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A simple and efficient approach to the synthesis of 4*H*-furo[3,4-*b*]pyrans via a three-component reaction of isocyanides

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ABSTRACT

A three-component reaction of an isocyanide, a dialkyl acetylenedicarboxylate, and tetronic acid in dichloromethane at room temperature afforded 4*H*-furo[3,4-*b*]pyran derivatives. These compounds are closely related with ring systems, TAN-2483B, TAN-2483A, and FD-211 which have a broad spectrum of biological activity.

Multi-component reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion.[1–4] Devising such types of MCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern organic synthesis.[5–9] As such processes avoid time-consuming and costly purification processes, as well as protection–deprotection steps, they are inherently more environmentally benign and atom-economic.[10,11] They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles.[12] MCRs that involve isocyanides are by far the most versatile reactions in terms of scaffolds and number of accessible compounds.[1–5,13]

Mizoue and co-workers reported the isolation of waol A (FD-211), which has a broad spectrum of activity against cultured tumor cell lines, including adriamycin-resistant HL-60 cells, from the fermentation broth of *Myceliophthora lutea* TF-0409.[14] TAN-2483B and TAN-2483A which have closely related compounds with this ring system (FD-211) show strong c-src kinase inhibitory action and inhibit PTH-induced bone resorption of a mouse femur.[15] Other related compounds include the antibacterial massarilactone B, which was isolated by Gloer from the freshwater aquatic fungus *Massarina tunicata* in 2001.[16] Fusidilactones A and B isolated by Krohn from an endophytic *Fusidium* sp. in 2002[17] show good antifungal activity against *Eurotium repens* and *Fusarium oxysporum* (Fig. 1).

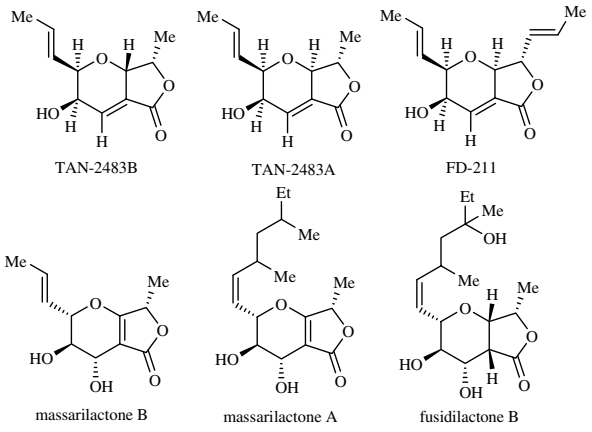

Figure 1. Structures of TAN-2483B, TAN-2483A, FD-211, massarilactone B, massarilactone A, and fusidilactone B.

Very recently, Snider and co-workers reported the synthesis of TAN-2483A, massarilactone B, fusidilactone B, and waol A (FD-211) via multi-step approach under very hard reaction conditions.[18,19]

As part of our continuing interest in the development of new synthetic methods in heterocyclic chemistry and our interest in isocyanide-based multi-component reactions,[20–27] herein we describe an efficient synthesis of 4*H*-furo[3,4-*b*]pyrans **4** via the reaction of an isocyanide **1** with an dialkyl acetylenedicarboxylate **2** and tetronic acid **3** in high yields without using any catalyst at ambient temperature[28] (Scheme 1).

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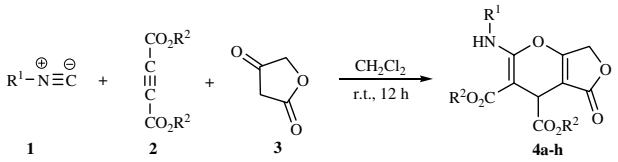


1 2 3 4a-h

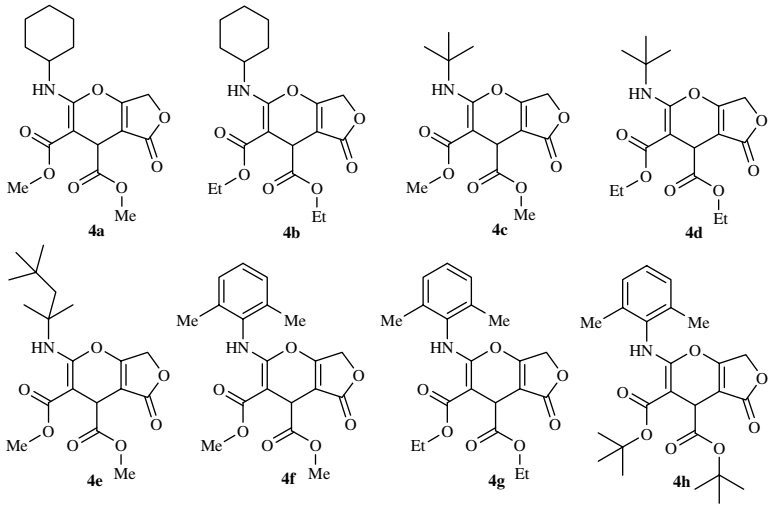
Scheme 1. Synthesis of 4*H*-furo[3,4-*b*]pyrans via three-component reaction.

As indicated in Table 1, isocyanides **1** with dialkyl acetylenedicarboxylate **2** and tetronic acid **3** undergo a smooth 1:1:1 addition reaction in dichloromethane at ambient temperature to produce 4*H*-furo[3,4-*b*]pyrans **4**. The structures of the products were deduced from their IR, mass, ^{1}H NMR and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values. The ^{1}H NMR spectrum of **4a** consisted of a multiplet for the cyclohexyl ring (δ = 1.25–1.91 ppm), a multiplet for the NH–C*H* cyclohexyl proton (δ = 3.60 ppm), two singlet for methoxy groups (δ = 3.67 ppm and δ = 3.72 ppm,), a singlet for the C*H*–CO_2Me (δ = 4.30 ppm), an AB-q for CH_2–O protons (δ = 4.78, 4.83 ppm, $^2J_{AB}$ = 16.4 Hz), and a doublet for NH (δ = 8.89 ppm, $^3J_{HH}$ = 7.8 Hz) protons. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 17 distinct resonances, and partial assignment of these resonances is given in Experimental section.

The reaction proceeds under mild conditions and is compatible with a wide range of functional groups. Two constituents in the products can be varied independently of each other. Representative examples of this reaction are shown in Table 1.

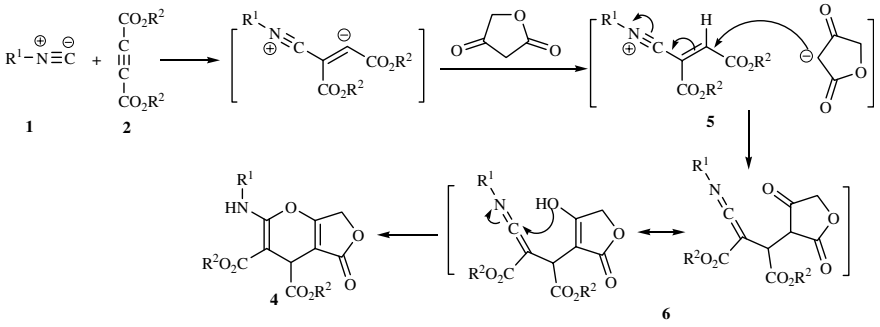
Although the mechanism of this reaction has not been established experimentally, the formation of these heterocycles can be rationalized by initial Michael-type vinylisonitrilium cation **5**.[29–33] Then, the positively charged ion might be attacked by the anion of the tetronic acid leading to the keteneimine **6**. Such an addition product may isomerize under the reaction conditions employed to produce the fused heterocyclic system **4** (Scheme 2).

Table 1
Synthesis of furo[3,4-*b*]pyran derivatives



4a 4b 4c 4d 4e 4f 4g 4h

Entry	R^1	R^2	Product	Yield (%)
1	Cyclohexyl	Me	**4a**	71
2	Cyclohexyl	Et	**4b**	73
3	*tert*-Butyl	Me	**4c**	80
4	*tert*-Butyl	Et	**4d**	79
5	1,1,3,3-Tetramethyl-butyl	Me	**4e**	70
6	2,6-Dimethyl-phenyl	Me	**4f**	75
7	2,6-Dimethyl-phenyl	Et	**4g**	75
8	2,6-Dimethyl-phenyl	^{t}Bu	**4h**	68



1 2 5 6 4

Scheme 2. Proposed mechanism.

In conclusion, we have developed a new and efficient approach to the synthesis of a wide range of furo[3,4-*b*]pyran derivatives from various isocyanides and dialkyl acetylenedicarboxylates in the presence of tetronic acid. The reaction has been shown to display good functional group tolerance and is high yielding and product isolation is very straightforward. We hope that this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry such as ring system of waol A.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.06.014.

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28. *Typical procedure for preparation of dimethyl 2-(cyclohexylamino)-5,7-dihydro-5-oxo-4H-furo[3,4-b]pyran-3,4-dicarboxylate* (**4a**): To a magnetically stirred solution of tetronic acid (0.10 g, 1.0 mmol) and dimethyl acetylenedicarboxylate (0.14 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was added, dropwise, a solution of cyclohexyl isocyanide (0.11 g, 1 mmol) in CH_2Cl_2 (2 mL) at −10 °C over 10 min. The mixture was allowed to warm up to room temperature and was finally stirred for 12 h. The solvent was removed under vacuum and the residue was crystallized from an *n*-hexane/dichloromethane (2:1) mixture and washed with ether (3× 5 mL) and the product **4a** was obtained. White crystals (0.25 g, yield 71%). Mp 128–130 °C. IR (KBr) (ν_{max}/cm^{-1}): 2935, 2857, 1766, 1734, 1715. MS, *m/z* (%): 352 (M^++1, 3), 292 (100), 210 (65), 178 (70), 88 (25), 59 (30), 55 (65), 41 (60). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.25–1.91 (10H, m, $5CH_2$ of cyclohexyl), 3.60 (1H, m, C*H*–NH), 3.67 (3H, s, O–CH_3), 3.72 (3H, s, O–CH_3), 4.30 (1H, s, C*H*–CO_2Me), 4.78 (1H, d, $^2J_{AB}$ = 16.4 Hz, CH_2–O), 4.83 (1H, d, $^2J_{AB}$ = 16.4 Hz, CH_2–O), 8.89 (1H, d, $^3J_{HH}$ = 7.8 Hz, CH–N*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 24.29, 24.32, 25.26, 33.53, 33.75 (C–cyclohexyl), 35.53 (*C*H–CO_2Me), 50.14 (CH–NH), 51.31, 52.69 (2O–CH_3), 65.47 (CH_2–O), 71.46, 102.92, 158.90, 167.30 (C-alkene), 169.11, 169.52, 172.53 (3C=O). Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99%. Found: C, 58.02; H, 5.96; N, 4.02%.
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