Review Article

Atom Economy in Drug Synthesis is a Playground of Functional Groups

Kartik R. Patel*, Dr. Dhrubo Jyoti Sen and Viraj P. Jatakiya

Department of Pharmaceutical Chemistry, Shri Sarvajanik Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana-384001, Gujarat, India

Address for Correspondence

Department of Pharmaceutical Chemistry, Shri Sarvajanik Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana-384001, Gujarat, India

E-mail:
kartikp70@gmail.com

ABSTRACT

Like most other people, chemists are concerned with environmental pollution. This concern has given rise to a field called green chemistry, which involves the design of chemical products and processes that minimize environmental problems. One of the principles, called atom economy, involves—among other things—designing reactions in such a way that the quantity of reactants that end up in the desired final product is the maximum possible. We can define the percent atom economy (% AE) of a reaction by the formula. Atom economy also must consider substances such as solvents, separation agents and drying agents that are used in the process but are not directly part of the chemical reaction. Using a green chemistry approach, chemists attempt to either reduce the amount of or eliminate completely as many of these substances as possible. Those that cannot be eliminated are reused or recycled when possible. Atom economy (atom efficiency) describes the conversion efficiency of a chemical process in terms of all atoms involved (desired products produced). In an ideal chemical process, the amount of starting materials or reactants equals the amount of all products generated and no atom is wasted. Recent developments like high raw material (such as petrochemicals) costs and increased sensitivity to environmental concerns have made atom economical approaches more popular. Atom economy is an important concept of green chemistry philosophy and one of the most widely used ways to measure the "greenness" of a process or synthesis.

Atom economy can be written as: % atom economy = (Molecular weight of desired product ÷ Molecular weight of all reactants) × 100

Atom economy can be poor even when chemical yield is near 100%. Atom economy can also be adjusted if a pendant group is recoverable. However, if this can be avoided it is more desirable, as recovery processes will never be 100%. Atom economy can be

improved upon by careful selection of starting materials and a catalyst system. Atom economy is just one way to evaluate a chemical process. Other criteria can include energy consumption, pollutants released and price. Poor atom economy is common in fine chemicals or pharmaceuticals synthesis and especially in research, where the aim to readily and reliably produce a wide range of complex compounds leads to the use of versatile and dependable, but poorly atom-economical reactions. It is fundamental in chemical reactions of the form A+B→C+D that two products are necessarily generated though product C may have been the desired one. That being the case, D is considered a byproduct. As it is a significant goal of green chemistry to maximize the efficiency of the reactants and minimize the production of waste, D must either be found to have use, be eliminated or be as insignificant and innocuous as possible. With the new equation of the form A+B→C, the first step in making chemical manufacturing more efficient is the use of reactions that resemble simple addition reactions with the only other additions being catalytic materials. Functional groups of all the starting substances have been converted into another group by synthetic step by green chemistry reaction followed by atom economy.

Keywords: Green Chemistry, Atom Economy, Environmental Pollution, Actual Yield, Theoretical Yield, Percentage Yield.

INTRODUCTION

Atom economy (atom efficiency) describes the conversion efficiency of a chemical process in terms of all atoms involved (desired products produced). In an ideal chemical process, the amount of starting materials or reactants equals the amount of all products generated (as per stoichiometry aspects) and no atom is wasted. Recent developments like high raw material (such as petrochemicals) costs and increased sensitivity to environmental concerns have made atom economical approaches more popular. Atom economy is an important concept of green chemistry philosophy, one of the most widely used ways to measure the "greenness" of a process or synthesis.[1-3]

Note that atom economy can be poor even when chemical yield is near 100%, e.g. the **Cannizzaro reaction** or the **Wittig reaction**. If the desired product has an enantiomer, the reaction needs to be sufficiently stereoselective even when atom economy is 100%. A **Diels-Alder reaction** is an example of a potentially very atom efficient reaction that also can be chemo-, regio-, diastereo- and enantioselective. Catalytic hydrogenation comes the closest to being an ideal reaction that is extensively practiced both industrially and academically.[4] **The Gabriel synthesis** of amines is an example of extremely low atom economy, as stochiometric quantities of phthalic acid derivatives are formed. In most cases, the atom economy of the **Gabriel synthesis** is <<50%. Atom economy can also be adjusted if a pendant group is recoverable, for example Evans auxiliary groups. However, if this can be avoided it is more desirable, as recovery processes will

never be 100%. Atom economy can be improved upon by careful selection of starting materials and a catalyst system.

Atom economy is just one way to evaluate a chemical process. Other criteria can include energy consumption, pollutants released and price.

Poor atom economy is common in fine chemicals or pharmaceuticals synthesis and especially in research, where the aim to readily and reliably produce a wide range of complex compounds leads to the use of versatile and dependable, but poorly atom-economical reactions. For example, synthesis of an alcohol is readily accomplished by reduction of an ester with lithium aluminum hydride, but the reaction necessarily produces a voluminous flock of aluminum salts, which have to be separated from the product alcohol and disposed of. The cost of such hazardous material disposal can be considerable. Catalytic hydrogenolysis of an ester is the analogous reaction with a high atom economy, but it requires catalyst optimization, is a much slower reaction and is not applicable universally.

THE TWELVE PRINCIPLES OF GREEN CHEMISTRY

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product. Use all reagents.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary whenever possible and, innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material feedstock should be renewable rather than depleting whenever technically and economically practical.
8. Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be further developed to allow for real-time in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

Green chemistry, also called sustainable chemistry, is a philosophy of chemical research and engineering that encourages the design of products and processes that minimize the use and generation of hazardous substances. Whereas environmental chemistry is the chemistry of the natural environment, and of pollutant chemicals in nature, green chemistry seeks to reduce and prevent pollution at its source.As a

chemical philosophy, green chemistry applies to organic chemistry, inorganic chemistry, biochemistry, analytical chemistry, and even physical chemistry. While green chemistry seems to focus on industrial applications, it does apply to any chemistry choice. Click chemistry is often cited as a style of chemical synthesis that is consistent with the goals of green chemistry. The focus is on minimizing the hazard and maximizing the efficiency of any chemical choice. It is distinct from environmental chemistry which focuses on chemical phenomena in the environment.[5]

$$CH_3CH_2CH_2CH_2OH \; + \; NaBr \; + \; H_2SO_4 \longrightarrow$$

$$1 \qquad\qquad 2 \qquad\quad 3$$
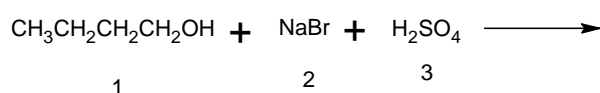
ATOM ECONOMY: A Measure of the Efficiency of a Reaction

Efficiency of a Reaction:Although the efficiency of a reaction can be measured in many ways, by far the most common way is to calculate the yield (percentage yield). We are often required, especially in laboratory, to determine the theoretical yield based upon the limiting reagent and then to calculate the percentage yield based upon the ratio of the actual yield ÷ theoretical yield × 100. In general organic chemists consider yields of 90% or better as excellent while 20% or less are poor.
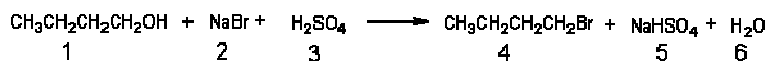
Theoretical yield =
(moles of limiting reagent) ×
(stoichiometric ratio; desired product/limiting reagent) × (MW of desired product)

Percentage yield=
(actual yield/theoretical yield) × 100

In order to illustrate the calculation of the percentage yield (and the measurement of the efficiency of a reaction) consider the following acid promoted nucleophilic substitution reaction. A typical procedure[1]for this reaction begins with dissolving 1.33 g of

sodium bromide (2) in 1.5 mL of water, followed by addition of 0.80 mL of 1-butanol (1) and 1.1 mL (2.0 g) of concentrated sulfuric acid (3).

$$CH_3CH_2CH_2CH_2OH \; + \; NaBr + \; H_2SO_4 \longrightarrow CH_3CH_2CH_2CH_2Br \; + \; NaHSO_4 \; + \; H_2O$$

$$1 \qquad\qquad 2 \qquad\quad 3 \qquad\qquad\qquad 4 \qquad\qquad 5 \qquad 6$$

Equation:1a

The following Reagents Table (Table-1) and Desired Product Table (Table-2) can then besetup. Dividing the weight of each reactant that is used, by the molecular weight of the reactant, gives the number of moles of each reagent used.

From the stoichiometry of the reaction (Equation 1a) it is clear that one mole of each reactant is required to produce one mole of product (1-bromobutane) and since 1-butanol (0.0108mole) is used in the smallest amount it is the limiting reagent. Calculation of the (as shown below) theoretical yield of 1-bromobutane gives 1.48g. This means that using theabove quantities of reagents the maximum amount (assuming 100% yield) of 1-bromobutane that can be produced is 1.48g. In fact no reaction ever proceeds with 100% yield due to such factors as the formation of side products, incomplete conversion of the starting materials, loss upon workup of the reaction mixture, and loss upon isolation and purification of the desired product.

Theoretical yield =
(moles of limiting reagent) × (stoichiometric ratio; desired product /limiting reagent) × (MW of desired product)

= (moles of 1-butanol)× (stoichiometric ratio; 1-romobutane/1-butanol)×(MW of 1-bromobutane)

=(0.0180mole)×(1 mole /1 mole)×(137.03g/mole)

=1.48g

This reaction typically produces actual yields of 1-1.2g. Assuming that the actual yield is 1.20g calculation of the % yield is as follows. Thus 81% of the theoretical yield is actually isolated, which is a very respectable yield that would please most chemists.

Percentage yield=
(actual yield ÷ theoretical yield) × 100
= (1.20g/1.48g) × 100
= 81%

Atom Economy in a Substitution Reaction

As indicated previously most chemists have traditionally measured the efficiency of a reaction by the percentage yield, however this only tells part of the story. If one considers the above reaction where a total of 4.13g of reactants (0.8g of 1-butanol, 1.33g of NaBr and 2.0g of H_2SO_4) was used and that at best this reaction will only yield 1.48g of the desired product, the question might be asked" what happens to the bulk (4.13g -1.48g = 2.7g) of the mass of reactants?". The answer is they end up in side products ($NaHSO_4$ and H_2O) that may be unwanted, unused, toxic and/or not recycled/reused. The side products are oftentimes treated as wastes and must be disposed of or otherwise treated. At best only 36% (1.48g/4.13 g × 100) of the mass of the reactants end up in the desired product. If the actual yield is 81% then only 29% (0.81 × 0.36 × 100) of the mass of the reactants actually ends up in the desired product!

In an effort to foster awareness of the atoms of reactants that are incorporated into the desired product and those that are wasted (incorporated into undesired products), *Barry Trost* developed the concept of atom economy.[6] In 1998 Trost was awarded a Presidential Green Chemistry Challenge Award for the concept of atom economy. In light of the concept of atom economy, the above acid promoted nucleophilic substitution

must now be reconsidered. In Equation 1b we have illustrated the atom economy of this reaction by showing all of the reactant atoms that are incorporated into the desired product in green, while those that are wasted are shown in brown.

$$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}OH + Na\text{-}Br + H_2SO_4 \longrightarrow CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}Br + NaHSO_4 + H_2O$$
$$\quad\quad 1 \quad\quad\quad\quad 2 \quad\quad 3 \quad\quad\quad\quad\quad\quad 4 \quad\quad\quad\quad 5 \quad\quad 6$$

Equation: 1b

Likewise the atoms of the desired product are in green and the atoms composing the unwanted products are in brown. Table 3 provides another view of the atom economy of this reaction. In columns 1 and 2 of this table, the formulas and formula weights (FW) of the reactants are listed. Shown in green (columns 3 and 4) are the atoms and weights of the atoms of the reactants that are incorporated into the desired product (4), and shown in brown (columns 5 and 6) are the atoms and weights of atoms of the reactants that end up in unwanted side products. Focusing on the last row of this table it can be seen that of all the atoms of the reactants (4C, 12H, 5O, 1Br, 1Na and 1S) only 4C, 9H and 1Br are utilized in the desired product and the bulk (3H, 5O, 1Na and 1S) are wasted as components of unwanted products. This is an example of poor atom economy! A logical extension of Trost's concept of atom economy is to calculate the percentage atom economy.[7]

This can be done by taking the ratio of the mass of the utilized atoms (137) to the total mass of the atoms of all the reactants (275) and multiplying by 100. As shown below this reaction has only 50% atom economy.

% Atom Economy=
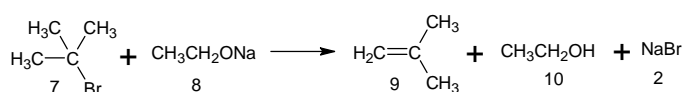(FW of atoms utilized ÷ FW of all reactants)×100
= (137/275) × 100
= 50%

Thus at best (if the reaction produced 100% yield) then only half of the mass of the reactants would be incorporated into the desired product while the rest would be wasted in unwanted side products.

Atom Economy in Elimination Reactions

In the substitution reaction above (Equation 1a) it was revealed that the poor atom economy resulted from the fact that the atoms of the leaving group (OH) that is being replaced, the counter ion (sodium) of our nucleophile (bromide), and the sulfuric acid that is required for this reaction all are wasted in forming unwanted products in this reaction. By virtue of the fact that elimination reactions require only the loss of atoms (while gaining none) from the reactant, means that elimination reactions are in general even worse, in terms of their atom economy, than substitution reactions.

As an example consider the atoms of the following elimination reaction. Base promoted dehydrohalogenation of alkyl halides is a common method of producing alkenes from alkyl halides via elimination. In Equation 2 the formation of methyl propene is accomplished by the reaction of 2-bromo-2-methylpropane (7) with sodium ethoxide (8). In this reaction, the atoms of the reactants that are incorporated into the desired product (9) and the atoms of the desired product are indicated in green, while the unutilized atoms of the reactants are shown in brown as are the atoms in the unwanted products of the reaction. Table 4 illustrates the atom economy of this reaction and calculation of the % atom economy gives a very poor 27%. The poor atom economy is a result not only of the loss of the HBr but also because this is a base

promoted reaction and all of the atoms of the sodium ethoxide base are found in unwanted side products.

% Atom Economy =
(FW of atoms utilized÷FW of all reactants) × 100

$$= (56 \div 205) \times 100$$
$$= 27\%$$

Atom Economy in Addition Reactions

Because addition reactions in general lead to the incorporation of all the atoms of the reactants into the final desired products, addition reactions result in high atom economy. From an atom economy point of view, addition reactions are thus environmentally preferable to elimination and substitution reactions. As a case in point consider the following addition of hydrogen bromide to methyl propene. In this example all the atoms of the reactants (9 and 11) are shown in green since all of these atoms are utilized in the final desired product (7). The table of atom economy (Table 5) and the calculation of 100% atom economy further emphasize the excellent atom economy of this reaction.
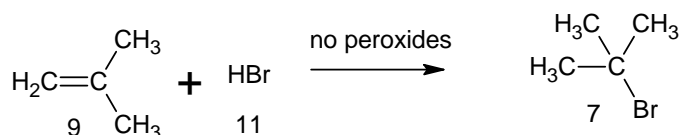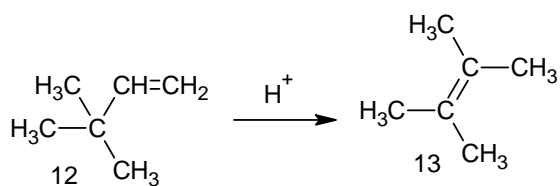

Equation: 3

% Atom Economy =
(FW of atoms utilized÷FW of all reactants) × 100
$$= (137 \div 137) \times 100$$
$$= 100\%$$

Atom Economy in Rearrangement Reactions

Rearrangement reactions involve reorganization of the atoms of a molecule. Because elimination, addition or substitution

Equation: 2

of atoms is taking place, in the molecule undergoing rearrangement, the atom economy of rearrangement reactions is 100% and they are environmentally preferable reactions from an atom economy standpoint. To illustrate this, consider the acid catalyzed rearrangement of 3,3-dimethyl-1-butene (12) to 2,3-dimethyl-2-butene (13). In this case the atoms of the reactant 12 are all shown in green since they are all incorporated into the desired product 13. As in the previous examples one can set up an atom economy table and calculate the % atom economy. Although the acid (H^+) used in this reaction is not incorporated into the desired product it is used only in catalytic amountsand therefore indicated in black (not green or brown) and it is not considered in the atom economy table or the calculation of the atom economy. As was predicted above for rearrangements, the % atom economy of this reaction is 100%.

Equation: 4

% Atom Economy =

(FW of atoms utilized ÷ FW of all reactants) × 100
= (84 ÷ 84) × 100
= 100%

Virtually all organic reactions fall into the categories of substitution, addition, elimination or rearrangement reactions. From the perspective of atom economy, addition and rearrangement reactions are environmentally preferable, with substitution reactions next, while eliminations are the least environmentally preferable. As one encounters reactions, in the study of chemistry, one should examine each reaction from the point of not only the yield, but also the atom economy of the reaction.
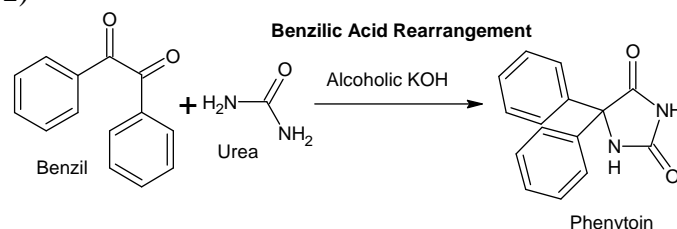
Other examples of laboratory scale:

1)
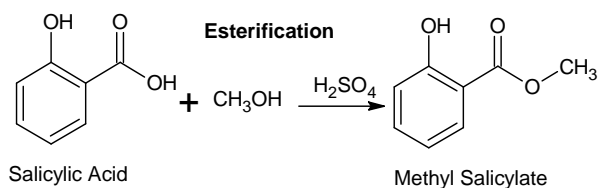
ATOM ECONOMY: 89.41%;
% YIELD: 60%

Methyl salicylate:Conversion of -COOH of salicylic acid into ester with –OH of methanol (Esterification reaction) NSAID.
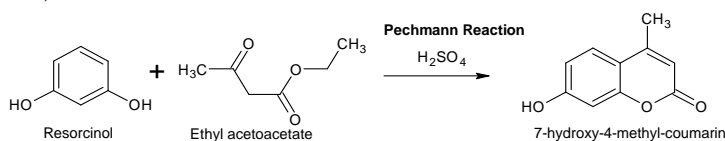
2)

ATOM ECONOMY: 93.33%;
% YIELD: 33.33%

Phenytoin: *Conversion of –C=O of benzil into phenytoin with urea (NH_2-CO-NH_2) in alcoholic KOH* (Benzilic acid reaction) Antiepileptic.
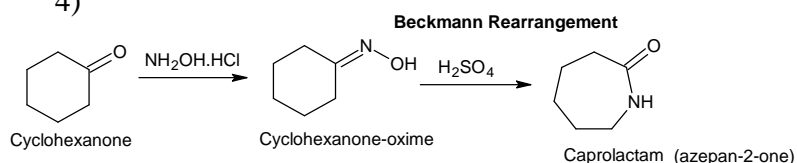
3)

ATOM ECONOMY: 73.33%;
% YIELD: 75%

Coumarin: *Condensation of –OH of resorcinol with =C-OH of ethyl acetoacetate in presence of sulfuric acid* (Pechmann reaction) Anticoagulant.
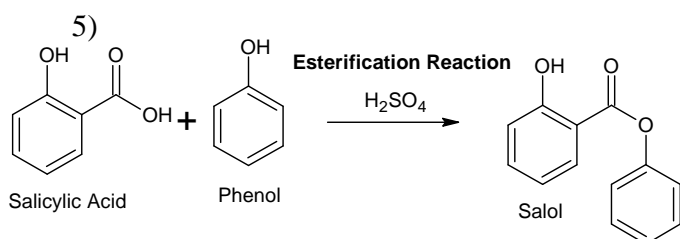
4)

ATOM ECONOMY: 73.13%;
% YIELD: 65.05%

Caprolactam: *Condensation of –C=O of cyclohexanone oxime with H_2SO_4* (Beckmann rearrangement) Polymer.

5)

ATOM ECONOMY: 92.24%;
% YIELD: 81.36%

Salol: *Condensation of –OH of phenol with –COOH of salicylic acid* (Esterification reaction)Enteric coating tablet.

SUMMARY

Functional groups of all the starting substances have been converted into another group by synthetic steps by green chemistry reaction followed by atom economy percentage which is completely different from percentage yield.Atom economy and experimental atom economy go beyond the calculation of the yield of a reaction and offer a second way to measure the efficiency of a reaction taking into account the utilized and unutilized atoms of the reactants. The percentage atom economy and the percentage experimental atom economy, give one the means to quantify the atom economy, and allows for a quantitative comparison of the atom economy of one reaction (or synthesis) vs. another. Perhaps the best measure of the efficiency of a reaction is to take into consideration both the atom economy and the yield by calculating the *percentage yield × experimental atom economy* (PE ×

EAE). Of course in assessing the environmental suitability of a reaction (or synthesis) not only should one consider the efficiency of the reaction but also (as discussed above) other factors such as toxicity, the use of auxiliary substances, energy requirements, feedstock origins, and catalytic vs. stoichiometric reagents.

ACKNOWLEDGEMENTS

REFERENCES

1. Trost B. M., "Atom Economy: A Challenge for Organic Synthesis", *Angew. Chem. Int. Ed. Engl.* **1995,** *34(3)*, 259–281.
2. Sheldon R. A., "Atom efficiency and catalysis in organic synthesis". *Pure and Applied Chemistry* **2000,** *72(7)*, 1233–1246.
3. Terrence J. Collins, "Introducing Green Chemistry in Teaching and Research", *J. Chem. Edu.*, **1995**, *72(11)*, 965-970.
4. Solaza B., Huguet J., Karpf M. and Dreiding AS, "The Synthesis of (+/-) Isoptychanolide by Application of the α-Alkynone Cyclization",*Tetrahedron* **1987**, *43(21)*: 4875–4886.
5. Anastas PT. and Warner J C., Green Chemistry Theory and Practice, Oxford University Press, New York, **1998**.
6. Trost BM., "The Atom Economy-A Search for Synthetic Efficiency", *Science* **1991**, *254*, 1471-1477.
7. Sheldon, Roger A. "Consider the Environmental Quotient" *CHEMTECH* **1994**, *24(3)*, 38–47.

Table 1. Reagents Table

Reagent	MW	Weight Used (g)	Moles Used	Theoretical Moles Needed	Density	BP (^{o}C)
C_4H_9OH	74.12	0.80	0.0108	0.0108	0.810	118
NaBr	102.91	1.33	0.0129	0.0108		
H_2SO_4	98.08	2.0	0.0200	0.0108	1.84	

Table 2. Desired Product Table

Compound	MW	Theoretical Yield (Moles)	Theoretical Yield (Grams)	Actual Yield (Grams)	% Yield	Density	BP (^{o}C)
C_4H_9Br	137.03	0.011	1.48 (100%)	1.20	81	1.275	101.6

Table 3. Atom Economy of Equation 1

Reagents Formula	Reagents FW	Utilized Atoms	Weight of Utilized Atoms	Unutilized Atoms	Weight of Unutilized Atoms
C_4H_9OH	74	4C, 9H	57	HO	17
NaBr	103	Br	80	Na	23
H_2SO_4	98	_____	0	2H, 4O, S	98
Total 4C,12H,5O,Br, Na, S	275	4C, 9H, Br	137	3H, 5O, Na, S	138

Table 4. Atom Economy Equation 2

Reagents Formula	Reagents FW	Utilized Atoms	Weight of Utilized Atoms	Unutilized Atoms	Weight of Unutilized Atoms
C_4H_9Br	137	4C, 8H	56	HBr	81
C_2H_5ONa	68	——	0	2C, 5H, O, Na	68
Total	205	4C, 8H	56	2C, 6H, O,	149
C_4H_9Br	137	4C, 8H	56	HBr	81

Table 5. Atom Economy Equation 3

Reagents Formula	Reagents FW	Utilized Atoms	Weight of Utilized Atoms	Unutilized Atoms	Weight of Unutilized Atoms
C_4H_8	56	4C, 8H	56	——	0
HBr	81	HBr	81	——	0
Total 4C,9H,Br	137	4C, 9H, Br	137	——	0

Table 6. Atom Economy Equation 4

Reagents Formula	Reagents FW	Utilized Atoms	Weight of Utilized Atoms	Unutilized Atoms	Weight of Unutilized Atoms
C_6H_{12}	84	6C, 12H	84	——	0
Total	84	6C, 12H	84	——	0

Figure.1. Atom Economy Triangle