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

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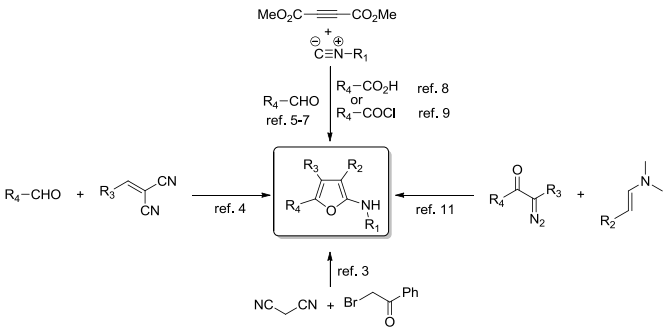
Three series of methyl 5-substituted 2-aminofuran-4-keto-3-carboxylates have been prepared following a multicomponent reaction strategy by the addition of an isocyanide to 4-oxo-2-butynoate in the presence of an aldehyde. The cycloaddition regioselectivity is generally high (>95%) but decreases when 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 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 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 acetyledicarboxylate in the presence of majoritarily aromatic aldehydes,[5] but also conjugated aldehydes,[6] or modified aldehydes,[7] acids,[8] acyl chlorides[9] (Scheme 1).

Diaroylacetylenes (1,4-diarylbut-2-yne-1,4diones) 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 C_3 and C_4, so far. Recently, the two-step synthesis of three 3,4,5-trisubstituted-2-aminofurans in which the 3- and 4-position 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-position are functionalized with an ester and keto group.

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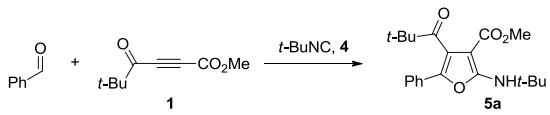
Table 1 Screening of the reaction conditions for 2-aminofurane synthesis

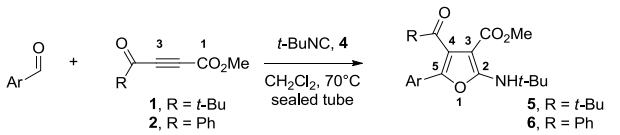


Entry	Solvent, conditions	Yield (%)
1	PEG 400,[a] RT, 24hrs	0
2	$C_6H_5CH_3$, reflux, 24hrs	0
3	[Bmim]BF_4, RT, 24hrs	0
4	H_2O, RT, 24hrs	69
5	H_2O, 110°C, sealed tube, 24hrs	66
6	CH_2Cl_2, RT, 24hrs	55
7	CH_2Cl_2, 70°C, sealed tube, 24hrs	72

[a] PEG = poly(ethylene glycol)

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 as 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 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 cycloaddition 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 signed 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]

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



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)

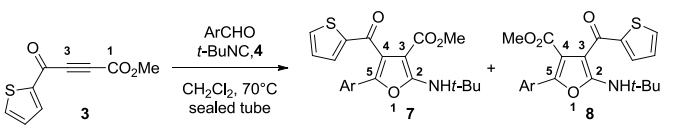
[a] Reactions were conducted using 1 Eq. of **1** (or **2**) and 1.1 Eq. of *tert*-butyl isocyanide (**4**); [b] Isolated yields; [c] 5-Benzo[d][1,3]dioxole.

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).

Then, to evaluate the influence of the C_4-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, associated with slightly lower chemical yield compared to those observed with **1**.

More contrasted results were obtained when methyl 4-oxo-4-(thiophen-2-yl)but-2-ynoate[15] (**3**) was used. In this case, and 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 the similar attack at β-position of the keto group (Table 3).

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



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.

The structure of **7b** and **8b** (Ar=*p*-NO2-C_6H_4) were unambiguously solved by X-ray crystallography (Figure 1). The high reactivity of the α-position of the methoxycarbonyl group of alkynes as **1**-**3** towards nucleophilic attack has generally been assumed since the pioneer 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] Fukui condensed indices[19] f_k^+ and f_k^-[20] widely used to study of 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).

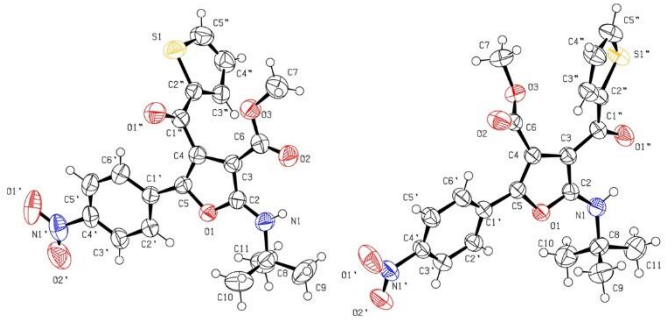


Figure 1 ORTEP (50% ellipsoid probability) diagram of regioisomer **7b** (left) and **8b** (right).

Conversely, alkynes **2** and **3** displayed a more balanced Fukui indice distribution. Indeed, whereas the highest f_k^+ was again concentrated on carbon 2 (0.051 and 0.105 unit for **2** and **3**, respectively) but f_k^+ indice on carbon 3 were calculated 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**.Therefore a more intrusive computational study needs to be performed. Such study is currently in progress in our Laboratory.

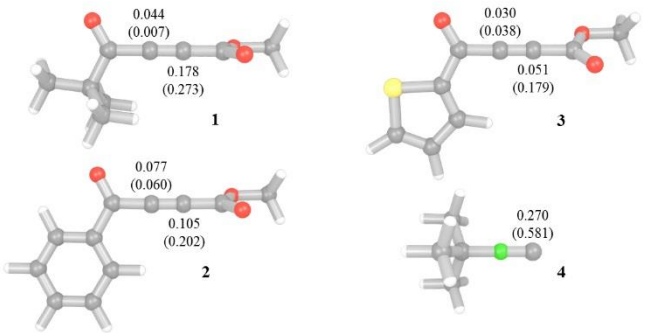


Figure 2 Calculated DFT-based reactivity indices at the M062X/6-31G(d,p) level of theory. (Fukui f_k^+ electrophilic indices are specified over reactive carbons and f_k^- nucleophilic indices are specified in parentheses)

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 high regioselective manner that could be however reduced if the keto substituent is electron rich.

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