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Glyoxylic Acid and MP-Glyoxylate: Efficient Formaldehyde Equivalents in the 3-CC of 2-Aminoazines, Aldehydes, and Isonitriles

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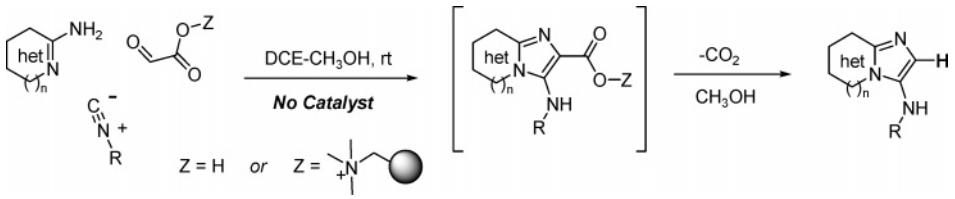
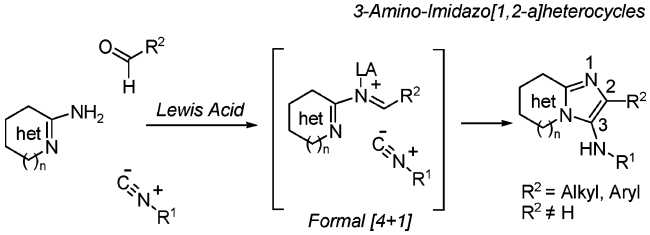
ABSTRACT



Glyoxylic acid, either in solution or immobilized on MP-carbonate (MP-glyoxylate), participates in an uncatalyzed 3-CC with 2-aminoazines and isonitriles to afford novel 2-unsubstituted-3-amino-imidazoheterocycles. MP-glyoxylate serves as a particularly efficient and experimentally convenient formaldehyde equivalent and readily liberates products through decarboxylation/self-release from the resin. These examples furthermore constitute the first application in which MP-CO_3 serves as a solid support for transformations involving carboxylic acids.

A recently discovered variation of the Ugi reaction[1] involving the three-component coupling (3-CC) of 2-aminoazines, isonitriles, and aldehydes[2] has proven to be an efficient means by which to generate fused, imidazo[1,2-*a*]heterocycles in a one-pot transformation (Scheme 1). Subsequent developments of this 3-CC methodology involve application of microwave techniques[3] in addition to polymer-supported adaptations.[4] The industrial relevance of this powerful 3-CC transformation is significant because imidazo[1,2-*a*]heterocycles of this nature have received a great deal of attention in drug discovery. Imidazopyridines, imdazopyrazines, and imidazopyrimidines in particular have been the focus of pharmaceutical investigations across a broad range of therapeutic areas,[5] and these heterocycles are represented by the launched drugs zolimidine, zolpidem, and alpidem.

Scheme 1. Imino-Isonitrile [4 + 1] Cycloaddition (3-CC)



Although the scope of this 3-CC reaction spanning all three substrates is quite impressive, there is, however, no literature precedence for the successful inclusion of formaldehyde as the aldehyde component, thus enabling the synthesis of *2-unsubstituted*-3-amino-imidazoheterocyles. In fact, ex-

(1) For recent reviews describing the Ugi reaction as well as other multicomponent coupling reactions, see: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123.

(2) (a) Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. *Tetrahedron Lett.* **1998**, *39*, 3635. (b) Bienayme, H.; Bouzid, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2234. (c) Groebke, K.; Weber, L.; Mehlin, F. *Synth. Lett.* **1998**, 661.

(3) (a) Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 7665. (b) Ireland, S. M.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2003**, *44*, 4369.

(4) (a) Blackburn, C.; Guan, B. *Tetrahedron Lett.* **2000**, *41*, 1495. (b) Chen, J. J.; Golebiowski, A.; McClenaghan, J.; Klopfenstein, S. R.; West, L. *Tetrahedron Lett.* **2001**, *42*, 2269.

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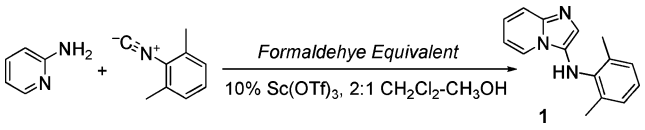
amples of successful preparations of 2-unsubstituted-3-amino-imidazoheteocycles are scarce, and those reported are low-yielding. One report, involving the nitration of an imidazo[1,2-*a*]pyridine and subsequent nitro reduction,[6] provided the desired amino derivative in only 9% overall yield. A second preparation has been achieved in 30% yield through the condensation of 2-aminopyridine, cyanide, and aldehydes in aqueous $NaHSO_3$.[7] A more recent method involves the preparation of 1,2-bis(benzotriazolyl)-1,2-(dialkylamino) ethanes followed by reaction with either aminopyridines or aminopyrimidines in 35−62% yield.[8] None of these methods offer the synthetic efficiency, high yield, and broad scope of the one-pot, convergent 3-CC approach. Moreover and in contrast to the 3-CC reaction, these routes are not readily adaptable toward rapid and diversity-oriented parallel synthesis, a technique of increasing utility in the pharmaceutical industry.

We report herein an efficient and experimentally convenient formaldehyde equivalent prepared by simple immobilization of glyoxylic acid on macroporous polystyrene carbonate (MP-CO_3). This reagent furnishes 2-unsubstituted-3-amino-imidazoheterocyles in good yield when used in the 3-CC reaction and, to the best of our knowledge, *constitutes the first application in which MP-CO_3 serves as a solid support for transformations involving carboxylic acids*.[9] As an alternative to MP-glyoxylate, commercial glyoxylic acid monohydrate in solution may also be applied, affording yields comparable to the resin-bound reagent in most cases.

We initiated our investigation by screening a panel of potential formaldehyde equivalents (Table 1) utilizing the established, $Sc(OTf)_3$-catalyzed 3-CC conditions[2a] with 2-aminopyridine and a readily available aryl isonitrile. This panel included formaldehyde hydrate and paraformaldehyde (entries 1 and 2), both of which did provide the desired product **1** but in low yield primarily as a result of the formation of multiple products and difficult purification. Attempted in situ deprotection and subsequent 3-CC of dimethoxymethane in wet solvent failed to demonstrate any significant reactivity (entry 3). As a result of these initial findings, attention was turned to other potential formaldehyde equivalents.

Table 1. Screen of Potential Formaldehyde Equivalents



entry	CH_2O equivalent	reaction conditions	yield of **1** (%)
1	aq CH_2O	rt, 20 h	36[b]
2	$(CH_2O)_n$	reflux, 20 h	44[b]
3	$CH_2(OCH_3)_2$	4:1 CH_3CN-H_2O, rt, 20 h	nr[a]
4	$CHOCH(OCH_3)_2$	rt, 20 h	10[a]
5	HO_2CCHO	rt, 20 h	31[b]
6	HO_2CCHO	no catalyst, rt, 20 h	51[b]
7	AP-Wang[c]/HO_2CCHO	no catalyst, rt, 20 h	50[a]
8	AP-OH[d]/HO_2CCHO	no catalyst, rt 20 h	47[a]
9	MP-CO_3[e]/HO_2CCHO	no catalyst, rt, 20 h	48[b]
10	**MP-CO_3[e]/HO_2CCHO**	**no catalyst, 50 °C, 20 h**	**71[b]**

[a] Yield determined from LC−MS analysis of crude reaction mixture. [b] Yield after purification via SiO_2 chromatography. [c] Loading of 0.65 mmol/g. [d] Loading of 0.73 mmol/g. [e] Loading of 2.62 mmol/g.

Since there exists precedence for the C-2 and C-3 lithiation of imidazo[1,2-*a*]pyridines,[10] we rationalized that this ability to accommodate a negative charge could translate into facile decarboxylation of 2-carboxyl-imidazo[1,2-*a*]heterocycles derived from a 3-CC reaction employing glyoxylic acid. Along these lines, glyoxylic acid and derivatives thereof were screened in the 3-CC reaction (entries 4−6). Gratifyingly, the reaction of 2-aminopyridine, the aryl isonitrile, and glyoxylic acid provided the desired decarboxylated product **1** with or without Lewis acid activation (entries 5 and 6). In comparison, the yield of the desired product was found to be higher *without* catalytic $Sc(OTf)_3$. It was also discovered during these studies that glyoxylic acid monohydrate could be conveniently used in the reaction, eliminating the need for anhydrous substrate.

In an effort to further optimize the yield and develop a route amendable to parallel synthesis techniques, glyoxylic acid was bound to methanol-compatible resins such as ArgoPore-Wang-OH and ArgoPore-OH[11] via esterification as well as immobilized on MP-CO_3 (entries 7−10). When subjected to the 3-CC, all three resin-bound variants furnished the desired product **1** presumably through a facile decarboxylation/self-cleavage from the resin in the protic solvent system. The most favorable results were achieved in the case of MP-CO_3, which was found to be the most advantageous with respect to yield, experimental simplicity, and high loading capacity.[12] Reagent immobilization was simply executed via premixing the MP-CO_3 and excess

(5) (a) Hamdouchi, C.; de Blas, J.; del Prado, M.; Gruber, J.; Heinz, B. A.; Vance, L. *J. Med. Chem.* **1999**, *42*, 50. (b) Lhassani, M.; Chavignon, O.; Chezal, J.-M.; Teulade, J.-C.; Chapat, J.-P.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clerque, E.; Gueiffier, A. *Eur. J. Med. Chem.* **1999**, *34*, 271. (c) Trapini, G.; Franco, M.; Latrofa, A.; Ricciardi, L.; Carotti, A.; Serra, M.; Sanna, E.; Biggio, G.; Liso, G. *J. Med. Chem.* **1999**, *42*, 3934. (d) Lober, S.; Hubner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 97. (e) Georges, G.; Vercauteren, D. P.; Vanderveken, D. J.; Horion, R.; Evrard, G. H.; Durant, F. V.; George, P.; Wick, A. E. *Eur. J. Med. Chem.* **1993**, 28, 323. (f) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170. (g) Meurer, L, L.; Tolman, R. L.; Chapin, E. W.; Saperstein, R.; Vicario, P. P.; Zrada, M.; MacCoss, M. M. *J. Med. Chem.* **1992**, *35*, 3845. (h) Kaminski, J. J.; Wallmark, B.; Briving, C.; Andersson, B.-M. *J. Med. Chem.* **1991**, *34*, 533. (i) Sablayrolles, C.; Cros, G. H.; Milhavet, J. C.; Rechenq, E.; Chapat, J.-P.; Boucard, M.; Serrano, J. J.; McNeill, J. H. *J. Med. Chem.* **1984**, *27*, 206.

(6) Kaminski, J. J.; Hilbert, J. M.; Pramanik, B. N.; Solomon, D. M.; Conn, D. J.; Rizvi, R. K.; Elliott, A. J.; Guzik, H.; Lovey, R. G. Domalski, M. S.; Wong, S.-C.; Puchalski, C. Gold, E. H.; Long, J. F.; Chiu, P. J. S.; McPhail, A. T. *J. Med. Chem.* **1987**, *30*, 2031.

(7) Groziak, M. P.; Wilson, S. R.; Clauson, G. L.; Leonard, N. J. *J. Am. Chem. Soc.* **1986**, *108*, 8002.

(8) Katritzky, A. R.; Xu, Y.-J.; Tu, H. *J. Org. Chem.* **2003**, *68*, 4935.

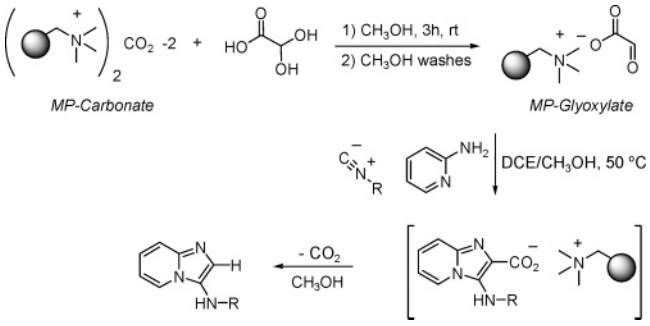
(9) MP-CO_3, available through Argonaut Technologies (www.argotech.com), has been widely used as a polymer-bound base, free-basing agent, and scavenger of acidic species in parallel synthesis.

(10) (a) Lumma, W. C., Jr.; Springer, J. P. *J. Org. Chem.* **1981**, *46*, 3735. (b) Gudmundsson, K. S.; Drach, J. C.; Townsend, L. B. *J. Org. Chem.* **1997**, *62*, 3453.

(11) ArgoPore is a registered trademark of Argonaut Technologies.

(12) MP-CO_3 was purchased from Argonaut Technologies at a claimed loading of 2.62 mmol/g.

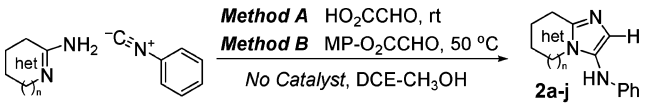
Scheme 2. Immobilization−3CC−Decarboxylation Sequence

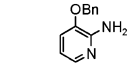
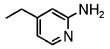
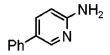
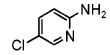
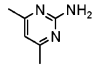
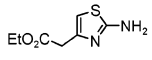


glyoxylic acid monohydrate in methanol at room temperature for 2−3 h followed by wash and immediate use of the resulting MP-glyoxylate in the 3-CC reaction (Scheme 2).[13] The 3-CC/decarboxylation sequence was optimally carried out at 50 °C, which allowed for complete decarboxylation (Table 1, entry 10). There were consequently no instances for which the intermediate C-2 carboxylates were observed in the crude product mixtures.

The scope of the 3-CC reaction, employing both MP-glyoxylate and glyoxylic acid, was explored using a variety of 2-aminoazines in conjunction with phenyl isonitrile

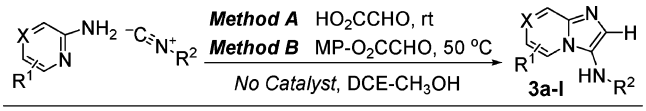
Table 2. Survey of 2-Aminoazines

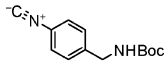
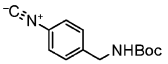
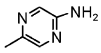
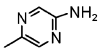
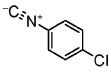
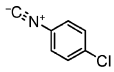
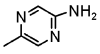
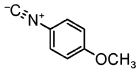
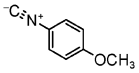
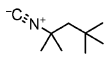
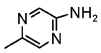
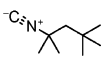
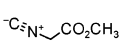
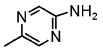
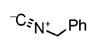


entry	2-aminoazine	product	method A yield (%)	method B yield (%)
1		**2a**	79[a]	78[a]
2		**2b**	60[a]	61[a]
3		**2c**	77[b]	75[a]
4		**2d**	76[b]	72[a]
5		**2e**	85[a]	73[a]
6		**2f**	30[c]	N.D.
7		**2g**	34[c]	31[c]
8		**2h**	34[c]	34[c]
9		**2j**	0[c]	N.D.

[a] Yield after purification by SiO_2 chromatography. [b] Yield after purification by recrystallization. [c] Yield determined from LC−MS analysis of crude reaction mixture.

Table 3. Survey of Isonitriles



entry	isonitrile	2-aminoazine	product	method	yield (%)
1			**3a**	B	63
2			**3b**	A	60
3			**3c**	B	72
4			**3d**	B	71
5			**3e**	B	66
6			**3f**	B	47
7			**3g**	B	53
8			**3h**	A	58
9			**3i**	B	60
10			**3j**	B	56
11			**3k**	A	59
12			**3l**	B	13

(Table 2). Analogous to reported 3-CC reactions involving alkyl and aryl aldehydes,[2] the most favorable yields of purified products were generated from 2-aminopyridines and 2-aminopyrazines providing the corresponding imidazopyridines **2a**−**2d** and imidazopyrazines **2e**−**2f** (entries 1−6).[14] Both electron-donating and electron-withdrawing groups were tolerated on the aminopyridine as well as substitution ortho to the 2-amino functionality. An observed exception was the deactivated 6-chloro-2-aminopyrazine,

(13) Freshly prepared MP-glyoxylate was employed for all reactions. See Supporting Information for experimental procedures.

(14) All isolated compounds were characterized by ^1H NMR, ^{13}C NMR, and MS analysis.

which gave only 30% of the desired product (entry 6). For the majority of substrates examined, similar yields were obtained from either glyoxylic acid (method A) or MP-glyoxylate (method B), thus providing experimental flexibility for size of scale and application. Alternative aminoazines including aminopyrimidines and aminothiazoles produced significantly lower quantities of the imidazoheterocycles **2g**−**2h** in both the MP-glyoxylate and glyoxylic acid reactions as determined by LC−MS analysis of the crude reaction mixture (entries 7 and 8). Isolation of pure product in these instances proved to be extremely difficult.[15] Substrate incompatibility was observed for 3-CC reactions involving aminotriazole, which failed to produce any detectable product (entry 9).

Studies with 2-aminopyridines and 2-aminopyrazines that included variation of the isonitrile component in the 3-CC reaction (Table 3) demonstrated favorable reactivity for both electron-rich (entries 7 and 8) and electron-deficient aryl isonitriles (entries 5 and 6) in addition to functionalized aryl isonitriles such as a Boc-protected aminomethyl derivative (entries 1 and 2). The sterically encumbered 2,6-dimethylphenylisonitrile also exhibited good reactivity (entries 3 and 4). Concerning aliphatic isonitriles, tetramethylbutyl isonitrile proved most interesting because, in addition to providing the 3-CC products (entries 9−10), it may also be utilized as a hydrogen cyanide equivalent upon acid-promoted *N*-dealkylation of the formed *N*-tetramethylbutyl-3-amino-imidazoheterocycles to give primary 3-amino-imidazoheterocycles.[4a] Interestingly, methyl isocyanoacetate (entry 11) reacted smoothly with glyoxylic acid in solution (method A) but failed to provide any desired 3-CC product when MP-glyoxylate was employed (method B). This result may be rationalized by incompatibility between the acidic methyl isocyanoacetate and the basic reaction conditions of method B. The lowest yields observed in this survey of isonitriles occurred when benzylisonitrile was used, furnishing only 13% of the purified 3-CC product (entry 12).

In conclusion, a practical method for the one-pot synthesis of novel *2-unsubstituted*-3-aminoimidazo[1,2-*a*]heterocycles has been achieved using glyoxylic acid as a fomaldehyde equivalent in the three-component coupling of aminoazines, aldehydes, and isonitriles. Glyoxylic acid may be introduced either in solution or immobilized on macroporous polystyrene carbonate resin (MP-CO_3), the latter of which constitutes an unprecedented application of commercial MP-CO_3 and provides a convenient source of immobilized glyoxylic acid capable of partitioning into multiple, parallel reactions. The highest yields for the reaction were obtained from either aminopyridines or aminopyrazines as the aminoazine substrate. This synthetic approach involving MP-glyoxylate as a novel formaldehyde equivalent is potentially applicable to other reactions in which glyoxylic acid is utilized as a key reagent.

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Supporting Information Available: General experimental procedures used for the preparation of **2a**−**e** and **3a**−**l** including ^{1}H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) During the attempted purification of products **2f**−**h**, significant amounts of unreacted aminoazine substrate were detected. When method A was used with prolonged reaction times, the imine derived from methyl glyoxylate and the aminoazine was also isolated, thus suggesting esterification as a competitive reaction in the absence of 3-CC/decarboxylation activity.