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A Facile and Efficient Reaction of Aromatic Aldehydes with the Isocyanide-Dialkylacetylenedicarboxylate Zwitter Ions: Formation of 2-Amino-5-aryl Furan Derivatives

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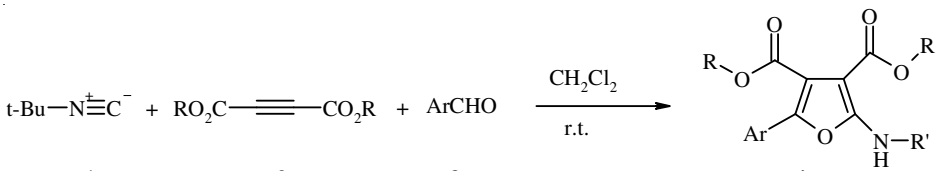
The 1:1 intermediate generated by the addition of *t*-butyl isocyanide to dialkyl acetylene dicarboxylate is trapped by various aromatic aldehydes to yield 2-amino-5-aryl furan derivatives.

Key Words: *tert*-Butyl isocyanide, Benzaldehyde, Furfural, Biphenyl carbaldehyde, 2-Amino-5-aryl furan.

INTRODUCTION

Isocyanides are known to form zwitter ions with activated acetylenic compounds such as dialkyl acetylene dicarboxylates[1-4]. In recent years it has been shown that these type of zwitter ions can be trapped by a variety of electrophiles and proton donors, for the synthesis of heterocyclic compounds[5-9]. Polysubstituted furan play an important role in organic chemistry not only due to their presence as key structural units in many natural products[10] and in important pharmaceuticals[11]. They can also be employed in synthetic chemistry as building blocks. There have been numerous approaches towards their synthesis of substituted one[12]. Herein, a facile and efficient synthetic route to poly functionalized furans using *tert*-butyl isocyanide and dialkyl acetylene dicarboxylate in presence of aromatic aldehydes such as benzaldehyde, furfural and biphenyl carbaldehyde is reported.

Thus 1:1 intermediate generated by the addition of *tert*-butyl isocyanide (**1**) to dialkyl acetylenedicarboxylate (**2**) was trapped by aromatic aldehyde (**3**) to yield dimethyl-2-(*tert*-butyl amino)-5-aryl-3,4-furan dicarboxylate (**4**) (**Scheme-I**).



1 **2** **3** **4**

4	R	Ar	Yield (%)
4a	Me	Phenyl	88
4b	Me	Biphenyl	90
4c	Et	Biphenyl	85
4d	t-Bu	Furyl	82

Scheme-I

The structures of compounds **4a-d** were deduced from their elemental analysis and their IR, ^{1}H and ^{13}C NMR spectra.

The ^{1}H NMR of **4a** exhibited three singlets identified as *tert*-butyl (δ = 1.47 ppm), methoxy (δ = 3.75 and 3.89 ppm) protons, a broad band signal for the NH proton along with a triplet of triplet (δ = 7.24 ppm, ^3J = 7.5 Hz and ^4J = 1.2 Hz), a triplet (δ = 7.34 ppm, ^3J = 7.5 Hz) and a doublet of doublet (δ = 7.51 ppm, ^3J = 7.5 Hz and ^4J = 1.2 Hz) for *para*, *meta* and *ortho*-protons, respectively. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 14 distinct resonances that confirms the proposed structure. The structural assignment of compound **4a** made on the basis of its NMR spectra was supported by its IR spectrum. Of special interest is the NH absorption band at 3357 cm^{-1} and the carbonyl groups at 1734 cm^{-1}.

The nature of **4a** as 1:1:1 adducts was apparent from its mass spectrum, which displayed the molecular ion peak at 331.

The ^{1}H and ^{13}C NMR spectra of **4b-d** are similar to those for **4a** except for the ester and aromatic moieties. The mass spectra data for **4b-d** exhibited the molecular ion peaks at 409, 435 and 405, respectively.

EXPERIMENTAL

Isocyanides, aromatic aldehydes and dialkyl acetylene dicarboxylates were obtained from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHN-O- Rapid analyzer. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-500 Avance spectrometer at 500 and 125.8 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV.

General procedure: To a magnetically stirred solution of aromatic aldehyde (2 mmol) and dialkyl acetylene dicarboxylate (2 mmol) in dry CH_2Cl_2 (10 mL), dropwise, 2 mmol of *tert*-butyl isocyanide in CH_2Cl_2 (4 mL) was added at room temperature. The mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was separated by silica gel (Merck silica gel, 230-400 mesh) column chromatography using hexane:ethyl acetate (70:30) as eluent.

Dimethyl-2-(*tert*-butylamino)-5-phenyl-3,4-furan dicarboxylate (4a): Yellow powder, m.p. 78-80 °C, yield 88 %, IR (KBr, ν_{max}, cm^{-1}): 3357, 1734, 1679, 1618, 1415. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 (s, 9H, CMe_3), 3.75 and 3.89 (2s, 6H, 2 × OCH_3), 6.79 (br s, 1H, NH), 7.24 (tt, $^3J_{HH}$ = 7.5 Hz and $^4J_{HH}$ = 1.2 Hz, 1H, H_{para}), 7.34 (t, $^3J_{HH}$ = 7.5 Hz, 2H, H_{meta}), 7.51 (dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.2 Hz, 2H, H_{ortho}); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 29.8 ($NHCMe_3$), 51.1 ($NCMe_3$), 52.5, 52.76 ($2OCH_3$), 88.5 (NC=C), 113.1 (OC=C), 124.4, 127.6, 128.7, 129.2 (aromatic carbons), 141.2 (C), 161.5 (C), 165.0, 166.0 (2CO); MS: m/z (%): 331 (M^+, 85), 300 (10), 275 (100), 243 (68), 211 (83), 105 (81), 77 (30), 57 (24). Anal. calcd. for $C_{18}H_{21}NO_5$: C 65.24, H 6.38, N 4.22. Found: C 65.10, H 6.26, N 4.19.

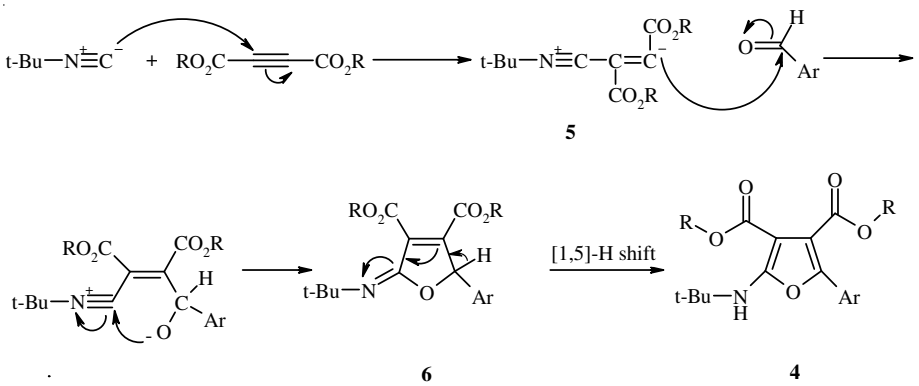
Dimethyl-2-(*tert*-butylamino)-5(4')-biphenyl-3,4-furan dicarboxylate (4b): Yellow powder, m.p. 105-107 °C, yield 90 %, IR (KBr, ν_{max}, cm^{-1}): 3332, 1730, 1679, 1618, 1474. ^1H NMR (500 MHz, $CDCl_3$): δ 1.49 (s, 9H, CMe_3), 3.76 and 3.91 (2s, 6H, 2 × OCH_3), 6.82 (br s, 1H, NH), 7.33 (t, $^3J_{HH}$ = 7.5 Hz, 1H, H_{para}), 7.43 (t, $^3J_{HH}$ = 7.1 Hz, 2H, H_{meta}), 7.59 (m, 6H, aromatic protons); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 29.9 ($NHCMe_3$), 51.1 ($NCMe_3$), 52.6, 52.8 (2 × OCH_3), 88.5 (NC=C), 113.3 (OC=C), 124.9, 126.9, 127.3, 127.4, 128.1, 128.8, 140.2, 140.4 (aromatic carbons), 141.2 (C), 161.6 (C), 165.0, 166.0 (2 × CO); MS: m/z (%): 407 (M^+, 94), 376 (7), 351 (84), 319 (45), 287 (63), 181 (100), 153 (34), 152 (57), 77 (13), 57 (90). Anal. calcd. for $C_{24}H_{25}NO_5$: C 70.74, H 6.18, N 3.43. Found: C 70.65, H 6.11, N 3.38.

Diethyl-2-(*tert*-butylamino)-5-biphenyl-3,4-furan dicarboxylate (4c): Yellow powder, m.p. 65-67 °C, yield 85 %, IR (KBr, ν_{max}, cm^{-1}): 3342, 1724, 1669, 1613, 1476. ^1H NMR (500 MHz, $CDCl_3$): δ 1.31 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_3), 1.38 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_3), 1.49 (s, 9H, CMe_3), 4.31 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.39 (q, $^3J_{HH}$ = 7.1 Hz, 2H, OCH_2), 6.89 (br s, 1H, NH), 7.33 (t, $^3J_{HH}$ = 7.5 Hz, 1H, H_{para}), 7.40 (t, $^3J_{HH}$ = 7.5 Hz, 2H, H_{meta}), 7.56-7.62 (m, 6H, aromatic protons); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.1, 14.4 (2 × CH3), 29.9 ($NHCMe_3$), 52.7 ($NCMe_3$), 59.6, 61.6 (2 × OCH2), 88.8 (NC=C), 113.7 (OC=C), 124.8, 126.8, 127.3, 127.4, 128.3, 128.8, 140.1, 140.4 (aromatic carbons), 140.7 (C), 161.6 (C), 164.7, 165.6 (2 × CO); MS: m/z (%): 435 (M^+, 81), 390 (7), 379 (65), 333 (13), 305 (37), 287 (42), 181 (100), 153 (37), 152 (47), 77 (9), 57 (29). Anal. calcd. for $C_{26}H_{29}NO_5$: C 71.70, H 6.71, N 3.21. Found: C 71.68, H 6.76, N 3.19.

Di-*tert*-butyl-2-(*tert*-butylamino)-5-furyl-3,4-furan dicarboxylate (4d): Yellow powder, m.p. 95-97 °C, yield 82 %, IR (KBr, ν_{max}, cm^{-1}): 3337, 1734, 1679, 1610, 1475. ^1H NMR (500 MHz, $CDCl_3$): δ 1.41, 1.50 and 1.56 (3s, 27H, 3 CMe_3), 6.41 (dd, $^3J_{HH}$ = 3.4 Hz, $^4J_{HH}$ = 1.7 Hz, 1H, CH), 6.48 (d, $^3J_{HH}$ = 3.4 Hz, 1H, CH), 6.81 (br s, 1H, NH), 7.37 (d, $^3J_{HH}$ = 1.7 Hz, 1H, CH); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 28.2, 28.6, 29.8 ($3CMe_3$), 52.5 ($NCMe_3$), 80.3, 81.8 (2 × $OCMe_3$), 89.1 (NC=C), 106.4 (CH), 111.2 (CH), 114.8 (OC=C), 134.2 (C), 141.4 (CH), 144.9 (C), 161.3 (C), 162.8, 164.4 (2 × CO); MS: m/z (%): 405 (M^+, 24), 293 (100), 276 (13), 237 (98), 219 (46), 175 (7), 147 (5), 132 (4), 57 (39). Anal. calcd. for $C_{22}H_{31}NO_6$: C 65.17, H 7.72, N 3.45. Found: C 65.12, H 7.71, N 3.42.

RESULTS AND DISCUSSION

On the basis of the well-established chemistry of isocyanides[13-17], it is reasonable to assume that polyfunctionalized furan **4a-d** result from nucleophilic addition of *t*-butyl isocyanide to dialkyl acetylene dicarboxylate and subsequent nucleophilic attack to aromatic aldehyde **3** to produce intermediate **5**. Then, the positively charged ion **5** is attacked by the negative oxygen to produce the cyclic intermediate **6**, that may tautomerize under the reaction condition, to form aromatic compound **4** (**Scheme-II**).



Scheme-II

Conclusion

In summary, a facile and efficient method is developed for the preparation of some 2-amino-5-aryl furan derivatives. The present method carries the advantage that not only is the reaction performed under neutral conditions, but also the starting materials and reagents can be mixed without any activation or modification.

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