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A diastereoselective synthesis of 4-azidotetrahydropyrans via the Prins-cyclization

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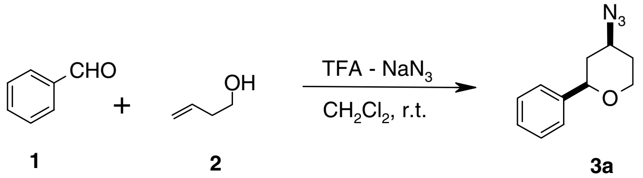
Abstract—A three component coupling of aldehydes, homoallylic alcohols and sodium azide is achieved in the presence of trifluoroacetic acid in dichloromethane to produce 4-azidotetrahydropyran derivatives in high yields with all *cis*-selectivity. The use of trifluoroacetic acid makes this procedure simple and cost-effective.

The 4-aminotetrahydropyran skeleton is a core structure in a number of natural products such as ambruticins VS, glycamino acid and others.[1,2] Tetrahydropyran derivatives are generally prepared via Prins-cyclization using acid catalysis.[3,4] Multicomponent one-pot reactions are highly important because of their wide range of applications in pharmaceutical chemistry for production of structural scaffolds and combinatorial libraries for drug discovery.[5] Organic azides are versatile building blocks for the synthesis of natural products and nitrogen-containing heterocycles such as triazoles, tetrazoles and isocyanates of pharmacological relevance.[6] Recently, they have been somewhat popularized due to their pivitol role in the emerging field of 'click chemistry',[7] and in particular, since the discovery of the Cu(I) catalyzed Huisgen[8] cycloaddition between organic azides and terminal alkynes.[9] This powerful and reliable bond-forming process has found widespread application, for example, in combinatorial drug discovery,[10] material science[11] and bioconjugation.[12,13] The development of a simple and more versatile approach for the direct preparation of 4-azidotetrahydropyrans would be very useful for the synthesis of natural products possessing a 4-aminotetrahydropyran framework.

In continuation of our research on the Prins-cyclization,[14] we report a more versatile approach to 4-azidotetrahydropyran derivatives via a three component coupling (3CC) involving condensation of a homoallylic alcohol with an aldehyde and sodium azide. The 3CC reaction was carried out in the presence of trifluoroacetic acid. This approach allows for the preparation of a diverse range of 4-azidotetrahydropyrans. Accordingly, we initially studied the three component coupling of benzaldehyde (**1**), but-3-en-1-ol (**2**) and sodium azide using 10 equiv of trifluoroacetic acid in dichloromethane. The reaction went to completion within 5 h at room temperature and the product, 4-azido-2-phenyl-tetrahydro-2*H*-pyran **3a** was isolated in 89% yield with all *cis*-selectivity (Scheme 1).

This result encouraged us to extend this process to various aldehydes and homoallylic alcohols. Interestingly, aryl aldehydes such as 3,4,5-trimethoxybenzaldehyde, *p*-methylbenzaldehyde, *p*-bromobenzaldehyde and *p*-nitrobenzaldehyde underwent smooth coupling with but-3-en-1-ol to give the corresponding 2,4-disubstituted tetrahydropyrans in high yields (Table 1, entries b–e). In addition, aliphatic aldehydes such as isobutyraldehyde, cyclohexanecarboxaldehyde, *n*-pentanal, *n*-decanal and 3-phenylpropanaldehyde also participated well in this



Scheme 1.

Keywords: Prins-cyclization; Sodium azide; Homoallylic alcohol; 4-Azidotetrahydropyrans.

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Table 1. Preparation of 4-azidotetrahydropyran derivatives using TFA/NaN$_3$

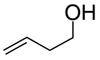
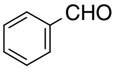
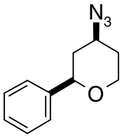
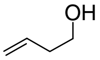
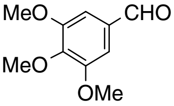
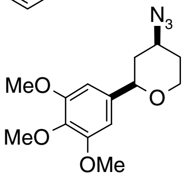
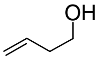
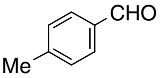
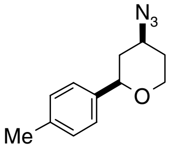
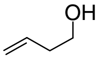
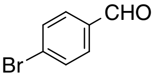
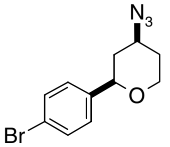
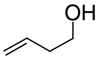
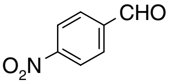
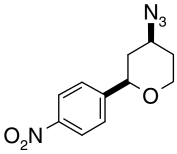
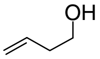
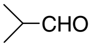
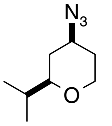
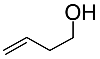
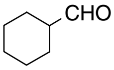
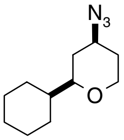
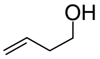
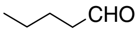
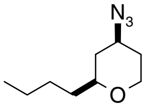
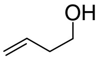
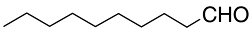
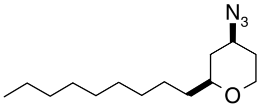
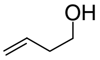
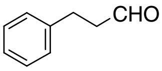
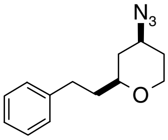
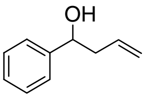
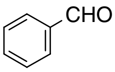
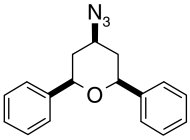
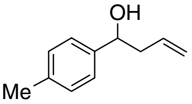
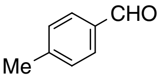
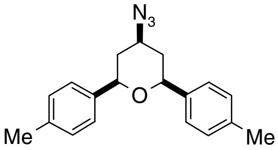
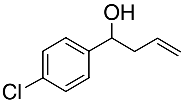
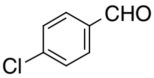
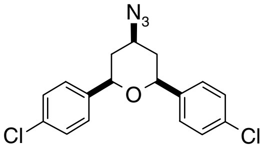
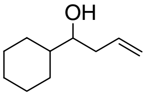
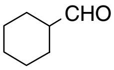
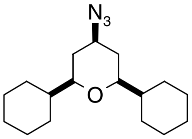
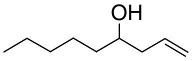
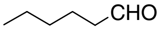
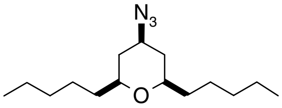
Entry	Homoallylic alcohol	Aldehyde	Azidopyran[a]	Time (h)	Yield[b] (%)
a				5.0	89
b				6.0	84
c				5.5	90
d				5.5	91
e				6.5	80
f				3.0	86
g				4.0	91
h				3.5	87
i				3.5	90
j				4.5	83
k				6.5	85

Table 1 (*continued*)

Entry	Homoallylic alcohol	Aldehyde	Azidopyran[a]	Time (h)	Yield[b] (%)
l				6.0	88
m				6.5	84
n				4.0	91
o				3.5	92

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.

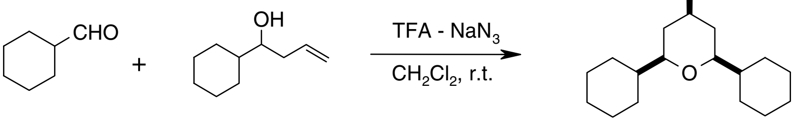
[b] Isolated and unoptimized yield.

reaction (Table 1, entries f–j). Aryl substituted homoallylic alcohols also reacted efficiently with aryl aldehydes to produce 2,4,6-trisubstituted tetrahydropyran derivatives (Table 1, entries k–m). The coupling between 1-cyclohexylbut-3-en-1-ol and cyclohexanecarboxaldehyde gave the symmetric 4-azido-2,6-dicyclohexyltetrahydro-2*H*-pyran with all *cis*-configuration (Table 1, entry n; Scheme 2).

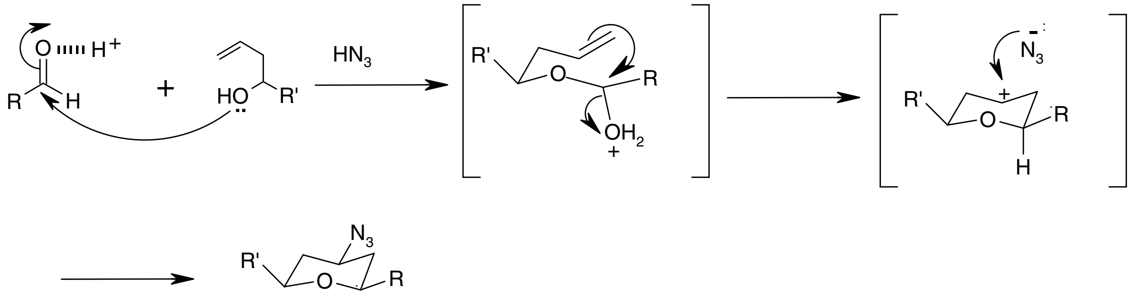
Similarly, the coupling of non-1-en-4-ol with *n*-hexanal afforded the symmetrical 4-azido-2,6-dipentyltetrahydro-2*H*-pyran under identical conditions (Table 1, entry o). However, no reaction was observed in the absence of trifluoroacetic acid even after an extended reaction time (12 h). As solvent, dichloromethane gave the best result. In all cases, the reactions proceeded rapidly at room temperature under mild conditions. The reactions were clean and the products were obtained in excellent yields and with high diastereoselectivity as determined from the NMR spectra of the crude products. Only a single diastereoisomer was obtained from each reaction, the structure of which was confirmed by coupling constants (*J* values) and NOE experiments.[15] The formation of the products can be explained by hemi-acetal formation followed by a Prins-type cyclization and subsequent azidation (Scheme 3).

A rationale for the all *cis*-selectivity involves formation of an (*E*)-oxocarbenium ion via a chair-like transition state, which has increased stability relative to the open oxocarbenium ion due to delocalization. The optimal geometry for this delocalization places the hydrogen atom at C4 in a pseudo-axial position, which favours equatorial attack of the nucleophile.[16] Lewis acid catalysts including metal halides such as $InCl_3$, $InBr_3$, $BiCl_3$ and $ZrCl_4$ or metal triflates such as $Sc(OTf)_3$, $In(OTf)_3$ and $Bi(OTf)_3$ failed to give the desired product. Furthermore, solid acids such as Montmorillonte KSF clay, PMA/SiO_2 and $HClO_4/SiO_2$ were also found to be ineffective. Surprisingly, no product was obtained in acetic acid. The scope and generality of this process is illustrated with respect to various aldehydes and homoallylic alcohols (Table 1).[17]

In conclusion, we have developed a three component, one-pot strategy for the synthesis of highly substituted 4-azidotetrahydropyrans via Prins-cyclization and azidation using trifluoroacetic acid as promoter. This meth-



Scheme 2.



Scheme 3.

od provides a direct access to 2,4-di- and 2,4,6-trisubstituted azidotetrahydropyran derivatives.

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17. *General procedure*: To a stirred solution of trifluoroacetic acid (10 mmol) and sodium azide (2 mmol, *Caution*: Reactions to be carried out with utmost care to avoid possible explosion of NaN$_3$) in dichloromethane (10 mL) was added slowly a solution of aldehyde (1 mmol) and homoallylic alcohol (1 mmol) in dichloromethane (5 mL). The resulting mixture was stirred at 23 °C for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the mixture was quenched with saturated sodium bicarbonate solution and extracted with dichloromethane (2×10 mL). The combined organic layers were washed with brine and dried over anhydrous Na$_2$SO$_4$. Removal of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) gave the pure 4-azidotetrahydropyran. The products thus obtained were characterized by IR, NMR and mass spectroscopy. *Spectral data for selected products* **3a**: 2-Phenyl-tetrahydro-2*H*-4-pyranyl azide: Liquid, IR (KBr): ν 3030, 2926, 2853, 2095, 1779, 1496, 1451, 1369, 1253, 1165, 1081, 1035, 756, 698 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ 1.42–1.85 (m, 2H), 1.89–2.23 (m, 2H), 3.52–3.68 (m, 2H), 4.17–4.37 (m, 2H), 7.30 (m, 5H). LCMS: m/z (%): (M+Na) 226. HRMS Calcd for C$_{11}$H$_{13}$N$_3$ONa: 226.0956. Found: 226.0962. Compound **3f**: 2-Isopropyltetrahydro-2*H*-4-pyranyl azide: Liquid, IR (KBr): ν 2924, 2853, 2093, 1365, 1252, 1083, 1037, 812 cm^{-1}. ^{1}H NMR (200 MHz,

$CDCl_3$): δ 0.89 (d, 3H, $J = 6.5$ Hz), 0.93 (d, 3H, $J = 6.5$ Hz), 1.68–2.07 (m, 5H), 2.94 (m, 1H), 3.27–3.48 (m, 2H), 4.02 (m, 1H). LCMS: *m*/*z* (%): (M+Na) 192. HRMS Calcd for $C_8H_{15}N_3ONa$: 192.1112. Found: 192.1120. Compound **3n**: 2,6-Dicyclohexyltetrahydro-2*H*-4-pyranyl azide: Liquid, IR (KBr): ν 2925, 2853, 2092, 1781, 1705, 1450, 1364, 1266, 1166, 1070, 1039, 996 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.75–1.47 (m, 20H), 1.40–1.98 (m, 6H), 3.02 (dd, 1H, $J = 6.8$, 10.5 Hz), 4.09 (dd, 2H, $J = 6.8$, 14.3 Hz). LCMS: *m*/*z* (%): (M+Na) 314. HRMS Calcd for $C_{17}H_{29}N_3ONa$: 314.2208. Found: 314.2217.