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Dioxane Dibromide–Mediated Solvent-Free Synthesis of Vicinal Dibromides

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Abstract: Structurally varied vicinal dibromides have been synthesized in high yield and good purity through highly stereoselective *anti*-addition of bromine across the olefinic linkages using dioxane dibromide (DD) under solvent-free conditions.

Keywords: electrophilic addition, regioselectivity, solid-phase synthesis, stereoselectivity

INTRODUCTION

Addition of bromine across the olefinic linkage[1] is an important protocol in organic synthesis because the brominated products serve as important precursors (through various organometallics) in C-C bond formation reactions.[2] This is generally accomplished with molecular bromine[3] in various organic (mainly halogenated) solvents, bromine on γ-alumina,[4] N-bromosuccinimide (NBS) in tetrabutylammonium bromide (TBAB),[5] and many others. The corrosive, lachrymatory, volatile, and fuming nature of molecular bromine along with its inherent toxicity cause serious procedural hazards. Also, the reaction products are generally complicated and contaminated with by-products because of various side reactions such as overbromination, oxidative decomposition, and polymeric transformations of the

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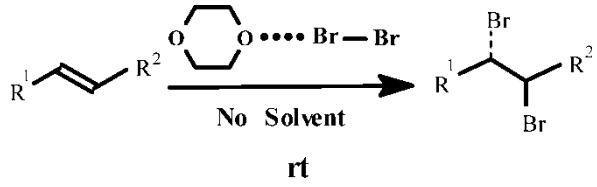


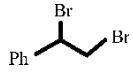
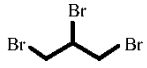
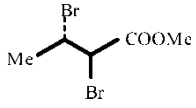
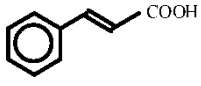
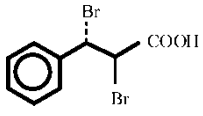
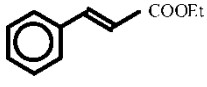
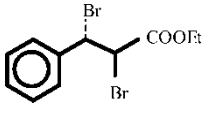
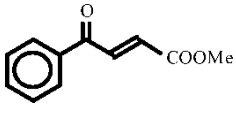
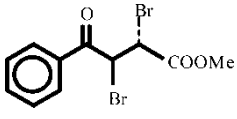
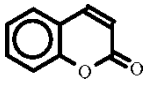
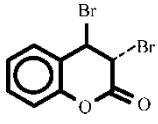
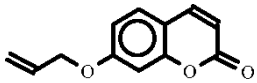
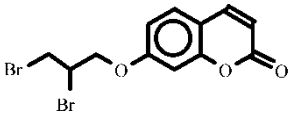
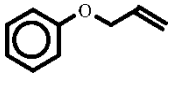
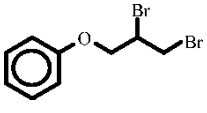
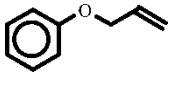
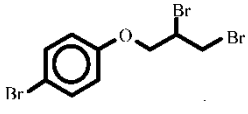
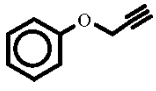
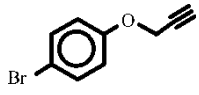
Scheme 1.

sensitive substrates and products. As part of our endeavor[6] to develop highly selective, operationally simple, economically viable, and environmentally benign methodologies for synthetically important organic transformations, we report herein improved applications of dioxane dibromide (DD) as bromine source under solvent-free condition (Scheme 1). Detailed results are furnished in Table 1.

As delineated in Scheme 1 and Table 1, electrophilic addition of bromine across various nucleophilic and electrophilic double bonds produced *vicinal* dibromides with high *anti*-diastereoselectivity (determined from the coupling constants of vicinal protons using Karplus's equation) under solvent-free conditions in practically pure form with negligible formation of by-products. Many of the products serve as commercially[7] and synthetically[1,3] important intermediates. In the presence of excess (6 eq.) nucleophilic reagents such as water and methanol, ethyl cinnamate yielded the major product as the vicinal *anti*-dibromide; about 30% of methanol addition product and no trace of 1,2-bromohydrin (water-addition product) were obtained. The COOH group also survived instead of the Hunsdiecker reaction.[5] An isolated double bond was selectively brominated in the presence of the conjugated one using critically weighed amount of DD as per the stoichiometric requirement (entry 8 in Table 1). Similarly, the isolated double bond preferentially underwent bromination in the presence of activated aromatic ring (entry 9 in Table 1); both the double bond and the activated ring were brominated when an excess amount of DD was used (entry 10 in Table 1). It is noteworthy that phenyl propargyl ether underwent preferential ring bromination in moderate yield and purity, keeping the triple bond intact (entry 11 in Table 1). The aforesaid reactions with DD in various organic solvents have been found to end up with incomplete conversions and the formation of a considerable amount of by-products. This demonstrates the very efficacy of the solvent-free protocols compared to their homogeneous counterparts.

The present solvent-free method using DD provides a good preparative method for differently substituted synthetically and commercially important *vicinal anti*-dibromides with varied functional groups in good yield, high purity, and excellent selectivity through operationally simple and relatively green procedures.

Table 1. Electrophilic *anti*-addition of bromine across the double bond with dioxane dibromide under solvent-free conditions

Entry	Substrate	Product	Time (min)	Yield[a] (%)
1			10	85[7]
2			10	82[7]
3			10	78[3]
4			20	70[3]
5			15	85[3]
6			20	68
7			30	76
8			30	78
9			30	62
10			30	80[b]
11			45	66

[a]Yield refers to that of isolated pure racemic products, characterized spectroscopically.

[b]2.5 eq. of DD used.

EXPERIMENTAL

General Procedure for Bromination Using DD

DD (6.0 mmol) was added in portions to the neat substrate (5 mmol, cooled at 0–5°C in ice water) and intimately mixed. The mixture was allowed to attain the ambient temperature and left for the stipulated time period (as mentioned in Table 1). Crushed ice was then added to the reaction mixture and filtered (if the product was solid) or extracted with ether (for a semisolid or liquid mass), washed successively with saturated aqueous sodium bicarbonate solution and water, and dried to get the product in almost pure form. The products were further purified by crystallization, short-path distillation, or filtration chromatography on a short column of silica gel using 5% ethyl acetate–petroleum ether, if needed.

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