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Regioselective synthesis of 3,4,5-trisubstituted 2-aminofurans†

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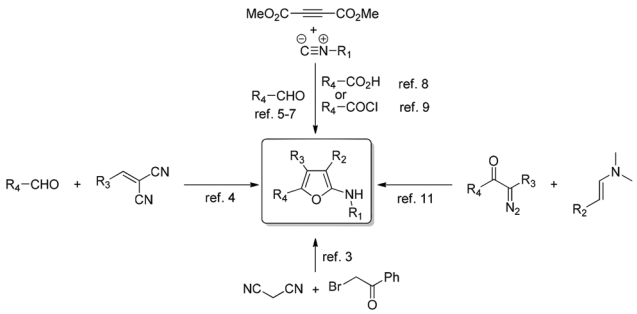
Three series of methyl 5-substituted 2-aminofuran-4-keto-3-carboxylates have been prepared following a multicomponent reaction strategy by the addition of an isocyanide to 4-oxo-2-butynoate in the presence of an aldehyde. The cycloaddition regioselectivity is generally high (>95%) but decreases when an electron-rich substituent is located at the butynoate 4-position.

Furan is an important five membered O-heterocycle frequently present in biologically important natural products and pharmaceutical substances.[1] 2-Aminofurans are powerful synthetic intermediates[2] whose use is somehow hampered by their limited availability. Such a limitation is particularly stressed for 3,4,5-trisubstituted 2-aminofurans. Indeed, if 3-cyano-4,5-disubstituted-2-aminofurans can be prepared by reaction of α-bromoacetophenones with malononitrile,[3] or by a cascade Stetter-γ-keto nitrile cyclization reaction of aromatic aldehydes and acylidenemalononitriles,[4] most of the reported 3,4,5-trisubstituted-2-aminofurans have been prepared by nucleophilic addition of isocyanides to dimethyl acetylenedicarboxylate in the presence of mainly aromatic aldehydes,[5] but also conjugated aldehydes,[6] or modified aldehydes,[7] acids,[8] or acyl chlorides[9] (Scheme 1).

Diaroylacetylenes (1,4-diarylbut-2-yne-1,4-diones) have also been scarcely but successfully used in place of dimethyl acetylenedicarboxylate[10] (Scheme 1). However, despite its chemical efficiency the isocyanide-based multicomponent approach has exclusively been applied to symmetrical alkynes, allowing the preparation of 3,4,5-trisubstituted-2-aminofurans presenting simultaneously either a diketo- or a diester-functionality at C3 and C4, so far. Recently, a two-step synthesis of three 3,4,5-trisubstituted-2-aminofurans in which the 3- and 4-positions are functionalized with an ester and keto group, respectively, has been reported[11] (Scheme 1).



Scheme 1 Known strategies to prepare 3,4,5-trisubstituted 2-aminofurans.

This synthesis necessitates the oxidation of a 2-amino-2,3-dihydrofuran initially resulting from the reaction of carbenoids with enamines. Taking advantage of the high isocyanide reactivity, we report the regioselective one-step synthesis of 3,4,5-trisubstituted 2-aminofurans in which the 3- and 4-positions are functionalized with an ester and keto group.

First we screened experimental conditions of the three component reaction using benzaldehyde, the known methyl 4-oxo-2-alkynoate (**1**),[12] and *tert*-butyl isocyanide (**4**) in various solvents (Table 1). Even though [Bmim]BF_4, toluene/benzene, or PEG 400 have been reported to be suitable solvents for such cycloaddition reactions,[5a–f,6] in our hands those solvents failed to deliver the expected furan (Table 1, entries 1–3). Interestingly, the use of H_2O as a solvent led to 2-aminofuran **5a** in around 68% yield, depending on the reaction temperature (Table 1, entries 4 and 5). Replacement of water with dichloromethane afforded the expected 2-aminofuran in 55% yield when the reaction was performed at room temperature and 72% upon heating at 70 °C (sealed tube) (Table 1, entries 6 and 7). Furthermore and delightedly, the ^{1}H-NMR spectrum of the crude reaction mixture evidenced that the successful cyclo-

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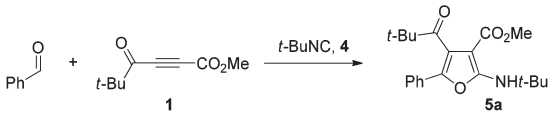
†Electronic supplementary information (ESI) available: Synthesis, characterization of new compounds, computational details and crystallographic data of **7b** and **8b**. CCDC 949882 and 949883. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01037j

Table 1 Screening of the reaction conditions for 2-aminofuran synthesis



1 5a

Entry	Solvent, conditions	Yield (%)
1	PEG 400,[a] RT, 24 hours	0
2	$C_6H_5CH_3$, reflux, 24 hours	0
3	[Bmim]BF_4, RT, 24 hours	0
4	H_2O, RT, 24 hours	69
5	H_2O, 110 °C, sealed tube, 24 hours	66
6	CH_2Cl_2, RT, 24 hours	55
7	CH_2Cl_2, 70 °C, sealed tube, 24 hours	72

[a] PEG = poly(ethylene glycol).

Table 2 Cycloaddition yield (%) using methyl 5,5-dimethyl-4-oxohex-2-ynoate (**1**) or methyl 4-phenyl-4-oxo-2-butynoate (**2**) and various aromatic aldehydes

1, R = t-Bu
2, R = Ph
5, R = t-Bu
6, R = Ph

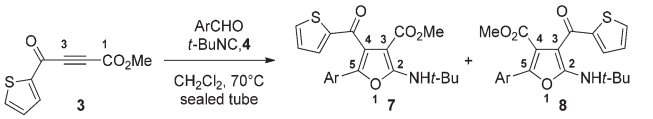
Ar	5[a,b]	6[a,b]
Ph	**5a** (72)	**6a** (52)
p-O_2N-C_6H_4	**5b** (93)	**6b** (79)
m-O_2N-C_6H_4	**5c** (92)	**6c** (78)
Piperonyl[c]	**5d** (53)	**6d** (45)
p-H_3C-C_6H_4	**5e** (61)	**6e** (57)
p-F-C_6H_4	**5f** (50)	**6f** (52)
2-(Pivaloyloxy)-C_6H_4	**5g** (60)	**6g** (58)
3-(Pivaloyloxy)-C_6H_4	**5h** (53)	**6h** (50)
4-(Pivaloyloxy)-C_6H_4	**5i** (62)	**6i** (52)
3,5-Dimethoxy-4-(pivaloyloxy)-C_6H_2	**5j** (70)	**6j** (63)
2-(3-Methyl)thiophenyl	**5k** (59)	**6k** (53)

[a] Reactions were conducted using 1 eq. of **1** (or **2**) and 1.1 eq. of *tert*-butyl isocyanide (**4**). [b] Isolated yields. [c] 5-Benzo[*d*][1,3]dioxole.

addition was accompanied by single regioisomer formation. Characteristic ^{13}C chemical shift of 2-aminofuran C3- and C4-atoms at δ 91.0 and 123.6, respectively,[11] unequivocally indicated the exclusive (above 95%) formation of **5a** (Table 1), the furan resulting from a nucleophilic attack of the isocyanide at the carbon alpha of the methyl 4-oxo-2-alkynoate ester group.[13]

Then, we focused on the cycloaddition regioselectivity. We observed that aldehydes had no influence on the regioselectivity since all eleven studied aromatic aldehydes afforded only one regioisomer with the yield of 50–95% after cycloaddition in the presence of **1** or **2** in CH_2Cl_2 at 70 °C (Table 2). If nitrobenzaldehydes and benzaldehyde afforded tetrasubstituted furans in high yield, 2-aminofurans **5f** or **5h**, and **6f** or **6h** resulting from 4-fluorobenzaldehyde or 4-pivaloyloxybenzaldehyde, respectively, were obtained in only 50% yield (Table 2).

Table 3 Cycloaddition yield (%) using methyl 4-oxo-4-(thiophen-2-yl)-but-2-ynoate (**3**) and various aromatic aldehydes



3 1 7 1 8

Ar	Isomer 7[a,b]	Isomer 8[a,b]
Ph	**7a** (40)	**8a** (10)
p-O_2N-C_6H_4	**7b** (62)	**8b** (30)
m-O_2N-C_6H_4	**7c** (61)	**8c** (25)
Piperonyl[c]	**7d** (23)	**8d** (9)
p-H_3C-C_6H_4	**7e** (32)	**8e** (8)
p-F-C_6H_4	**7f** (42)	**8f** (8)
2-(Pivaloyloxy)-C_6H_4	**7g** (47)	**8g** (–)
3-(Pivaloyloxy)-C_6H_4	**7h** (35)	**8h** (12)
4-(Pivaloyloxy)-C_6H_4	**7i** (41)	**8i** (12)
3,5-Dimethoxy-4-(pivaloyloxy)-C_6H_2	**7j** (40)	**8j** (13)
2-(3-Methyl)thiophenyl	**7k** (26)	**8k** (8)

[a] Reactions were conducted using 1 eq. of **3** and 1.1 eq. of *tert*-butyl isocyanide (**4**). [b] Isolated yields. [c] 5-Benzo[*d*][1,3]dioxole.

Then, to evaluate the influence of the C4-alkyne substituent on the regioselectivity, we used methyl 4-phenyl-4-oxo-2-butynoate (**2**)[12,14] in place of **1**. In that case, cycloaddition again nicely occurred with a higher than 95% regioselectivity (Table 2). However, it was associated with a slightly lower chemical yield compared to those observed with **1**.

More contrasting results were obtained when methyl 4-oxo-4-(thiophen-2-yl)but-2-ynoate[15] (**3**) was used. In this case, even though global chemical yields were similar to those observed with **1** or **2**, a minor regioisomer (**8**) resulting from the nucleophilic isocyanide attack at α-position of the keto group was isolated together with **7**, the regioisomer resulting from a similar attack at β-position of the keto group (Table 3).

The structures of **7b** and **8b** (Ar = *p*-NO2-C_6H_4) were unambiguously solved by X-ray crystallography (Fig. 1). A high reactivity of the α-position of the methoxycarbonyl group of alkynes such as **1–3** towards nucleophilic attack has generally been assumed since the pioneering work of Jones *et al.*[13] However, the reactivity of the Michael-acceptor is known to be reduced if it is substituted with an electron rich group.[16,17] It is very likely that the electron-rich thienyl group modifies the alkyne charge distribution, resulting in a lower regioselectivity of the isonitrile attack.

In order to explain the observed regioselectivity, we determined DFT-based reactivity[18] and Fukui condensed indices[19] f_k^+ and f_k^- [20] widely used to study 1,3-dipolar cycloadditions.[21] As expected, *tert*-butyl isocyanide (**4**) featured a f_k^- concentrated on the isocyanide carbon (0.581 unit). Interestingly, alkyne **1** featured a f_k^+ concentrated on carbon 2 (0.178 unit) associated with a high discrimination between the two reactive alkyne carbons (difference of 0.134 unit in favor of carbon 2).

Conversely, alkynes **2** and **3** displayed a more balanced Fukui indices distribution. Indeed, whereas the highest f_k^+ was again concentrated on carbon 2 (0.051 and 0.105 unit for **2** and **3**, respectively), f_k^+ indices on carbon 3 were calculated

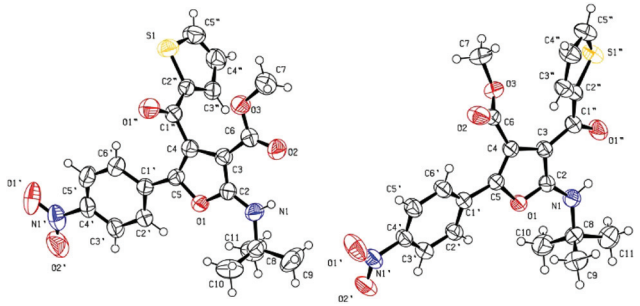


Fig. 1 ORTEP (50% ellipsoid probability) diagram of regioisomers **7b** (left) and **8b** (right).

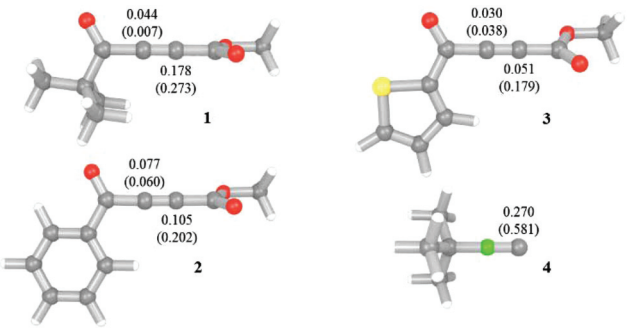


Fig. 2 Calculated DFT-based reactivity indices at the M062X/6-31G(d,p) level of theory. (Fukui f_k^+ electrophilic indices are specified over reactive carbons and f_k^- nucleophilic indices are specified in parentheses.)

to be 0.077 and 0.030 unit for **2** and **3**, respectively. These results are fully in accordance with the regioselectivity observed for the cycloaddition involving alkynes **1** and **2**, but do not explain the experimental results obtained for alkyne **3** (Fig. 2). Therefore a more detailed computational study needs to be performed. Such a study is currently in progress in our laboratory.

Conclusions

In conclusion, we have been able to prepare a large variety of 3,4,5-trisubstituted 2-aminofurans from 4-oxo-2-alkynoates and isocyanides. The reaction occurs in a highly regioselective manner that could be however reduced if the keto substituent is electron rich.

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