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COMMUNICATION

Synthesis of 2-aminofurans and 2-unsubstituted furans *via* carbenoid-mediated [3 + 2] cycloaddition†

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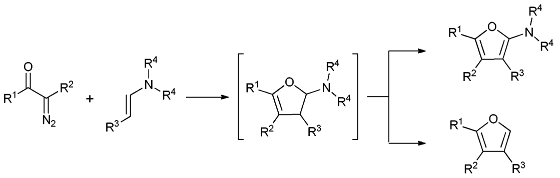
An efficient dual synthetic manifold for 2-aminofurans and 2-unsubstituted furans has been developed. The carbenoid-mediated [3 + 2] cycloaddition of copper carbenoids with enamines provides 2-amino-2,3-dihydrofurans which serve as common intermediates for both 2-aminofurans and 2-unsubstituted furans.

Furans represent an important class of heterocycles due to their prevalence in many biologically active compounds including natural products and pharmaceuticals.[1] 2-Aminofurans serve as versatile synthetic intermediates that have found their utility in the synthesis of various useful compounds including aniline derivatives,[2] cyclohexenones,[3] pyrroles,[4] and maleic anhydrides.[5] Despite their broad utility, the availability of synthetic methods is rather limited, typically relying on cyclization of nitriles[6] and reduction of 2-nitrofurans.[7] Limitations of these methods, however, include requirement of multistep synthesis and inability to provide furans with a wide range of amino groups, typically limited to those with primary amines. Nucleophilic displacement of activated furans with amines has also been reported.[8] While several synthetic methods for 2-*amido*furans have been developed,[9] those that provide 2-*amino*furans bearing substituted amines with simultaneous formation of furan cores are scarce.[10]

Carbenoids have shown their versatility in the synthesis of various heterocycles[11] for which effective strategies have been developed including insertion reaction,[12] cyclopropanation followed by rearrangement,[13] and cycloaddition.[14] Synthesis of furans based on the reaction of carbenoids has also been reported.[15] Given that enamines can be readily prepared with a variety of amines, we envisioned that cycloaddition of carbenoids with enamines may give rise to 2-aminofurans upon oxidation of the cycloadducts 2-amino-2,3-dihydrofurans (eqn (1)). Alternatively, this approach may also provide an efficient route to 2-unsubstituted furans by elimination of amines from the common intermediate, 2-amino-2,3-dihydrofurans. Herein, we wish to describe an efficient dual synthetic manifold for 2-aminofurans and 2-unsubstituted furans.

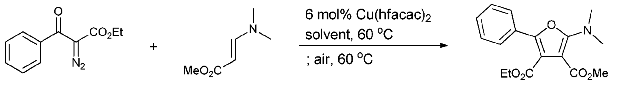


(1)

We commenced with screening of various metal salts for the cycloaddition of **1a** with **2a** (Table 1). The resulting cycloadducts were exposed to ambient air for oxidation to give **3aa**, which was identified as an optimal oxidant while screening various oxidation conditions (Table 2). While $Rh_2(OAc)_4$ failed to give the corresponding cycloadduct, use of copper salts gave more promising results, among which $Cu(hfacac)_2$ was found to be optimal, affording the product in 72% yield (Table 1, entry 6). A brief examination of reaction temperature and solvents revealed that the reaction proceeds most efficiently in dichloroethane at 60 °C. The yield of **3aa** was substantially lower when refluxing dichloroethane was employed (Table 1, entry 7). Among the solvents examined, dichloroethane was found to be optimal (Table 1, entries 6 *vs.* 8–10).

With the optimal conditions for the cycloaddition in hand, we turned our attention to the oxidation of 2-amino-2,3-dihydrofurans to 2-aminofurans (Table 2). Exposure of cycloadduct **3′aa** to various oxidants provided 2-aminofuran

Table 1 Optimization of cycloaddition



1a **2a** **3aa**

Entry	Catalyst[a]	Solvent[b]	Yield[c] (%)
1	$Rh_2(OAc)_4$	DCE	0
2	Cu(OTf)	DCE	31
3	$Cu(OTf)_2$	DCE	33
4	$Cu(acac)_2$	DCE	19
5	$Cu(OAc)_2$	DCE	20
6	$\mathbf{Cu(hfacac)_2}$	**DCE**	**72**
7	$Cu(hfacac)_2$	DCE	48[d]
8	$Cu(hfacac)_2$	Benzene	36
9	$Cu(hfacac)_2$	$PhCF_3$	45
10	$Cu(hfacac)_2$	1,4-Dioxane	trace

[a] acac = acetylacetonate, hfacac = hexafluoroacetylacetonate. [b] DCE = dichloroethane. [c] Determined by NMR *vs.* standard. [d] Reaction performed at 80 °C.

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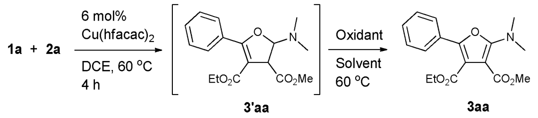
Table 2 Optimization of oxidation of 2-amino-2,3-dihydrofuran

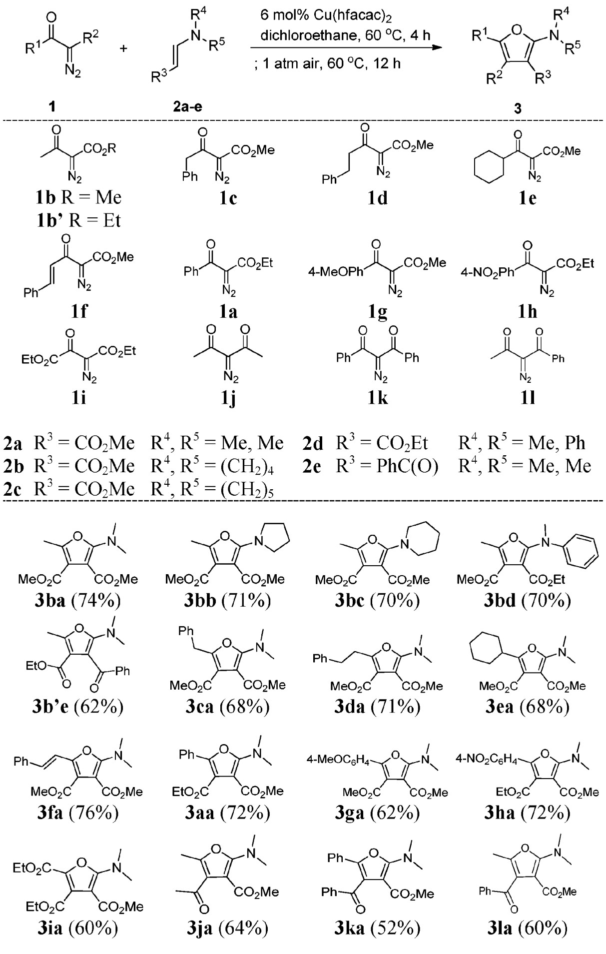


Entry	Oxidant[a]	Solvent[b]	Yield[c] (%)
1	MCPBA	DCM	34
2	DDQ	Toluene	52
3	Ag_2O	Benzene	36
4	$Cu(OAc)_2$	DCE	42
5	$Mn(OAc)_3$	AcOH	45
6	CAN	CH_3CN	49
7	1 atm O_2	DCE	—
8	1 atm **Air**	**DCE**	**72**

[a] MCPBA = *meta*-chloroperbenzoic acid, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, CAN = cerium ammonium nitrate. [b] DCE = dichloroethane. [c] Determined by NMR *vs.* standard.

3aa in *albeit* low to moderate yields (Table 2, entries 1–6). Also, use of 1 atm of oxygen resulted in complete decomposition of the substrate (Table 2, entry 7). Gratifyingly, when ambient air was used as an oxidant, the reaction proceeded smoothly to give **3aa** in 72% yield (Table 2, entry 8). Presumably, the sensitive nature of 2-aminofurans requires extremely mild oxidation conditions.

Table 3 Substrate scope for 2-aminofurans[a]



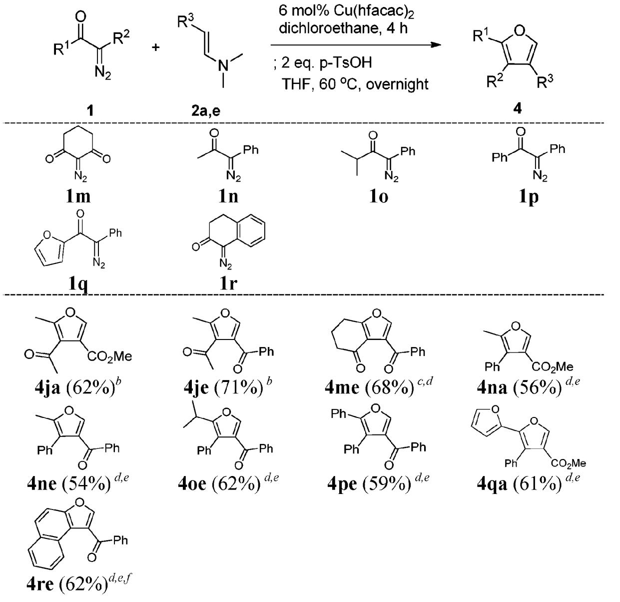
[a] Yield of isolated products.

Next, we examined the substrate scope for the synthesis of 2-aminofurans (Table 3). The reaction of various diazo compounds with enamines was shown to produce 2-aminofurans in good yields. Examination of β-amino acrylates bearing different amino substituents revealed that the reaction tolerates a wide range of amines including acyclic, cyclic, and aromatic amines to give the corresponding 2-aminofurans (Table 3, **3ba–bd**). In addition, 2-aminofurans functionalized with ketones could be readily prepared by employing 3-amino-2-alkenones in place of β-amino acrylates (Table 3, **3b′e**).

The generality of the reaction was also examined with a variety of α-diazo-β-keto esters bearing substituents with distinct steric and electronic influences. Alkyl substituted diazo compounds afforded the corresponding 2-aminofurans in good yields (Table 3, **3ca–ea**). Furthermore, vinyl substituted diazo compound **1f** also gave the corresponding 2-aminofuran **3fa** in 76% yield. Diazo compounds with electron-rich and deficient aryl groups also gave the corresponding products in good yields (Table 3, **3aa**, **3ga**, and **3ha**). In addition, use of γ-ethoxycarbonyl diazo compound **1i** led to the formation of the highly functionalized 2-aminofuran **3ia** in 60% yield. Reaction of α-diazo-β-diketones also smoothly provided 2-aminofurans functionalized with ketone moieties (Table 3, **3ja** and **3ka**). Furthermore, reaction of unsymmetrical α-diazo-β-diketone **1l** with **2a** led to regioselective formation of **3la** arising from the more reactive aliphatic ketone participating in the cycloaddition.

Next, we examined the feasibility of access to 2-unsubstituted furans by elimination of amines from 2-amino-2,3-dihydrofuran intermediates. Thus, subjection of α-diazo-β-diketone **1j** and β-amino acrylate **2a** to the same reaction conditions (6 mol% $Cu(hfacac)_2$, dichloroethane, 60 °C, 4 h) provided 2-amino-2,

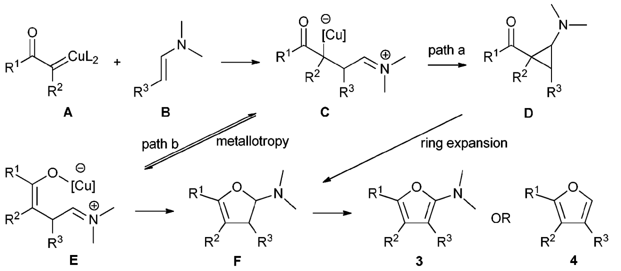
Table 4 Substrate scope for 2-unsubstituted furans[a]



[a] Yield of isolated products. [b] Reaction performed at 60 °C. [c] Reaction performed at 80 °C. [d] Product obtained without acid treatment. [e] Reaction performed at RT. [f] Reaction performed overnight.

3-dihydrofuran which upon heating in the presence of *p*-toluenesulfonic acid afforded furan **4ja**. Encouraged by this result, we examined the influence of structural alteration of coupling partners (Table 4). We observed that elimination of amines occurs spontaneously for the diazo compounds with mono ketones obviating acid treatment (see the footnotes to Table 4). Use of 3-amino-2-alkenone **2e** in place of β-amino acrylate also gave **4je** in 71% yield. Reaction of cyclic α-diazo-β-diketone **1m** smoothly proceeded to give fused bicyclic furan **4me**. In addition to α-diazo-β-dicarbonyl compounds, α-diazo-α-aryl ketone **1n** afforded aryl substituted furan **4na**. More elaborate α-diazo-α-aryl ketones bearing alkyl and aryl moieties allowed for the formation of the corresponding furans (Table 4, **4oe** and **4pe**). Furthermore, reaction of diazo compound **1q** bearing a 2-furanyl group with **1a** also smoothly proceeded to give **4qa** in 61% yield. Use of β-tetralone-derived diazo compound **1r** gave the tricyclic furan **4re** in good yield, resulting from spontaneous oxidation.

Mechanistically, we propose that nucleophilic attack of **B** on carbenoid **A** leads to formation of **C** that may undergo either cyclopropanation to give **D** followed by ring expansion or direct cyclization of **E** *via* metallotropy to afford **F** (eqn (2)).



(2)

In summary, we described an efficient dual synthetic manifold for both 2-aminofurans and 2-unsubstituted furans. This has been achieved by reaction of carbenoids with enamines to afford 2-amino-2,3-dihydrofurans, which depending on the choice of subsequent conditions furnish either 2-aminofurans or 2-unsubstituted furans in good yields.

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Notes and references

1 (*a*) S. F. Kirsch, *Org. Biomol. Chem.*, 2006, **4**, 2076–2080; (*b*) R. C. D. Brown, *Angew. Chem., Int. Ed.*, 2005, **44**, 850–852; (*c*) X.-L. Hou, Z. Yang, K.-S. Yeung and H. N. C. Wong, in *Progress in Heterocyclic Chemistry*, ed. W. G. Gordon and A. J. John, Elsevier, 2009, vol. 21, pp. 179–223; (*d*) W. Dennis L, in *Progress in Heterocyclic Chemistry*, ed. W. G. Gordon and A. J. John, Elsevier, 2005, vol. 17, pp. 1–32.

2 (*a*) F. R. Petronijevic and P. Wipf, *J. Am. Chem. Soc.*, 2011, **133**, 7704–7707; (*b*) B. M. Trost and P. J. McDougall, *Org. Lett.*, 2009, **11**, 3782–3785; (*c*) R. Medimagh, S. Marque, D. Prim, S. Chatti and H. Zarrouk, *J. Org. Chem.*, 2008, **73**, 2191–2197.

3 (*a*) J. Boonsompat and A. Padwa, *J. Org. Chem.*, 2011, **76**, 2753–2761; (*b*) H. Zhang, J. Boonsombat and A. Padwa, *Org. Lett.*, 2006, **9**, 279–282.

4 S. Kiren, X. Hong, C. A. Leverett and A. Padwa, *Org. Lett.*, 2009, **11**, 1233–1235.

5 K. C. Nicolaou, P. S. Baran, Y. L. Zhong, K. C. Fong and H. S. Choi, *J. Am. Chem. Soc.*, 2002, **124**, 2190–2201.

6 (*a*) M. Murai, K. Miki and K. Ohe, *Chem. Commun.*, 2009, 3466–3468; (*b*) P. Liu, M. Lei, L. Ma and L. Hu, *Synlett*, 2011, 1133–1136.

7 R. J. Rahaim and R. E. Maleczka, *Org. Lett.*, 2005, **7**, 5087–5090.

8 R. Medimagh, S. Marque, D. Prim and S. Chatti, *Org. Biomol. Chem.*, 2011, **9**, 6055–6065.

9 (*a*) S. Kramer, J. L. H. Madsen, M. Rottländer and T. Skrydstrup, *Org. Lett.*, 2010, **12**, 2758–2761; (*b*) H. Li and R. P. Hsung, *Org. Lett.*, 2009, **11**, 4462–4465; (*c*) A. Padwa, K. R. Crawford, P. Rashatasakhon and M. Rose, *J. Org. Chem.*, 2003, **68**, 2609–2617.

10 (*a*) V. Nair and A. U. Vinod, *Chem. Commun.*, 2000, 1019–1020; (*b*) R. Mossetti, D. Caprioglio, G. Colombano, G. C. Tron and T. Pirali, *Org. Biomol. Chem.*, 2011, **9**, 1627–1631.

11 (*a*) V. F. Ferreira, *Curr. Org. Chem.*, 2007, **11**, 177–193; (*b*) J. Barluenga, L. Riesgo, R. n. Vicente, L. A. López and M. Tomás, *J. Am. Chem. Soc.*, 2008, **130**, 13528–13529; (*c*) E. Lourdusamy, L. Yao and C.-M. Park, *Angew. Chem., Int. Ed.*, 2010, **49**, 7963–7967.

12 J. R. Davies, P. D. Kane and C. J. Moody, *Tetrahedron*, 2004, **60**, 3967–3977.

13 H. M. L. Davies, G. Ahmed, R. L. Calvo, M. R. Churchill and D. G. Churchill, *J. Org. Chem.*, 1998, **63**, 2641–2645.

14 (*a*) A. Padwa and S. K. Bur, *Tetrahedron*, 2007, **63**, 5341–5378; (*b*) S. Muthusamy and J. Krishnamurthi, in *Synthesis of Heterocycles via Cycloadditions I*, ed. A. Hassner, 2008, vol. 12, pp. 147–192.

15 (*a*) L.-B. Zhao, Z.-H. Guan, Y. Han, Y.-X. Xie, S. He and Y.-M. Liang, *J. Org. Chem.*, 2007, **72**, 10276–10278; (*b*) Y. R. Lee and J. Y. Suk, *Tetrahedron*, 2002, **58**, 2359–2367; (*c*) T. Johnson, D. R. Cheshire, M. J. Stocks and V. T. Thurston, *Synlett*, 2001, 0646–0648; (*d*) Y. Zhu, C. Zhai, L. Yang and W. Hu, *Chem. Commun.*, 2010, **46**, 2865–2867.