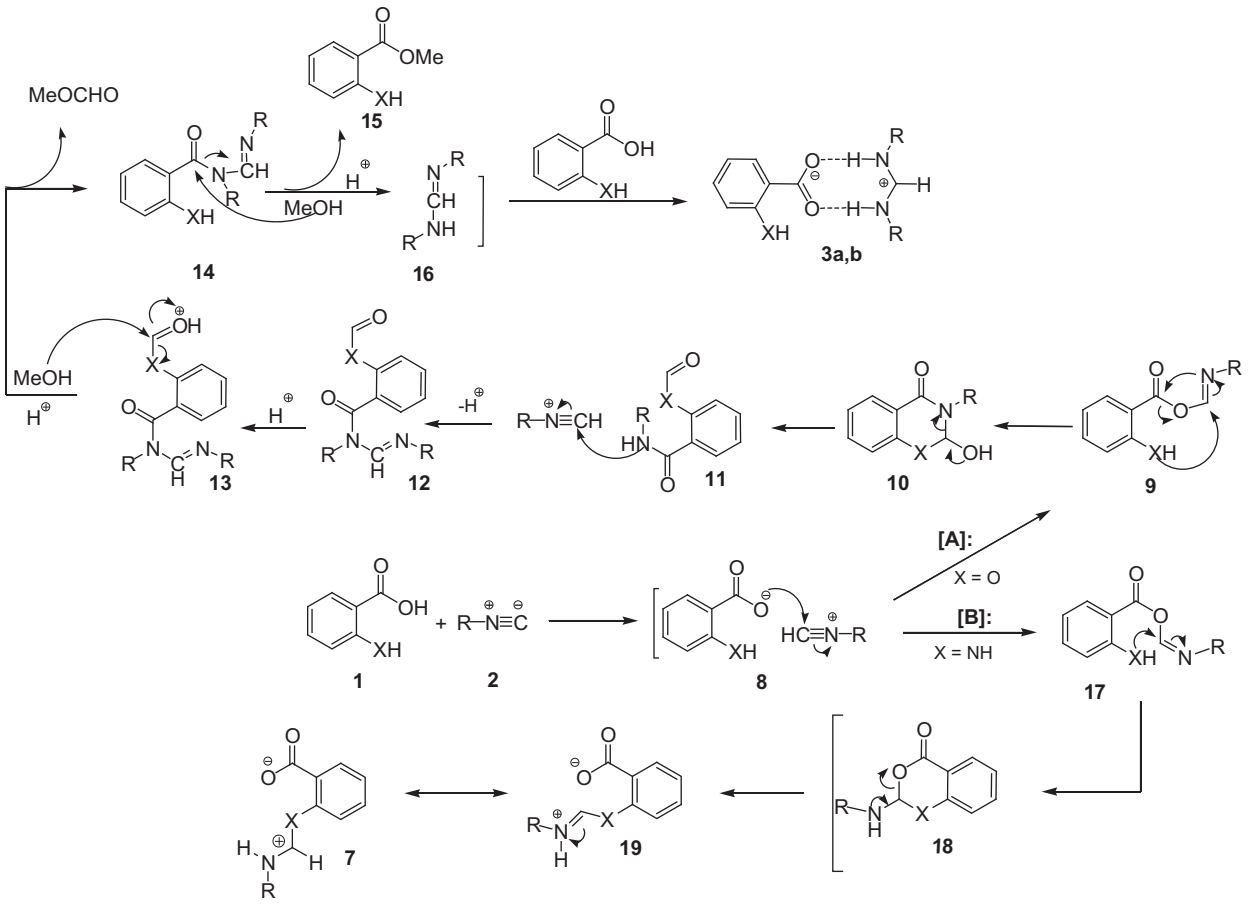
The structure of compound **7** was deduced from its IR, $^{1}$H NMR, and $^{13}$C NMR spectral data. The mass spectrum of this compound displayed a molecular ion peak at the appropriated *m*/*z* value.

The structure of **7** was confirmed unambiguously by single-crystal X-ray analysis (Fig. 2).

We previously reported the reaction of benzoic acid and *meta*- and *para*-substituted (H, Me, Cl, $NO_2$) benzoic acids with various isocyanides which led to benzoic acid-isocyanide salts.[11,12a] The results described herein have shown that an OH or an $NH_2$ group at an *ortho* position of a benzoic acid plays an important role in this reaction, as we obtained different products in comparison to those previously reported by Gloede[14a,b] and our group.[11]

Although the precise mechanistic details of this reaction are not known, plausible pathways (A and B) for the formation of products **3a**,**b** and **7** are proposed in Scheme 4. It is important to note that analysis of the reaction mixture by gas chromatography–mass spectrometry (GC–MS) identified the formation of methyl formate and methyl 2-hydroxybenzoate as by-products, which supports the proposed mechanism.

In conclusion, we have described two unexpected and interesting reactions between isocyanides and *ortho*-hydroxy- and *ortho*-amino-substituted benzoic acids in which several highly stable symmetrical and unsymmetrical alkylamidine and arylamidine carbocations are formed. The high stability of these carbocations can be attributed to delocalization of the positive charge by the two amine groups. Further reactivity studies and investigation of the synthetic applications of this methodology are in progress in our laboratory.




**Scheme 4.** Proposed mechanistic pathways.

## Acknowledgment

We gratefully acknowledge the financial support from the Research Council of Shahid Beheshti University.

## Supplementary data

Crystallographic data (**3a**: CCDC 759357; **7**: 759358). Supplementary data (experimental procedures and spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.132.

## References and notes

1. *Carbonium Ions*; Olah, G. A., Schleyer, P. V. R., Eds.; Wiley-Interscience: New York, 1968–1976; Vols. I–V,. and references therein.
2. Schormann, M.; Garratt, S.; Hughes, D. L.; Green, J. C.; Bochmann, M. *J. Am. Chem. Soc.* **2002**, *124*, 11266–11267.
3. Richard, J. P.; Amyes, T. L.; Toteva, M. M. *Acc. Chem. Res.* **2001**, *34*, 981–988.
4. Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345–375.
5. Baeyer, O.; Villiger, V. *Ber. Dtsch. Chem. Ges.* **1901**, *35*, 1189; 3013.
6. Laube, T. *Chem. Rev.* **1998**, *98*, 1277–1312.
7. Laube, T.; Olah, G. A.; Bau, R. *J. Am. Chem. Soc.* **1997**, *119*, 3087–3092.
8. Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1393–1405.
9. Stadler, D.; Goeppert, A.; Rasul, G.; Olah, G. A.; Prakash, G. K. S.; Bach, T. *J. Org. Chem.* **2009**, *74*, 312–318.
10. Bofill, J. M.; Albericio, F. *Tetrahedron Lett.* **1999**, *40*, 2641–2644.
11. Shaabani, A.; Soleimani, E.; Rezayan, A. H. *Tetrahedron Lett.* **2007**, *48*, 6137–6140.
12. (a) Li, X.; Yuan, Y.; Berkowitz, W. F.; Todaro, L. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13222–13224; (b) Li, X.; Yuan, Y.; Kan, C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13225–13227; (c) Jones, G. O.; Li, X.; Hayden, A. E.; Houk, K. N.; Danishefsky, S. J. *Org. Lett.* **2008**, *10*, 4093–4096; (d) Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 5446–5448; (e) Wu, X.; Li, X.; Danishefsky, S. J. *Tetrahedron Lett.* **2009**, *50*, 1523–1525.
13. (a) Restorp, P.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2008**, *130*, 11850–11851; (b) Hou, J.-L.; Ajami, D.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2008**, *130*, 7810–7811.
14. (a) Gloede, J.; Gross, H. *Z. Chem.* **1968**, *8*, 219; (b) Gloede, J. *J. Prakt. Chem.* **1982**, *324*, 667; (c) Basso, A.; Banfi, L.; Galatini, A.; Guanti, G.; Rastrelli, F.; Riva, R. *Org. Lett.* **2009**, *11*, 4068–4071; (d) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1.
15. (a) Pri-Bar, I.; Schwartz, J. *Chem. Commun.* **1997**, 347–348; (b) Yavari, I.; Roberts, J. D. *J. Org. Chem.* **1978**, *43*, 4689–4693; (c) Tang, J.; Mohan, T.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 4931–4938.
16. Ebert, B. M.; Ugi, I. K.; Grosche, M.; Herdtweck, E.; Herrmann, W. A. *Tetrahedron* **1998**, *54*, 11887–11898.
17. (a) Shaabani, A.; Rezayan, A. H.; Kishipour, S.; Sarvary, A.; Ng, S. W. *Org. Lett.* **2009**, *11*, 3342–3345; (b) Shaabani, A.; Soleimani, E.; Rezayan, A. H.; Sarvary, A.; Khavasi, H. R. *Org. Lett.* **2008**, *10*, 2581–2584; (c) Shaabani, A.; Rezayan, A. H.; Sarvary, A.; Heidary, M.; Ng, S. W. *Tetrahedron* **2009**, *65*, 6063–6068; (d) Shaabani, A.; Sarvary, A.; Rezayan, A. H.; Keshipour, S. *Tetrahedron* **2009**, *65*, 3492–3495; (e) Shaabani, A.; Ghadari, R.; Sarvary, A.; Rezayan, A. H. *J. Org. Chem.* **2009**, *74*, 4372–4374; (f) Shaabani, A.; Rezayan, A. H.; Ghasemi, S.; Sarvary, A. *Tetrahedron Lett.* **2009**, *50*, 1456–1458; (g) Shaabani, A.; Rezayan, A. H.; Rahmati, A.; Sarvary, A. *Synlett* **2007**, 1458–1460.
18. (a) Clare, J. P.; Statnikov, A.; Lynch, V.; Sargent, A. L.; Sibert, J. W. *J. Org. Chem.* **2009**, *74*, 6637–6646; (b) Das, U. K.; Trivedi, D. R.; Adarsh, N. N.; Dastidar, P. *J. Org. Chem.* **2009**, *74*, 7111–7121.
19. (a) Bon, R. S.; de Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Jahnke, M. C.; Hahn, F. E.; Groen, M. B.; Orru, R. V. A. *Organometallics* **2007**, *26*, 3639–3650; (b) Hokelek, T.; Kilic, Z.; Bilge, S. *Acta Crystallogr., Sect. C* **1999**, *55*, 248–250.